Functional Aliphatic Polyesters and Nanoparticles Prepared by Organocatalysis and Orthogonal Grafting Chemistry

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ABSTRACT: We describe the use of organic catalysis for the ring-opening polymerization of functionalized lactones and conversion of the resulting aliphatic polyesters into crosslinked nanoparticles that carry additional functional groups amenable to further modification. Specifically, highly functional aliphatic polyester homopolymers, as well as random and block copolymers, were prepared by 1,5,7-triazabicyclo[4.4.0]dec-5-ene catalysis, giving polyesters with pendent alkene and alkyne groups. Azide-alkyne click and thiol-ene chemistries were used for postpolymerization modification of diblock copolymers possessing alkene groups on one block and alkyne groups on the other block. The polyesters were crosslinked using azide/alkyne cycloaddition, by reaction of α,ω-diazides with the pendent alkynes on the polyester backbone. This gave polyester nanoparticles possessing alkene functionality, which were subjected to further modification using thiol-ene reactions to introduce additional functionality. © 2012 Wiley Periodicals, Inc. J Polym Sci Part A: Polym Chem 000: 000–000, 2012

KEYWORDS: click chemistry; CuAAC; diblock copolymers; functional polyesters; nanoparticles; organocatalyst; polyesters; ring-opening polymerization; thiol-ene; 1,5,7-triazabicyclo[4.4.0]dec-5-ene

INTRODUCTION Aliphatic polyesters are recognized for their useful combination of biocompatibility and biodegradability and, therefore, present new opportunities in applications ranging from drug delivery to implant materials to degradable plastics. In recent years, aliphatic polyesters have become especially interesting when chemical functionality is introduced that distinguishes novel structures from conventional forms. For example, functionalization of aliphatic polyesters can afford hydrophilic and water soluble derivatives of conventional poly(lactide) and poly(ε-caprolactone). When pendent functionality is introduced in a controlled manner, synthetic handles become available for subsequent attachment of solubilizing groups, drugs, targeting groups, and fluorophores. However, as aliphatic polyesters are subject to ester bond degradation during chemical transformations, there is a pressing need for efficient reactions that proceed effectively but do not cause significant backbone degradation.

A number of elegant methodologies have been reported to give functional aliphatic polyesters. Early on, Jerome,[1] Hedrick,[2] and others[3] prepared several examples, such as through Baeyer–Villager oxidation of 2-allyl-cyclohexanone to give an allyl-functionalized ε-caprolactone,[4] from which numerous polyester derivatives were prepared. We later prepared and polymerized α-propargyl-δ-valerolactone (PgVL), and used copper(I)-catalyzed azide-alkyne cycloaddition (CuAAC; "click chemistry") on the resulting alkyne-substituted polyesters, giving access to efficient attachment of phosphorylcholine (PC) groups,[5] poly(ethylene glycol) (PEG) and oligopeptides,[6] and the oncology drug camptothecin.[7] Hawker and coworkers[8] recognized the utility of thiol-ene coupling for postpolymerization reactions on alkene-functionalized polyesters, whereas Harth and coworkers[9] recently described the conversion of functionalized aliphatic polyesters into crosslinked polyester nanoparticles.

Traditionally, aliphatic polyesters have been prepared by ring-opening polymerization (ROP) of cyclic esters using metal catalysts, such as tin and aluminum salts. However, recent success in catalyst development has uncovered small organic molecules as appealing alternatives to metallic catalysts, including, for example, 4-(dimethylamino)pyridine (DMAP),[10] *N*-heterocyclic carbenes,[11] and 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD).[12] These compounds catalyze the ROP of lactones and lactides, offering the benefits of fast polymerization kinetics and low polydispersity index (PDI) products in a metal-free environment at ambient temperature. However, to date we are not aware of reports using organic catalysts, such as TBD which we have chosen for this study, to polymerize functional lactones, though we note they have been recently used to polymerize functional lactides.[13]

Additional Supporting Information may be found in the online version of this article.

