"Clickable" Polyglycolides: Tunable Synthons for Thermoresponsive, Degradable Polymers

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ABSTRACT: "Click" chemistry is a powerful method for post-polymerization modification of polymers and other materials. Because of the importance of lactide-based functional polymers in materials and medical applications, we synthesized 3,6-dipropargyl-1,4-dioxane-2,5-dione, an acetylene-functionalized glycolide monomer. Its subsequent polymerization and copolymerization with lactide provided a new polyglycolide homopolymer as well as random and block copolymers that have pendant acetylene groups available for the attachment of chemical functionality using "click" chemistry. A protocol was devised to permit "click" functionalization of polyglycolides with no degradation in molecular weight. As one demonstration of the power of this approach to substituted polyglycolides, we have prepared a family of degradable, thermoresponsive materials that exhibit lower critical solution temperatures (LCST) from room temperature to >60 °C.

Introduction

The biodegradability and biocompatibility of aliphatic polyesters have established polymers derived from lactide, glycolide, and ϵ-caprolactone as key materials for biomedical applications. However, the parent homopolymers have limitations. For example, they are often too hydrophobic for applications in aqueous environments, and more importantly, they lack chemical functionality that enables modification of the polymer backbone. Recent work describes successful strategies for appending hydroxyl,[1−3] carboxyl,[4] poly(ethylene oxide) (PEO),[1,5−7] allyl,[8,9] and acetylene[5] functionalities to polyesters by copolymerization with functional monomers, post-polymerization modification of polymers, or a combination of these two approaches. However, most strategies involve multistep monomer syntheses, provide a narrow range of functional groups, and offer limited flexibility in changing the polymer composition. It is highly desirable to have a single monomer that allows facile placement of a broad spectrum of pendant functional groups onto polyester substrates without backbone degradation and is compatible with a wide range of functional groups, solvents, and conditions.

Because of its high selectivity, reliability, and tolerance to a broad range of functional groups and reaction conditions, "click" chemistry, specifically the copper(I)-mediated 1,3-dipolar cycloaddition of azides and alkynes, is a powerful strategy for elaborating polymer architectures.[10,11] "Click" chemistry has been used for the preparation of block copolymers,[12,13] cross-linked adhesives,[14] dendrimers,[15−18] and the introduction of pendant and terminal functional groups into various polymers including polyesters.[5,7,19−26] The Emrick group first described the use of aqueous "click" chemistry to graft azide-terminated PEO and peptides onto polyesters containing pendant acetylene groups.[5] Later, Jérôme and co-workers found Emrick's conditions caused significant backbone degradation during functionalization.[7] Using less severe conditions (THF as the solvent), they were able to introduce PEO, tertiary amines, and ammonium salts onto caprolactone-based polyesters having pendant azides. Unfortunately, lactide copolymers are more hydrolytically sensitive than caprolactones, and the polymer hydroxyl groups must be protected to avoid significant backbone degradation under Jérôme's conditions. In addition, "click" reactions using CuI, the catalyst used by Jérôme, are subject to more side reactions than Cu(I) catalysts generated in situ.[27] Clearly, it would be useful to have a simpler and more reliable protocol for "click" functionalization of polyesters and especially polyesters based on lactide monomers.

We are interested in tailoring the properties of polylactides through the synthesis and polymerization of substituted lactides. Using this approach, we have successfully prepared poly(phenyllactide),[28] polymandelide,[29] alkyl,[30] cyclohexyl,[31] and allyl-substituted polylactides,[9] PEO-substituted polylactides,[32] and alkyl/PEO-substituted amphiphilic polylactides.[33] Stimulated by the versatility of "click" chemistry for post-polymerization modification of polyesters, as well as the importance of lactide-based functional polymers in materials and medical applications, we synthesized 3,6-dipropargyl-1,4-dioxane-2,5-dione (**1**), an acetylene-functionalized glycolide monomer (Scheme 1). Subsequent polymerization of **1** and copolymerizations with lactide provides new polyglycolide homo- and copolymers (both random and block) that have pendant acetylene groups available for the attachment of chemical functionality using "click" chemistry. Also, a revised "click" protocol has been devised to overcome limitations encountered when "click" functionalizations of polyglycolides were attempted using Emrick's or Jérôme's conditions. As a demonstration of the power of this approach to substituted polyglycolides, we have prepared a family of degradable thermoresponsive materials that exhibit lower critical solution temperatures (LCST) over a broad and physiologically relevant temperature range.

Experimental Section

Materials. 10-Azido-2,5,8-trioxadecane (mDEG azide) and methoxypoly(ethylene glycol)-550 azide (mPEG-550 azide) were prepared using literature procedures,[34] and 1-azidodecane[35] was synthesized by a modified procedure.[36] Ethyl glyoxylate (Alfa Aesar, 50 wt % in toluene) was distilled before use. THF was dried by passage through a column of activated alumina. DMF was dried over activated 4 Å molecular sieves. Zinc (Spectrum, 20 mesh) was treated with 2 M HCl and then washed sequentially with distilled water and absolute ethanol and dried under vacuum at 60 °C. Propargyl bromide (80 wt % in toluene) was purchased from Alfa Aesar. All other chemicals and solvents were ACS reagent

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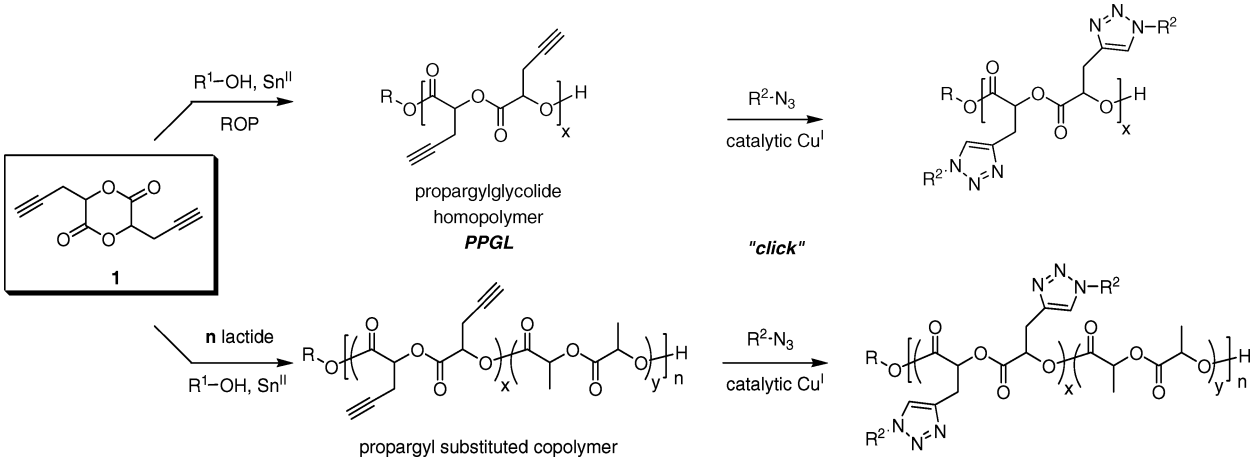
Scheme 1. "Click" Chemistry Strategy for Synthesizing Functionalized Glycolide Polymers and Copolymers



grade and used as received from Aldrich, except for triethylene glycol monomethyl ether, which was vacuum-distilled.