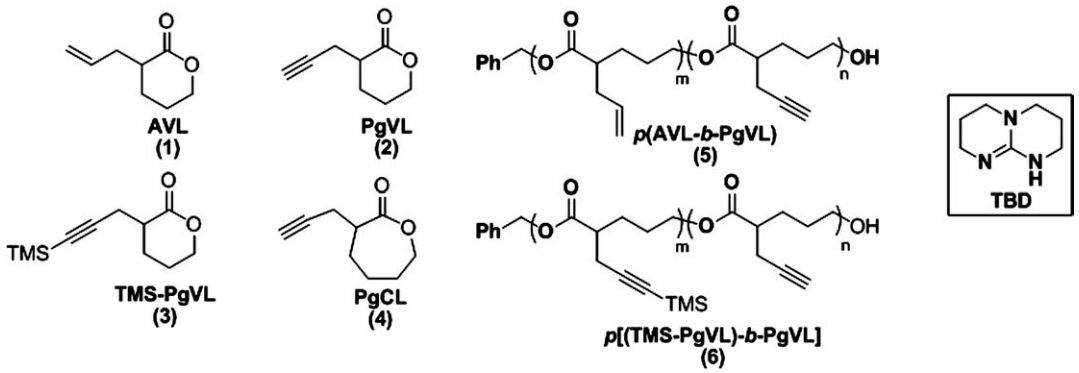


FIGURE 1 Structures of functional lactones **1–4** (AVL **1**, PgVL **2**, TMS-PgVL **3**, and PgCL **4**) used in TBD-catalyzed ROP, and diblock polyesters **5** and **6** formed from their polymerization.

We previously demonstrated the preparation of aliphatic polyester diblock copolymers that differentiated click cycloaddition between the two blocks by placing alkyne groups on one block and trimethylsilyl-protected alkyne groups on the other block.[14] A click-deprotection-click sequence gave a novel set of diblock structures, bearing different pendent groups on each block. Here, we report a simple route to highly functional polyester-based diblock copolymers, with alkyne groups on one block and alkene groups on the other. These structures are amenable to orthogonal azide-alkyne and thiol-ene coupling, without the need for protection/deprotection steps. Although prior work has explored end-group orthogonality of azide-alkyne and thiol-ene click reactions[8] and orthogonal surface-modification of SiO_2 nanospheres,[15] to our knowledge this is the first example of a diblock polyester possessing differentiated blocks by exploiting the distinct azide-alkyne and thiol-ene reactions. Moreover, this work demonstrates the ready adaptability of organic catalysis to these functional lactones, further extending their utility in polymer synthesis. In addition, these polyesters gave access to crosslinked nanoparticles, using the alkyne-containing block for crosslinking, and leaving the alkene-containing block for subsequent nanoparticle modification.

RESULTS AND DISCUSSION

Figure 1 shows the structures of lactone monomers **1–4** used in this study, specifically α-allyl-δ-valerolactone (AVL, **1**), α-propargyl-δ-valerolactone (PgVL, **2**), TMS-protected PgVL (TMS-PgVL, **3**), and α-propargyl-ε-caprolactone (PgCL, **4**). The diblock copolymers *p*(AVL-*b*-PgVL) (**5**) and *p*[(TMS-PgVL)-*b*-PgVL] (**6**) are also shown.

TBD-Catalyzed Polymerization of Functional Lactones 1–4

Lactones **1–4** were synthesized as reported previously[6,14,16,17] and tested in homopolymerization reactions using TBD catalysis. The polymerizations were conducted in flame-dried Schlenk flasks, using benzyl alcohol as initiator and a toluene solution of TBD. The benzyl alcohol/TBD mixture was stirred for ~30 min, after which monomer was added by syringe, and the reaction mixture was stirred at room temperature until monomer conversion reached 70–80%, as judged by ^{1}H NMR spectroscopy (we note that incubation of the benzyl alcohol/TBD solution was required for successful polymerization). Polymerizations were conducted at 2 M monomer concentration in toluene, using 2 mol % TBD relative to monomer, and monomer-to-initiator ratios ($[M]_0/[I]_0$) of ~140. Catalyst loadings of 2 mol % (relative to monomer) were needed to polymerize each of the alkene and alkyne-functionalized monomers **1–4**, about four times that needed for unsubstituted δ-VL and ε-CL.[12] The polymer products were isolated by precipitation into cold methanol, typically in ~85% yield. Attempts to achieve higher monomer conversion using longer reaction time led to higher PDI values, especially for monomer **2**, presumably due to transesterification at depleted monomer concentration.