Characterization. Polymer molecular weights were determined by gel permeation chromatography (GPC) at 35 °C using two PLgel 10μ mixed-B columns in series (manufacturer-stated linear molecular weight range of 500−10 000 000 g/mol) with THF as the eluting solvent at a flow rate of 1 mL/min. A Waters 2410 differential refractometer was used as the detector, and monodisperse polystyrene standards were used to calibrate the molecular weights. The concentration of polymer solutions used for GPC was 1 mg/mL. Additional GPC data were obtained using GPC-MALS (multiangle light scattering) at 35 °C using THF as the eluting solvent at a flow rate of 1 mL/min. An Optilab rEX (Wyatt Technology Co.) and a DAWN EOS 18 angle light scattering detector (Wyatt Technology Co.) with a laser wavelength of 684 nm were used to calculate absolute molecular weights. ^{1}H NMR (300 or 500 MHz) and ^{13}C NMR (75 or 125 MHz) spectra were acquired in $CDCl_3$ using either a Varian Gemini 300 spectrometer or a Varian UnityPlus 500 spectrometer. The residual proton and carbon signals from the solvent were used as chemical shift standards for the ^{1}H and ^{13}C NMR spectra. Mass spectral analyses were carried out on a VG Trio-1 Benchtop GC-MS. UV−vis spectra were recorded with a Varian Cary 300 Bio WinUV spectrophotometer.

Synthesis of 2-Hydroxy-4-pentynoic Acid Ethyl Ester (2). Propargyl bromide (~10 g) was added under a blanket of N_2 to a 3 L round-bottom flask containing 350 mL of anhydrous THF and Zn (230 g, 3.5 mol). The mixture was stirred at room temperature for 30 min and then cooled in an ice bath. A toluene solution of ethyl glyoxylate (51 wt %, determined by NMR, 473 g, 2.36 mol) and a toluene solution of propargyl bromide (80 wt %, 352 g, 2.36 mol) were combined in 500 mL of dry THF and 700 mL of dry ether. This mixture was then added dropwise to the stirred slurry. After the addition was complete, the mixture was stirred at 0 °C overnight. The reaction mixture was then poured into a 4 L Erlenmeyer flask containing 1 L of ice-cold 3 M HCl. After separation of the organic layer, the aqueous layer was extracted with ether (3 × 300 mL), and the combined organic layers were dried over $MgSO_4$. Filtration and removal of the solvents by rotary evaporation gave a dark blue oil, which was purified by column chromatography using silica gel with EtOAc/hexanes (30/70) as the eluent. Vacuum distillation of the resulting material (50−55 °C/100 mTorr) gave **2** as a colorless oil (170 g, 51%). ^{1}H NMR: δ 4.25 (m, 3H), 3.11 (d, 1H, J = 6.4 Hz), 2.65 (m, 2H), 2.03 (t, 1H, J = 2.7 Hz), 1.28 (t, 3H, J = 7.2 Hz). ^{13}C NMR: δ 172.99, 78.53, 71.25, 68.64, 62.11, 24.81, 14.13.

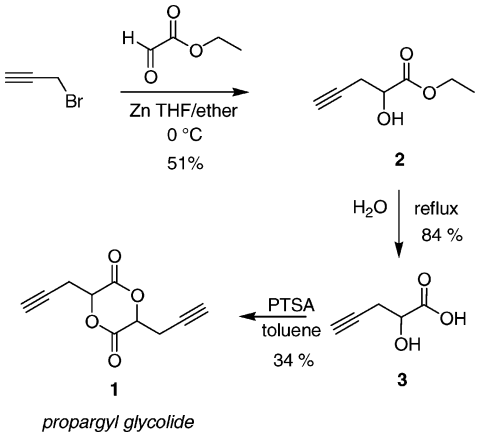
Synthesis of 2-Hydroxy-4-pentynoic Acid (3). Ester **2** (170 g) was added to 800 mL of distilled water and heated to reflux for 3 days. After cooling to room temperature, the solution was acidified by the addition of 100 mL of concentrated HCl and continuously extracted with ether for 2 days. The ether solution was diluted to 1.5 L with additional ether and dried over $MgSO_4$ for 2 h. After filtration, the solution was concentrated by rotary evaporation and dried under vacuum to give a light brown solid, which was purified by recrystallization from CH_2Cl_2 at 0 °C, followed by sublimation at 58 °C and a second recrystallization from CH_2Cl_2 at 0 °C to give **3** as colorless crystals (115 g, 84%). ^{1}H NMR: δ 4.42 (t, 1H, J = 5.0 Hz), 2.75 (m, 2H), 2.10 (t, 1H, J = 2.6 Hz). ^{13}C NMR: δ 177.28, 77.97, 71.96, 68.51, 24.66. MS (*m/z*) 115.3 (M + 1), mp 61−63 °C.

Synthesis of *meso/rac*-3,6-Di-2-propynyl-1,4-dioxane-2,5-dione (1). 2-Hydroxy-4-pentynoic acid (**3**) (18 g) and *p*-toluenesulfonic acid monohydrate (1.5 g) were added to a 2 L round-bottom flask charged with 1.8 L of toluene. The flask was heated to reflux for 3 days, and the water was removed azeotropically using a Barrett trap. After cooling to room temperature, the toluene was removed by rotary evaporation, and the residue was dissolved in 500 mL of CH_2Cl_2, washed with saturated $NaHCO_3$ (3 × 150 mL), and dried over $MgSO_4$. Filtration and removal of the CH_2Cl_2 gave the product as a light brown solid which was washed with diethyl ether (3 × 50 mL), sublimed at 75 °C, and recrystallized from toluene to give colorless crystals of **1** as a *meso/rac* isomer mixture (6.1 g, 34%). ^{1}H NMR: δ 5.29 (t, J = 4.6 Hz), 5.05 (dd, J = 7.1 Hz, J = 4.4 Hz) (resonances at 5.29 and 5.05 ppm are from the *rac* and *meso* isomers, integrating as 1H; isomers unassigned), 2.95 (m, 2H), 2.17 (t, J = 2.6 Hz), 2.11 (t, J = 2.7 Hz) (1H total for the signals at 2.17 and 2.11 ppm). ^{13}C NMR: δ 164.26, 163.44, 76.77, 76.67, 74.82, 74.15, 73.34, 72.02, 23.94, 21.24. Anal. Calcd for $C_{10}H_8O_4$: C, 62.50; H, 4.17. Found: C, 62.80; H, 4.01. HRMS (*m/z*, M^+) expected: 192.0423; found: 192.0419; mp 103−106 °C.

General Procedure for Bulk Polymerizations. Monomer(s) and a small magnetic stir bar were added to ampules prepared from $^3/_8$ in. diameter glass tubing. The ampules were connected via a Cajon fitting to a T-shaped vacuum adapter fitted with a stopcock and an air-free Teflon valve. The apparatus was attached to a vacuum line and evacuated through the Teflon valve. The ampule was backfilled with argon, and predetermined amounts of the Sn(2-ethylhexanoate)$_2$ and 4-*tert*-butylbenzyl alcohol solutions (~0.03 M in toluene) were added via syringe to the ampules through the stopcock. After removing solvent in vacuo, the ampule was flame-sealed. Sealed ampules were immersed in an oil bath at 130 °C for the desired period of time, and the melt was stirred magnetically. At the end of the polymerization, the ampule was removed from the bath, cooled in ice water, and opened. A portion of the polymer was analyzed by GPC to determine molecular weights and by NMR to evaluate conversion. The remaining polymer was dissolved in CH_2Cl_2 and precipitated by adding the solution to cold methanol. This process was repeated four times, after which the resulting polymer was dried under vacuum (4 mTorr) at 40 °C for 24 h. Representative syntheses of homopolymers, copolymers, and block copolymers are described below.

Polymerization of *meso/rac*-1. *meso/rac*-**1** (2.49 g) ([M]/[I] = 150) was polymerized for 25 min. The conversion of monomer to polymer calculated from ^{1}H NMR was 91%. Poly(propargyl

Scheme 2. Synthetic Route to Propargyl Glycolide (1)



glycolide) (PPGL) was obtained as a light brown solid (2.16 g, 87%). ^{1}H NMR: δ 5.31−5.46 (br, 1H), 2.79−3.03 (br m, 2H), 2.01−2.18 (br, 1H). GPC (THF): M_n = 28 600 g/mol, PDI = 1.30.

Copolymerization of *meso/rac*-1 and *rac*-Lactide. A mixture of *meso/rac*-**1** (0.384 g, 2 mmol) and *rac*-lactide (3.394 g, 23.6 mmol) ([M]/[I] = 300) was polymerized for 50 min. Precipitation and drying under vacuum gave the random copolymer as a white solid (3.59 g, 95%). ^{1}H NMR: δ 5.03−5.39 (br m, 12.7H), 2.75−2.96 (br m, 2H), 1.97−2.11 (br, 1H), 1.43−1.65 (br m, 38.8H). GPC (THF, light scattering and refractive index detectors): M_n = 83 200 g/mol, PDI = 1.20.

Preparation of PPGL-*block*-PLA. PPGL (1.0 g, M_n(GPC) = 28 600, PDI = 1.30) and *rac*-lactide (5.0 g) were placed in a 25 mL Schlenk flask fitted with a vacuum adapter. The flask was sealed and held under vacuum overnight to remove residual water. After the flask was filled with nitrogen through the sidearm, 1.21 mL of a 0.0288 M solution of Sn(2-ethylhexanoate)$_2$ in toluene and 8 mL of anhydrous THF were added via syringe through a septum that was fitted to the vacuum adapter. The flask was closed and placed in an oil bath at 70 °C, where the solution was magnetically stirred for 10 h. At the end of the polymerization, the polymer was isolated by precipitation into cold methanol. Dissolution and precipitation were repeated four more times. The resulting white solid was dried under vacuum at 45 °C overnight to give the block copolymer (2.8 g, 47% yield). ^{1}H NMR: δ 5.31−5.44 (br, 1H), 5.06−5.25 (br m, 2.6H), 2.80−3.02 (br m, 2H), 2.05−2.14 (br, 1H), 1.48−1.62 (br m, 8.1H). GPC (THF): M_n = 38 000 g/mol, PDI = 1.44.

General Procedure for "Click" Functionalization. The desired amount of acetylene-functionalized polymer, azide (3 equiv with respect to acetylene groups), and 12 mol % sodium ascorbate were dissolved in DMF. The resulting solution was transferred to a Schlenk flask and deoxygenated by three freeze−pump−thaw cycles. After the solution had warmed to room temperature, a 0.1 M solution of $CuSO_4 \cdot 5H_2O$ in deoxygenated DMF (5 mol % with respect to the acetylene groups) was added under nitrogen, and the reaction mixture was then stirred at room temperature for 2 h. At the end of the reaction, the solids in the reaction mixture were removed by filtration. The polymer was isolated by dialysis (MWCO = 12−14 000) in acetone/water (1:1) overnight and then dried under vacuum.

***n*-Decyl-Grafted PPGL.** PPGL (54 mg, M_n(GPC) = 35 500 g/mol, PDI = 1.44) and 300 mg of 1-azidodecane were dissolved in 5 mL of DMF for the "click" reaction. The *n*-decyl-grafted PPGL was isolated as a pale green solid (133 mg, 87%) with M_n(GPC, THF) = 49 400, PDI = 1.41.

mPEG-550-Grafted PPGL. PPGL (100 mg, M_n(GPC) = 35 500 g/mol, PDI = 1.44) and mPEG-550 azide (1.72 g) were dissolved in 10 mL of DMF for the "click" reaction. mPEG-550-grafted PPGL was isolated as a pale green oil (514 mg, 77%).