Homopolymers formed from the functional lactones **1**, **2**, and **4** were colorless oils, whereas TMS-PgVL **3** was an off-white powder; incorporation of significant amounts of δ-VL and ε-CL as comonomers gave solid polymer products in all cases.[10] The TBD-catalyzed polymerizations of functional lactones **1–4** proceeded much more rapidly than analogous polymerizations using $Sn(Oct)_2$-mediated catalysis: TBD gave high monomer conversion in minutes to <2 h, whereas the tin-mediated polymerizations required 24 h or more.

Table 1 summarizes polymerization conditions and characterization data for the isolated aliphatic polyesters. Molecular weights derived from ^{1}H NMR spectra of the polymers (by end-group analysis) were found to be in close agreement with, or slightly lower than, gel permeation chromatography (GPC)-estimated values obtained by eluting in THF (calibrated with polystyrene standards). End-group analysis integrated phenyl protons of the initiator (7.32 ppm) against pendent alkyne (2.05 ppm) or alkene (5.04 and 5.70 ppm) protons. By allowing the polymerizations to reach ~70–85% conversion, homopolymers with molecular weights ranging from 12 to 15 kDa, with PDI values of ~1.1–1.2, were obtained, as given in Entries 1–6 of Table 1.

We wanted to investigate the polymerization kinetics of functional monomers **1–4** relative to conventional (unsubsti-

TABLE 1 Results of Lactone Polymerizations Using 2 mol % TBD with Respect to Monomer[a]

Entry	Polymer	Time (min)	Conv (%)[b]	M_n (g mol^{-1})[c]	PDI[c]	M_{theor}[d] (g mol^{-1})	M_{NMR}[b] (g mol^{-1})	Feed Ratio	Comp[b]
1	*p*AVL	46	85	15,300	1.04	16,000	15,500	–	–
2	*p*PgVL	15	86	14,400	1.12	16,600	16,000	–	–
3	*p*(TMS-PgVL)	20	85	13,700	1.09	25,000	17,400	–	–
4	*p*PgCL	120	88	12,000	1.03	19,000	8,800	–	–
5	*p*CL	180	76	15,000	1.23	12,000	11,700	–	–
6	*p*VL	5	71	15,500	1.11	10,000	11,000	–	–
7	*p*(AVL-*b*-PgVL)[e]	40/20[f]	87	29,000	1.03	28,700	21,000	50/50	51/49
8	*p*[(TMS-PgVL)-*b*- PgVL][g]	20/20[f]	56	19,000	1.07	27,000	22,000	50/50	55/45
9	*p*(PgCL-*b*-AVL)[h]	90/45[f]	73	12,500	1.07	14,900	14,800	50/50	50/50
10	*p*(PgVL-*co*-VL)[i]	23	85	13,100	1.17	13,000	8,800	60/40	65/35

[a] Polymerizations used 2 mol % TBD relative to monomer, 2 M monomer concentration, and $[M]_0/[I]_0 = 140$.
[b] Relative monomer compositions determined by ^{1}H NMR spectroscopy.
[c] Measured by GPC in THF relative to polystyrene standards.
[d] Calculated from monomer molecular weight, $[M]_0/[I]_0$, and percent conversion.
[e] 2 mol % TBD relative to first monomer reacted, AVL.
[f] Reaction time of first/second monomer.
[g] 2 mol % TBD relative to first monomer reacted, TMS-PgVL.
[h] 2 mol % TBD relative to first monomer reacted, PgCL.
[i] 2 mol % TBD relative to total monomer (PgVL + VL).

tuted) versions. Thus, the rates of these TBD-catalyzed polymerizations were examined and are reported in Table 2 as apparent rate constant (K_{app}) values for each the monomer. Aliquots were withdrawn during the course of the polymerization, quenched with a benzoic acid solution in $CDCl_3$, and analyzed by ^{1}H NMR spectroscopy. Monomer concentrations (conversions) at given time points were determined from the methylene proton resonance of the lactone at 4.28 ppm, relative to the same protons in ring-opened (polymer) product at 4.03 ppm. Rate constants were approximated by first-order kinetics using:

$$\ln([M]_0/[M]) = kK[TBD]_0[ROH]_0 t = K_{app} t$$

where $[M]_0$ is the initial monomer concentration, [M] is monomer concentration at time t, k is the polymerization rate constant, K is the equilibrium constant for the formation of a TBD/ROH/M complex at zero percent monomer conversion,[12] and $[TBD]_0$ and $[ROH]_0$ are the initial concentrations of catalyst and benzyl alcohol, respectively. $[M]_0/[M]$ is equivalent to $1/(1 - p)$, where p represents monomer conversion, and K_{app} is obtained from the slope of the plot of $[\ln(1/1 - p)]$ versus time.

TABLE 2 Measured K_{app} for VL, CL, AVL (1), PgVL (2), (TMS-PgVL) (3), and PgCL (4)

Monomer	K_{app}
VL	0.258
CL	0.0064
AVL	0.0374
PgVL	0.274
TMS-PgVL	0.274
PgCL	0.0105

$[M]_0/[I] = 140$ at 2 mol% TBD relative to monomer; $[M]_0 = 2$ M in toluene.

Among functional monomers **1–4**, allyl-substituted AVL **1** ($K_{app} = 0.037$) exhibited the slowest polymerization, whereas the other lactones polymerized similarly, with K_{app} values determined experimentally for δ-VL (0.258), PgVL **2** (0.274), and TMS-PgVL **3** (0.274). Interestingly, all of the substituted δ-valerolactones polymerized faster than ε-CL using TBD, in contrast to that observed with $Sn(oct)_2$-mediated polymerization of the same monomers.[6,14,17–19] Each polymerization showed a linear dependence of molecular weight on conversion, as seen in Figure 2 for PgCL **4** (others given in the Supporting Information), indicative of good control over the ring-opening and chain growth process using TBD catalysis in conjunction with these functionalized lactones.

Copolymer Synthesis

TBD-catalyzed polymerization of functional lactones **1–4** also allowed excellent control over the formation of copolymers,

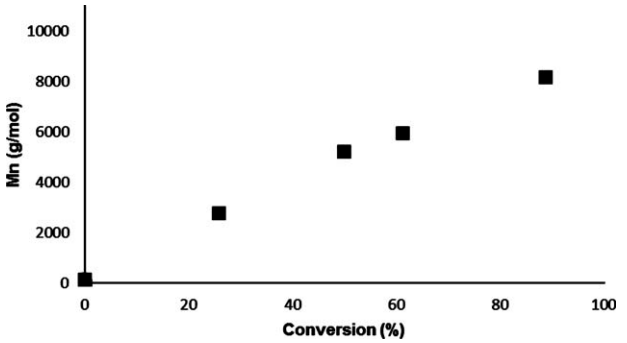


FIGURE 2 Increase in number-average molecular weight (M_n; *y*-axis) with monomer conversion (*x*-axis) in the polymerization of PgCL (**4**).