Poly(propargyl glycolide-*co*-lactide) Grafted with mPEG-550. PPGL-*ran*-PLA (550 mg) and mPEG-550 azide (990 mg) were dissolved in 20 mL of DMF for the "click" reaction. The product was isolated as a light green rubbery solid (650 mg, 74%). GPC (THF, light scattering): $M_n = 1.56 \times 10^5$ g/mol, PDI = 1.21.

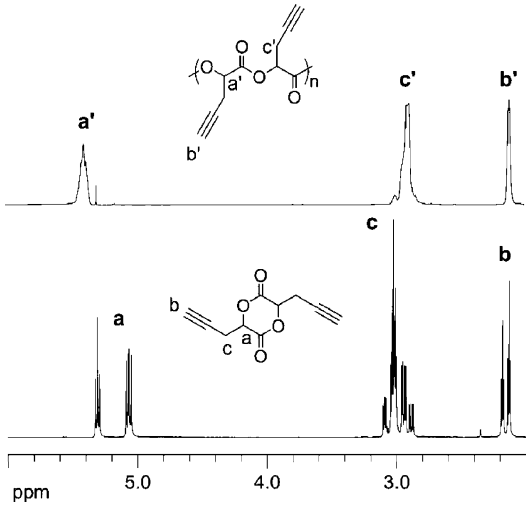


Figure 1. 300 MHz ^{1}H NMR spectra of **1** and poly(propargyl glycolide) (PPGL).

mDEG-Grafted PPGL. PPGL (250 mg, M_n(GPC) = 35 500 g/mol, PDI = 1.44) and mDEG azide (1.480 g) were dissolved in 20 mL of DMF for the "click" reaction. The mDEG-grafted PPGL was isolated as a light green elastomer (590 mg, 79%).

***n*-Decyl/mDEG-Grafted PPGL.** PPGL (122 mg, M_n(GPC) = 35 500 g/mol, PDI = 1.44), 1-(2-azidoethoxy)-2-(2-methoxyethoxy) ethane (480 mg, 2.6 mmol), and mDEG azide (240 mg, 1.3 mmol) were dissolved in 10 mL of DMF for the "click" reaction. The product was isolated as a light green elastomer (320 mg, 88%). ^{1}H NMR: δ 7.36−7.78 (br, 1H), 5.22−5.56 (br, 1H), 4.36−4.56 (br, 1H), 4.12−4.36 (br, 1.1H), 3.73−3.91 (br, 1H), 0.70−0.94 (br, 1.7H).

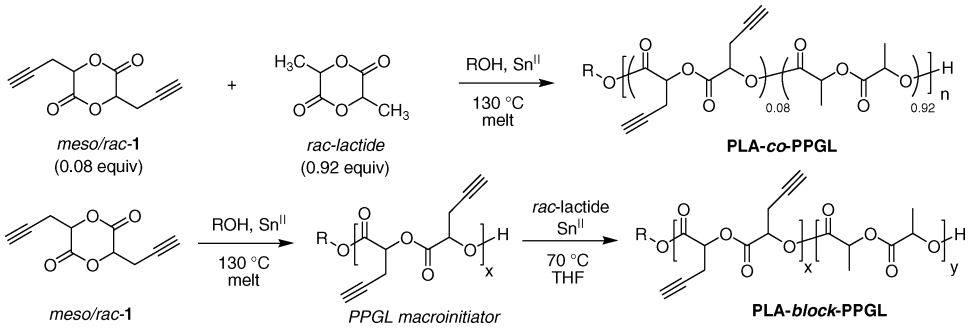
mPEG-550-Grafted PPGL-*block*-polylactide. The block copolymer (300 mg) and mPEG-550 azide (1.78 g, 3.2 mmol) were dissolved in 20 mL of DMF for the "click" reaction. The product was isolated as a light green viscous liquid (690 mg, 78%).

Results and Discussion

Monomer Synthesis. The preparation of monomer **1** was straightforward and is outlined in Scheme 2. The Reformatsky-type reaction of propargyl bromide with freshly distilled ethyl glyoxylate in the presence of activated zinc generated ethyl 2-hydroxy-3-butynoate (**2**) in 51% yield.[37] Despite the modest yield, elution of the crude reaction mixture through silica gel using a 70:30 mixture of hexane/ethyl acetate readily separated **2** from the reaction byproducts. Hydrolysis of the ester in refluxing water provided 2-hydroxy-3-butynoic acid (**3**) in 84% yield. Hydrolysis under basic conditions resulted in lower yields due to side reactions.

Cyclization to give **1** was accomplished by refluxing **3** with catalytic *p*-toluenesulfonic acid in toluene. Once azeotropic separation of water ceased, the reaction mixture was subjected to a standard aqueous work-up. Sublimation and recrystallization of the crude product afforded **1** in 34% yield as a mixture of *rac* (RR/SS) and *meso* (R, S) stereoisomers. The byproducts primarily consisted of linear oligomers, which could in principle be recycled or thermally cracked to yield additional monomer. The 300 MHz ^{1}H NMR spectrum of **1** is shown in Figure 1. The methine protons of the propargyl glycolide isomers appear as a triplet at 5.29 ppm and a doublet of doublets at 5.05 ppm. The 1:1 ratio of the *meso* to *rac* diastereomers reflects a statistical coupling of a racemic mixture of hydroxy acids. After

Scheme 3. Polymerization of *meso*/*rac*-1 and Copolymerizations with *rac*-Lactide



recrystallization, the diastereomeric ratio was 2:3 (isomers unassigned).

Polymerization. Bulk polymerizations of **1** at 130 °C, catalyzed by Sn(2-ethylhexanoate)$_2$ using *tert*-butylbenzyl alcohol as the initiator, yielded poly(propargyl glycolide) (PPGL) (Scheme 3). The catalyst-to-initiator ratio was 1:1 for all polymerizations, and the monomer-to-initiator ratio was varied from 50:1 to 300:1 to provide different molecular weight materials. Conversion of monomer to polymer was calculated by comparing the ^{1}H NMR integration of the monomer methine peaks at 5.05 and 5.29 ppm (monomer) with those in the polymer at ~5.38 ppm (Figure 1).

Typical results for the bulk polymerization of propargyl glycolide at different monomer-to-initiator ratios are listed in Table 1. The molecular weights measured by GPC prior to precipitation range from 9000 to 60 000 g/mol and are in good agreement with their theoretical values. In addition, the polydispersities are fairly narrow for bulk polymerizations, especially for polymerizations run at high monomer-to-initiator ratios. Figure 2 shows a plot of the molecular weight (measured by GPC) as a function of the calculated average degree of polymerization, X_n^{calc}, determined by multiplying the monomer-to-initiator ratio by percent conversion. The linear relationship seen in the data and the measured PDI's suggest fast initiation and minimal termination and intramolecular transesterification.