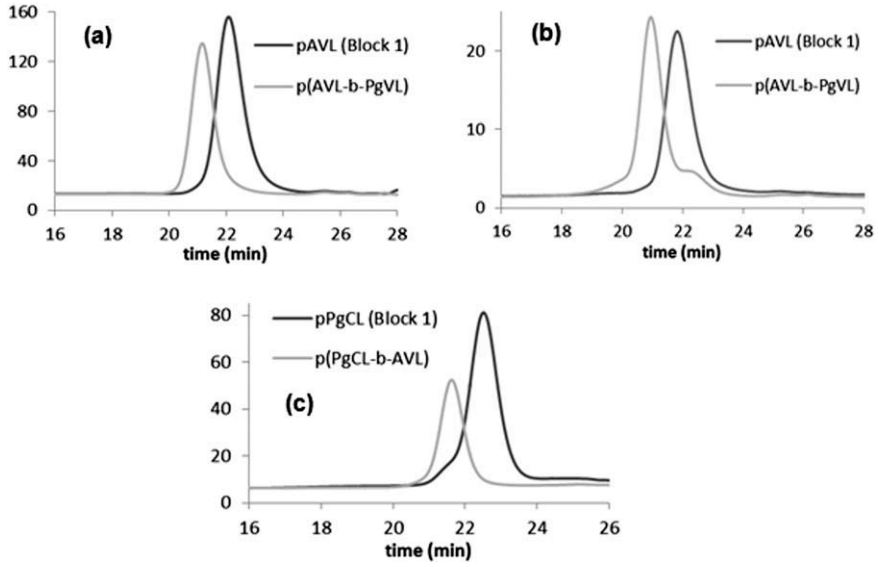


FIGURE 3 Representative GPC traces of (a) *p*(AVL-*b*-PgVL) synthesized by one-pot sequential addition of monomers, (b) *p*(AVL-*b*-PgVL) synthesized by the "macroinitiator" method, and (c) *p*(PgCL-*b*-AVL) synthesized by one-pot sequential addition of monomers.

including diblock copolymer structures. For example, the diblock copolyester *p*(AVL-*b*-PgVL) **5**, possessing pendent alkene (A) and alkyne (propargyl, Pg) groups, was prepared by sequential monomer addition. AVL **1** was added to a pre-incubated benzyl alcohol/TBD solution and stirred for 40 min to reach ~80% conversion; PgVL was then added, and the mixture was stirred for an additional 20 min. The polymer product was isolated by precipitation into cold methanol. GPC traces of the first block (*p*AVL) and the final diblock copolymer showed clear evidence of chain extension [Fig. 3(a)]. The relative monomer composition in the copolymer correlated closely to the feed ratio, as determined by ^{1}H NMR spectroscopy, integrating alkene (5.04 and 5.70 ppm) and alkyne (2.01 ppm) proton resonances against the backbone methylene group adjacent to the oxygen [4.03 ppm; Fig. 4(a)]. Evidence to support the desired diblock copolymer architecture was given by ^{13}C NMR spectroscopy, which showed two distinct peaks in the carbonyl region at 175.2 ppm (AVL block) and 173.8 ppm (PgVL block), whereas the random copolymer *p*(PgVL-*co*-VL) showed multiple peaks for each of the carbonyl resonances centered at 173.7 (PgVL) and 172.7 (VL) ppm [Fig. 4(b,c)]. The GPC trace of *p*(AVL-*b*-

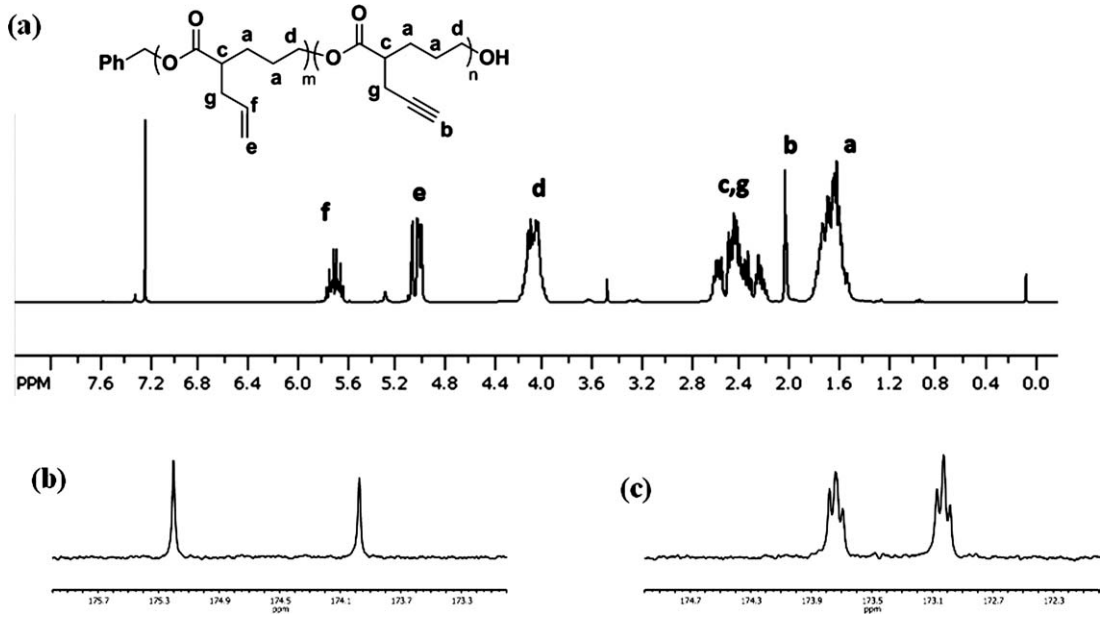


FIGURE 4 (a) ^{1}H NMR spectrum of *p*(AVL-*b*-PgVL); (b,c) carbonyl resonances of the ^{13}C NMR spectra for (b) *p*(AVL-*b*-PgVL) and (c) *p*(PgVL-*co*-VL).

PgVL) was monomodal with low polydispersity (1.03) [Fig. 3(a)], indicating the ability of TBD to maintain a well-controlled polymerization. We note some instances where a slight low molecular weight shoulder (or molecular weight broadening) was observed, indicative of incomplete initiation of the second block (Supporting Information).

To prepare *p*[(TMS-PgVL)-*b*-PgVL] (**6**), TMS-PgVL was added to an incubated benzyl alcohol/TBD solution and stirred for 20 min. PgVL was then added, the reaction mixture was stirred for 20 min, and the polymer recovered by precipitation into cold methanol. The relative monomer composition of the isolated diblock copolymer was determined by ^{1}H NMR spectroscopy, by integrating the terminal alkyne proton signal (2.01 ppm) against the backbone methylene (4.03 ppm) and trimethylsilyl (0.11 ppm) protons. For both *p*(AVL-*b*-PgVL) and *p*[(TMS-PgVL)-*b*-PgVL], diblock polyesters with molecular weights of 20,000–30,000 g mol^{-1} were obtained with low PDI (~1.2). Overall, molecular weights determined by GPC in THF compared closely with theoretical values and those derived from NMR spectroscopy end-group analysis; the final monomer compositions observed (51/49 for p(AVL-*b*-PgVL) and 55/45 for *p*[(TMS-PgVL)-*b*-PgVL]) closely reflected the feed ratios.

The diblock copolymer *p*(AVL-*b*-PgVL) was also prepared using a "macroinitiator" method, by isolating the homopolymer of the first block (*p*AVL) by column chromatography for subsequent initiation of PgVL. The *p*AVL macroinitiator was incubated in solution with TBD for 15 min; then, PgVL was added, and the resulting mixture stirred for 20 min. The isolated *p*(AVL-*b*-PgVL) copolymer showed two distinct peaks in the carbonyl region of the ^{13}C NMR spectrum (175.2 and 173.8 ppm), and the molecular weight obtained by GPC in THF (M_n = 29,000) matched closely to the theoretical (M_{theor} = 28,700) and NMR (M_{NMR} = 21,000) derived values. However, the presence of a low molecular weight shoulder in the GPC trace [Fig. 3(b)] suggests that the one pot sequential addition method [Fig. 3(a)] is preferable, at least in this case, over the macroinitiator approach.

Functionalized caprolactone PgCL **4** was also used for diblock copolymer preparation by one pot sequential addition. For example, after benzyl alcohol/TBD incubation, PgCL was added and stirred for 90 min; then, AVL was added, and the reaction mixture stirred for another 45 min. The final polymer contained 50% AVL, which correlated well with the feed ratio, and had a molecular weight of 12,500 g mol^{-1} (by GPC in THF), closely matching the theoretical (14,900) and NMR-derived (14,800) molecular weights. The ^{13}C NMR spectrum of the final polymer confirmed diblock copolymer formation, showing two distinct carbonyl resonances (175.2 ppm for the AVL block and 174.2 ppm for the PgCL block). The GPC trace was monomodal with narrow PDI [1.07; Fig. 3(c)].