In many applications, and especially in biological applications, it is essential to control the density and position of functional groups along the polymer backbone. To assess the suitability of **1** for copolymerization, we targeted a copolymer of *rac*-lactide incorporating 8 mol % **1** with $X_n = 300$. Using the same polymerization and work-up conditions for preparing PPGL, we obtained the copolymer in 95% yield. The incorporation of **1** was determined by ^{1}H NMR, comparing the integrated intensity of the propargyl methylene resonance at δ 2.85 to the polymer backbone methine resonances centered about δ 5.20. The calculated value of 7.9% agrees with the targeted value of 8%. GPC analysis returned $M_n = 83\,200$ g/mol ($X_n^{exptl} = 440$) with a PDI of 1.20, consistent with a well-behaved polymerization.

While we have not determined the reactivity ratios for *meso*/*rac*-**1** and *rac*-lactide, the carbonyl regions of ^{13}C NMR spectra of the homo- and copolymers show important differences that argue against incorporation of the comonomer as blocks. As shown in Figure 3, the carbonyl signals from PPGL and PLA are well-separated, with the PPGL resonances shifted ~3.0 ppm upfield relative to PLA. For PLA-*co*-PPGL, the "lactide" carbonyl resonances have virtually identical chemical shifts and intensities to the PLA homopolymer. However, the copolymer has unique peaks at 168.9 and 168.8 ppm, and the upfield position of these resonances suggests that they arise from carbonyls in lactide units flanking propargyl monomer insertions. Indeed, the low intensities of these resonances are consistent with 8% incorporation of the propargyl monomer in the copolymer. When compared to the homopolymer PPGL, the propargyl glycolide resonances in the copolymer are shifted *downfield* by ~0.2 ppm toward the "lactide" region. Using similar arguments to those above, this observation is consistent with the majority of the propargyl units having lactide nearest neighbors. On the basis of these data, and the ^{13}C NMR spectrum of a block copolymer formulation (vide infra), PLA-*co*-PPGL is most likely a statistical copolymer.[38]

Because statistical and block copolymers have distinct physical properties, a PPGL−PLA block copolymer was another important target. The synthesis of PPGL-*block*-PLA (Scheme 3) was accomplished by using scrupulously purified PPGL ($M_n = 28\,600$ g/mol, $X_n^{exptl} \sim 150$, PDI = 1.30) as a macroinitiator and Sn(2-ethylhexanoate)$_2$ as the catalyst for *rac*-lactide polymerization ([*rac*-lactide]:[macroinitiator]:[catalyst] = 1000:1:1). The polymerization was carried out in THF at 70 °C and

Table 1. Bulk Polymerizations of 1 at 130 °C[a]

entry	[M]/[I]	time (min)	conversion (%)[b]	X_n^{calc} [c]	X_n^{exptl} [d]	M_n[e] (g/mol)	PDI
1	50	10	85	43	47	9 100	1.13
2	100	15	89	89	96	18 500	1.21
3	150	25	91	136	149	28 600	1.30
4	200	30	73	146	159	30 500	1.31
5	250	55	78	195	199	38 300	1.37
6	300	60	90	270	284	54 600	1.38
7	300	75	94	280	294	56 500	1.49

[a] Using Sn(2-ethylhexanoate)$_2$ as the catalyst and *tert*-butylbenzyl alcohol as initiator. [b] Measured by ^{1}H NMR. [c] Calculated from the monomer to initiator ratio and corrected for conversion. [d] Calculated by dividing M_n by the formula weight of **1**. [e] Measured by GPC in THF and calibrated using polystyrene standards.

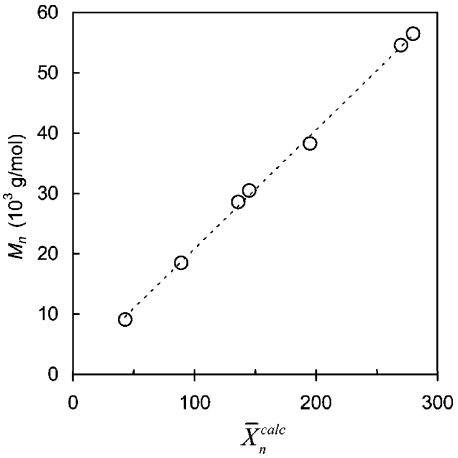


Figure 2. Relationship between M_n and X_n^{calc} for the bulk polymerization of **1** at 130 °C. Sn(2-ethylhexanoate)$_2$ was used as the catalyst and *tert*-butylbenzyl alcohol as initiator ([initiator]:[catalyst] = 1:1; [monomer]:[initiator] ratios range from 50 to 300 and correspond to the data in Table 1). The line is a least-squares fit to the data.

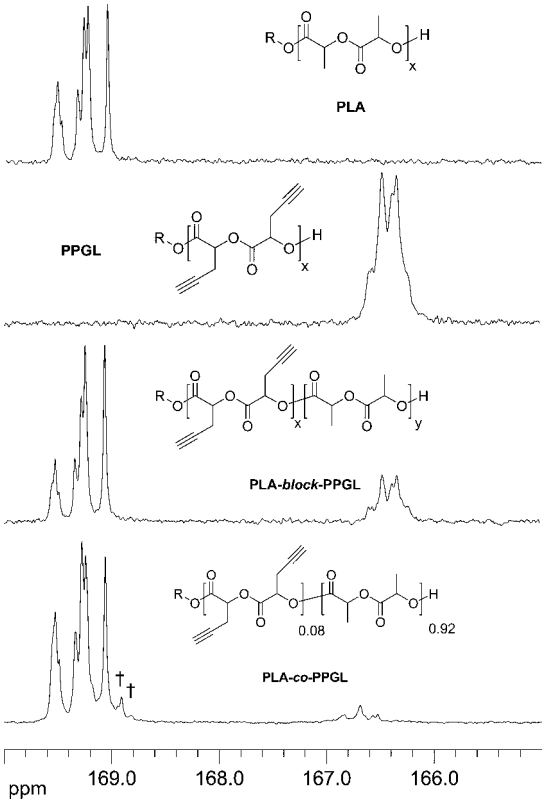


Figure 3. 75 MHz ^{13}C NMR carbonyl regions of propargyl glycolide homopolymer, copolymers, and polylactide (run in $CDCl_3$). Dagger indicates unique lactide carbonyl resonances in PLA-*co*-PPGL (see text).