Random copolymers from these functionalized lactones were also prepared using TBD catalysis. For example, *p*(PgVL-*co*-VL) was prepared by adding PgVL and δ-VL simultaneously to an incubated benzyl alcohol/TBD solution, stirring for 20 min at room temperature, and isolating the copolymer by precipitation into cold methanol. The feed ratio was reflected in the final composition, as observed by ^{1}H NMR (Table 1). ^{1}H NMR analysis of aliquots removed during the course of the polymerization showed that the amount of incorporated PgVL remained constant throughout the polymerization, rather than significantly favoring initial incorporation of either monomer. ^{13}C NMR spectroscopy suggested the formation of a random copolymer structure, with multiple peaks for each carbonyl resonance [centered at 172.7 ppm for the PgVL block and 173.7 ppm for the VL block; Fig. 4(c)]. These copolymers, obtained in ~85% yield, are colorless oils at 50% PgVL content; they appear waxy at lower PgVL incorporation (10–30%) and are white solids at low PgVL content where fewer pendent groups are available to interrupt polyester solidification/crystallization.

The successful random copolymerization of VL with PgVL stems from similar propagation rates of the two monomers in the presence of TBD. As AVL homopolymerization proceeds much slower than VL and PgCL, we examined the possibility of forming diblock polyesters in a simultaneous, one-pot copolymerization of these monomers. Copolymerization of VL with AVL, and PgCL with AVL, was performed by introducing a 1:1 molar ratio of the monomers to a previously incubated benzyl alcohol/TBD solution. However, random or gradient copolymers were obtained, as indicated by the appearance of multiple carbonyl peaks in the ^{13}C NMR spectra (as opposed to the two distinct carbonyl resonances in the diblock structures). Monitoring polymer composition during the course of the polymerization, by ^{1}H NMR spectroscopy on withdrawn aliquots, suggested a gradient copolymer formation. Lactones with faster apparent rates of homopolymerization (VL over AVL and AVL over PgCL) were incorporated preferentially into the polymer backbone at the early time-frame of the polymerization. Upon depletion of the faster polymerizing monomer, the amount of incorporated comonomer increased until the final observed polymer composition reflected the monomer feed ratio.

Taken together, the polymerization results described above confirm the capability of TBD as an organic catalyst to polymerize lactones carrying functional groups α to the carbonyl group, giving homopolymer and copolymer materials efficiently, with little interruption from transesterification, as indicated by low PDI values (~1.2) obtained up to relatively high monomer conversion (~85%). With these polymers in hand, we then examined the utility of *p*(AVL-*b*-PgVL) in nanoparticle formation and subsequent modification using CuAAC and thiol-ene reactions.

Polyester Nanoparticle Formation

The orthogonal nature of thiol-ene and CuAAC reactions was implemented to prepare functional nanoparticles from *p*(AVL-*b*-PgVL), bearing one block of pendent alkenes and one block of pendent alkynes. Crosslinking of the alkyne-containing PgVL block was accomplished in dilute solution, with 1,8-diazido-3,6-dioxaoctane (prepared according to a