stopped at low lactide conversion to minimize transesterification. GPC traces show a shift to higher molecular weight with the PDI increasing slightly (M_n = 38 000 g/mol, $X_n^{exptl} \sim 215$, PDI = 1.44, Figure S1, Supporting Information). The increase in M_n is consistent with addition of 65 lactide units, on average, to the polymer chain, and the small change in PDI suggests that intramolecular transesterification is minimal, consistent with a block architecture for the copolymer. The ^{13}C NMR spectrum in Figure 3 further supports the block microstructure. Specifically, the chemical shifts and relative intensities of the resonances in the "lactide" and "propargyl glycolide" regions are virtually identical to those in the corresponding homopolymers. Notably absent are high-field resonances in the "lactide" region and low-field resonances in the "propargyl glycolide" region, which were attributed to enchainment of isolated *meso*/*rac*-propargyl glycolide repeat units in a predominantly poly(*rac*-lactide) copolymer.

Alkyl-Grafted Polyglycolides via "Click" Chemistry. Emrick et al. have reported the Cu-catalyzed "click" functionalization of pendant acetylenes incorporated into polycaprolactone.[5] Unfortunately, their conditions (aqueous $CuSO_4$, 80 °C, 10−12 h) proved to be too harsh for PPGL as GPC analysis indicated significant reduction of M_n when PPGL was stirred in an acetone/water mixture at 50 °C for 8 h. This result was not surprising since the polylactide backbone is more sensitive to degradation than polycaprolactone. Recently, Jérôme et al. reported the "click" functionalization of a copolymer prepared from an azide-functionalized caprolactone and lactide using milder conditions, CuI in THF at 35 °C.[7] However, esterification of the terminal hydroxyl group was necessary to suppress backbone degradation, which complicates the synthetic procedure. Another drawback to this approach is that preformed copper(I) salts often exhibit reduced selectivity and generate undesired byproducts when employed as catalysts.[27]

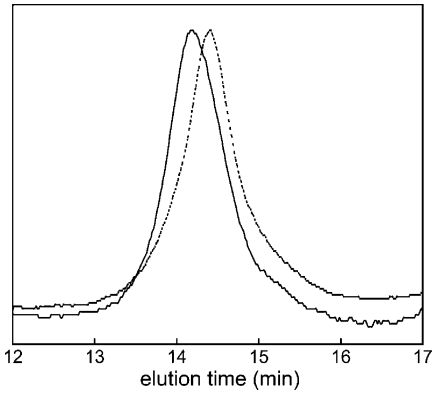


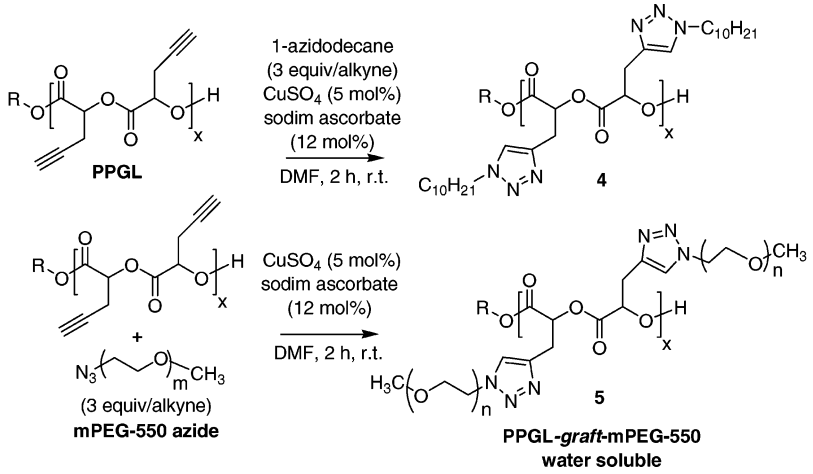
Figure 4. GPC traces of PPGL and C_{10}-grafted PPGL (**4**) (broken line: PPGL; solid line: C_{10}-grafted PPGL). The polymers were analyzed in THF at 35 °C, at a 1 mL/min flow rate.

We solved these problems by carrying out the "click" reaction in the presence of $CuSO_4$ and sodium ascorbate in DMF at room temperature. The azide partner, 1-azidodecane, was synthesized from 1-bromodecane and sodium azide. To test the DMF conditions, PPGL (M_n = 35 500, PDI = 1.44), 3 equiv of 1-azidodecane, and 12 mol % sodium ascorbate were dissolved in DMF (all equivalents and mole percentages are with respect to acetylene units in PPGL). A DMF solution of $CuSO_4 \cdot 5H_2O$ (5 mol %) was then added via syringe. ^{1}H NMR spectra taken after 2 h showed that resonances at 2.85 ppm ($-CH_2-CCH$) and 2.05 ppm ($-CH_2-CCH$) had completely disappeared, and a new peak appeared at 7.6 ppm (*H* of the triazole ring), indicating quantitative formation of the triazole. Notably, the low solubility of sodium ascorbate in DMF had no discernible effect on the reaction.

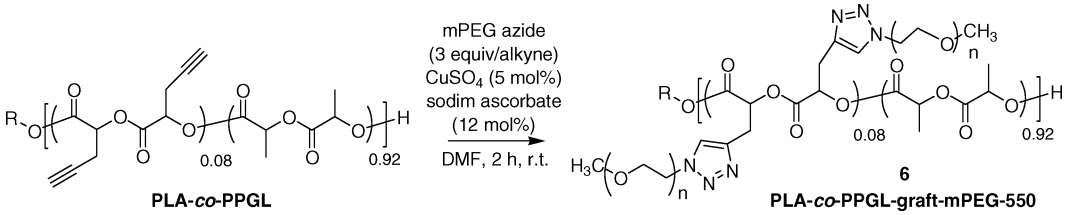
The GPC results (Figure 4) of the resulting alkyl-grafted polymer (**4**) (M_n = 49 400, PDI = 1.41) confirmed an increase in molecular weight, with the symmetry of the polymer peak and its polydispersity unchanged.[39] These experimental results strongly suggest that the backbone does not degrade under our modified "click" reaction protocol. To further confirm the stability of the polymer backbone under these conditions, we treated PPGL (M_n = 32 600, PDI = 1.45) using the same experimental protocol (DMF, RT, 0.12 equiv of sodium ascorbate, 0.05 equiv of $CuSO_4$, 2 h) without adding 1-azidodecane. The GPC trace showed no significant change in molecular weight or PDI (M_n = 32 100, PDI = 1.44) (see Figure S2, Supporting Information). Thus, "click" functionalization of PPGL can be effected quantitatively in DMF at room temperature without significant backbone degradation by generating Cu(I) in situ. The lower reaction temperature minimized the formation of undesired byproducts, and protection of the chain end hydroxyl group was unnecessary.

mPEG-Grafted Polyglycolides via "Click" Chemistry. Previous work on mPEG-substituted polylactides suggested that grafting mPEG chains onto a PPGL should provide hydrophilic and perhaps water-soluble polylactides.[32,40] The latter materials would be particularly interesting for targeted drug delivery and as degradable LCST materials.[32] We selected PEG-550 monomethyl ether (mPEG-550) as the azide precursor because of its ready availability from commercial suppliers. It was tosylated and then reacted with sodium azide to afford mPEG-550 azide. The azide group was easily identified by its IR absorption at 2105 cm^{-1}, the α-methylene resonance at 3.38 ppm in its ^{1}H NMR spectrum, and the C-α resonance at 50.5 ppm in its ^{13}C NMR spectrum. The "click" PEGylation of PPGL was performed using the alkyl grafting conditions described above (Scheme 4). Completion of the reaction was again confirmed

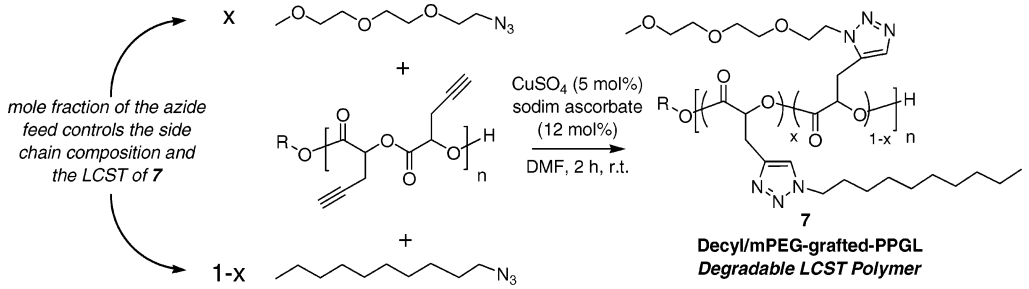
Scheme 4. "Click" Functionalization of PPGL with 1-Azidodecane and mPEG-550 Azide



Scheme 5



Scheme 6



by the disappearance of the ^{1}H NMR resonances at 2.85 ppm ($-CH_2-CCH$) and 2.05 ppm ($-CH_2-CCH$) and the appearance of a new resonance at 7.6 ppm (H of triazole). The crude PPGL-*graft*-mPEG-550 (**5**) was purified by dialysis in acetone/water (1:1) mixture. After drying under vacuum, it was isolated as a viscous liquid, tinted light green due to traces of Cu(II). (We recently found that we can reduce the Cu(II) to <ppm levels using an anion exchange resin, by filtering sodium ascorbate from the click reaction solution, and directly adding the beads to the DMF solution of the polymer.)

Direct GPC analysis of polymer **5** was problematic. When THF was used as solvent, the differential refractometer did not detect polymer eluting from the column. We speculated that either the polymer and THF were isorefractive, the polymer had degraded, or the polymer had adsorbed onto the column. We ran several control experiments to rule out backbone degradation during "click" PEGylation. We first subjected PPGL (M_n = 32 600, PDI = 1.45) to the same experimental conditions (DMF, RT, 0.12 equiv of sodium ascorbate, 3 equiv of mPEG-550 azide, 2 h) but in the absence of $CuSO_4$. GPC results for the recovered PPGL (M_n = 32 200, PDI = 1.44) showed no sign of backbone degradation. In a related experiment, a mixture of PPGL (M_n = 32 600, PDI = 1.45) and polylactide (M_n = 18 600, PDI = 1.26) was subjected to the "click" mPEG grafting conditions. GPC results for the treated polylactide (M_n = 18 300, PDI = 1.26) again showed no decrease in molecular weight.

If polymer **5** was isorefractive with THF, altering the polymer composition sufficiently should resolve the detection issue. To accomplish this, we turned to the PLA-*co*-PPGL copolymer comprised of 92 mol % lactide and 8 mol % propargyl glycolide ($M_{n,GPC}$ = 63 600, PDI = 1.66). The copolymer was grafted with mPEG-550 azide using the identical conditions in Scheme 4 to afford the PLA-*co*-PPGL-*graft*-mPEG-550 (**6**), as depicted in Scheme 5. GPC analysis of this mPEG-grafted copolymer showed a shift of peak molecular weight to *longer* retention time than the starting copolymer (Figure 5), indicating a *lower* relative molecular weight ($M_{n,GPC}$ = 16 800, PDI = 1.43)! Since previous control experiments showed no change in molecular weight for polymers under "click" conditions, we suspected that the hydrodynamic radius of the polymer decreased after mPEG grafting, thus accounting for the apparent decrease in molecular weight. Using a GPC system equipped with a light scattering detector, we determined that the molecular weight of the mPEG-grafted copolymer ($M_{n,LS}$ = 156 000, PDI = 1.21) was indeed higher than that of the starting copolymer ($M_{n,LS}$ = 83 200, PDI = 1.20). Gratifyingly, the $M_{n,LS}$ value for **6** is only slightly larger than the theoretical value of 136 000 g/mol calculated using the density of propargyl groups and $M_{n,LS}$ = 83 200 for PLA-*co*-PPGL, with the assumption that all alkyne groups have undergone cycloaddition. Thus, the combined results from these control experiments ruled out backbone degradation during the "click" PEGylation of propargyl glycolide homopolymers and

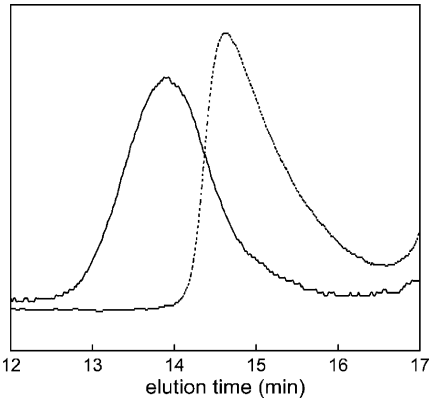


Figure 5. GPC traces for PLA-*co*-PPGL and the "click" mPEG-550-grafted product (**6**). The concentration of propargyl glycolide in the copolymer was 8 mol % (solid line: copolymer before the "click" reaction; broken line: copolymer after the "click" reaction). The polymers were analyzed in THF at 35 °C, at a 1 mL/min flow rate.

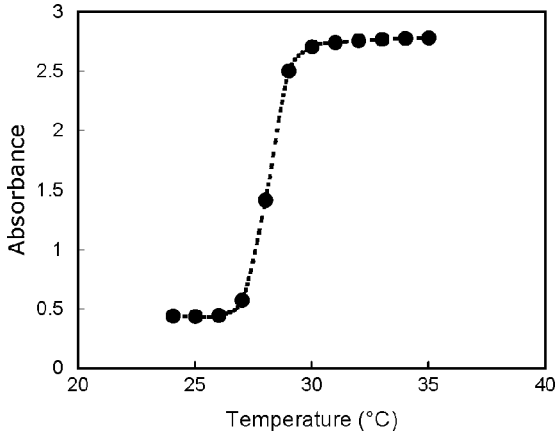


Figure 6. Cloud point determination at 450 nm for PPGL "clicked" with a mixture of hydrophobic and hydrophobic chains. The composition of the "clicked" polymer (59% mDEG chains, 41% decyl chains) was determined by ^{1}H NMR.

copolymers and also uncovered interesting solvent-induced changes in the size of the mPEG-550-grafted polymer.

Lower Critical Solution Temperature (LCST) Studies. Recently, several polymer systems have been investigated that exhibit LCST behavior in aqueous solutions.[41] At the LCST, these materials undergo a solution−gel transition that corresponds to the entropically driven expulsion of solvating water molecules from the polymer. Such materials have a variety of interesting and potentially useful applications. For example, a thermally responsive bioadhesive surface becomes resistant to protein adsorption below its LCST, enabling facile growth and removal of biomaterials grown on polymer scaffolds.[42,43] The most widely studied polymers that exhibit LCST behavior are poly(methacrylates), poly(*N*-isopropylacrylamide) (PNIPAM), and polymers that contain thermosensitive PNIPAM segments.[44] Unfortunately, neither poly(methacrylates) nor PNIPAM are degradable and acrylamides pose health risks.[45] Recent research on responsive LCST materials, especially those that contain mPEG segments,[46−54] shows that tuning the hydrophobic/hydrophilic balance in materials can shift the LCST over a broad temperature range.[47,55,56] The few examples of LCST materials based on biodegradable polymers[55−58] and the breadth of applications for polylactides in medical applications[59] made the synthesis of biodegradable LCST materials an ideal venue for showcasing the facile and versatile elaboration of PPGL using "click" chemistry.

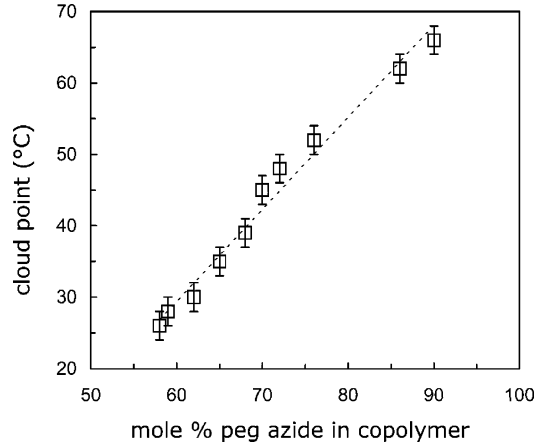


Figure 7. Relationship between the cloud point observed at 450 nm and the mole percentage peg chains "clicked" onto the PPGL homopolymer. The error bars represent the estimated uncertainty in the temperature, as controlled by the UV−vis instrument. The broken line is a least-squares fit to the data.

The design of polyglycolide-based thermally responsive materials is simple and is illustrated in Scheme 6. Using PPGL as a scaffold, we carried out "click" functionalization using mixtures of 1-decyl and mDEG azides. ^{1}H NMR confirmed that the side-chain compositions in the resulting polymers **7** were comparable to the ratio of the azides in the feed. After isolating the polymer and purification by dialysis, we used cloud point measurements to screen samples for LCST behavior. Samples were dissolved in Milli-Q water, and solution turbidity was monitored by measuring absorbance at 450 nm as a function of temperature. At the LCST, the "apparent absorbance" increases as gel formation causes a dramatic increase in scattering. A representative plot in Figure 6 shows the transition to be relatively sharp, spanning a temperature range of ∼3 °C.

Significantly, the relationship between the cloud point temperature and the mole fraction of mDEG chains in the polymer is nearly linear, as shown in Figure 7. This allows for simple and precise adjustment of the LCST in a degradable material, with the mDEG/alkyl ratio serving as a "molecular thermostat" for the LCST. These results are preliminary, and it may be possible to expand the LCST window to beyond the 25−65 °C range shown in Figure 7 by varying the lengths of the alkyl and PEG side chains.

Conclusions

Propargyl glycolide (**1**) provides a convenient entry to "click" modification of polyglycolides. This functional monomer undergoes controlled polymerization to yield poly(propargyl glycolide), a polyglycolide with pendant acetylene groups. The preparation of random and block copolymers of propargyl glycolide with lactide is also straightforward. The development of milder "click" reaction conditions allows for facile preparation of functionalized polyglycolides, while avoiding backbone degradation and eliminating the need to end-cap the polyester chain. "Click" functionalization of these acetylene-containing polyglycolides with organic azides provided mPEG-550-grafted water-soluble polyglycolides, mPEG-550-grafted random copolymers, and new amphiphilic block copolymers. Grafting mixtures of mDEG and alkyl azides provides water-soluble polymers that show lower critical solution temperature (LCST) behavior. Notably, a new family of biodegradable LCST materials can be accessed where the transition temperatures can be tuned in a range from 25 to 65 °C by simply adjusting the mDEG:alkyl ratio in the azide feed. Considering polylactide's

sensitivity to backbone degradation, this protocol should also be applicable to the "click" functionalization of range of polyesters and their copolymers.

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Supporting Information Available: Figure S1, GPC traces of the PPGL macroinitiator and PPGL-*block*-polylactide, and Figure S2, showing the GPC results for PPGL exposed to "click" conditions, but without added azide. This material is available free of charge via the Internet at http://pubs.acs.org.

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