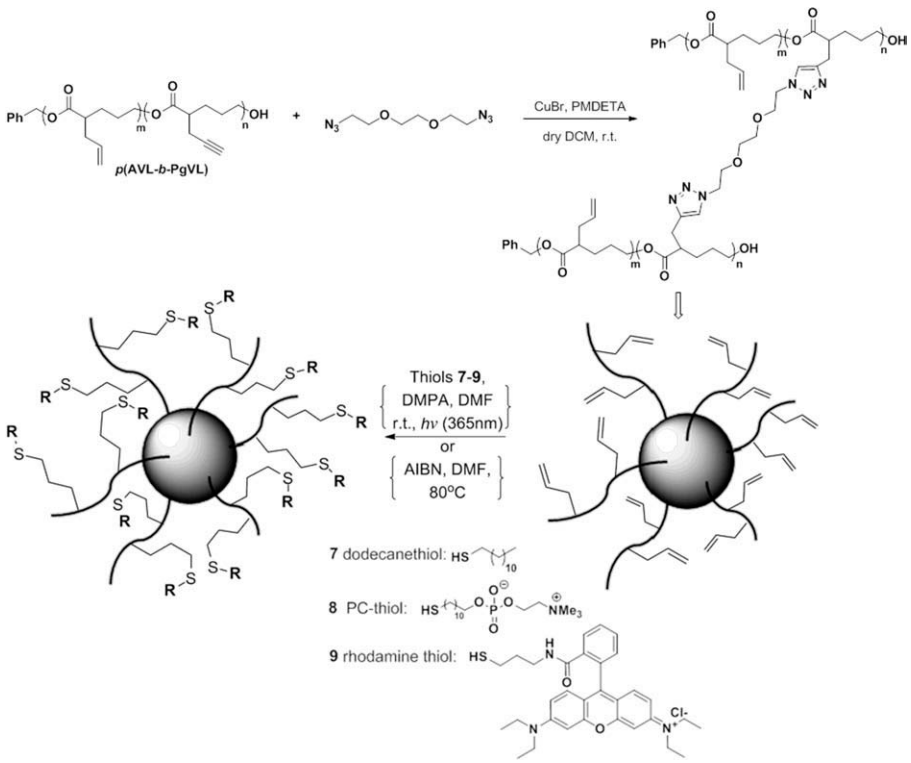


FIGURE 5 Crosslinked nanoparticles obtained by CuAAC of *p*(AVL-*b*-PgVL) (**5**) with 1,8-diazido-3,6-dioxaoctane and subsequent thiol-ene reactions using thiols **7**–**9**.

published procedure[19]) in a 1:1 azide-to-alkyne ratio (Fig. 5). For nanoparticle formation and CuAAC crosslinking, *p*(AVL-*b*-PgVL) was dissolved in degassed CH_2Cl_2 and stirred with 1,8-diazido-3,6-dioxane, copper(I) bromide (1.0 equiv with respect to alkyne) and *N*,*N*,*N*′,*N*′,*N*″-pentamethyldiethylenetriamine (PMDETA; 2.0 equiv with respect to alkyne) at room temperature overnight. Nanoparticle size was controlled by varying the alkyne concentration during the CuAAC reaction (while the alkyne-to-azide ratio was kept constant). Three concentrations of alkyne were used: [3.6 mM], [54 mM], and [215 mM].

Nanoparticle Characterization

The crosslinked polyester nanoparticles were characterized by ^{1}H NMR spectroscopy, transmission electron microscopy (TEM), and dynamic light scattering (DLS). Nanoparticle formation was monitored by ^{1}H NMR spectroscopy, noting the disappearance of the terminal alkyne protons (2.01 ppm) and differentiation of peaks b and c (methine protons, Fig. 6) after diazide crosslinking of the PgVL block. We noticed that the polyester resonances corresponding to the crosslinked block (2.6–3.0 ppm) appeared broader than the signals representing the alkene-functional block (2.1–2.4 ppm), a likely consequence of their constrained conformation in solution when crosslinked; the alkene peaks themselves were unchanged (5.04 and 5.70 ppm; Fig. 6).

DLS measurements of these polyester nanoparticles in CH_2Cl_2 indicated that nanoparticle size was controllable by varying the alkyne concentration, with higher alkyne concentration giving larger particles at a constant alkyne-to-crosslinker ratio of 2:1. At alkyne concentrations of 3.6, 54, and 215 mM, the crosslinked nanoparticles obtained had average hydrodynamic diameters of 13 ± 0.5, 18 ± 1, and 41 ± 0.8 nm, respectively. As expected, higher alkyne (and thus polymer) concentration increases the extent of interchain coupling, resulting in larger nanostructures.

Crosslinked *p*(AVL-*b*-PgVL) nanoparticles were characterized further by TEM (staining with phosphotungstic acid, PTA) to give additional evidence supporting the presence of discrete polyester nanostructures. TEM samples were prepared by drop-casting a CH_2Cl_2 solution of nanoparticles onto a TEM grid. Figure 7(a) shows spherical nanoparticles, about 10–20 nm diameter, formed from crosslinked *p*(AVL-*b*-PgVL) (0.36 mg mL^{-1}), correlating closely to the DLS-derived size. This image also shows a worm-like connectivity, in which many of the particles appear to merge into a continuous structure. This feature is most likely a concentration effect, though the potential influence of the staining reagent has not been ruled out. In contrast to Figure 7(a), the TEM image of Figure 7(b), from a 0.18 mg mL^{-1} solution of nanoparticles, showed a less-extensive network due to the lower concentration used. Nanoparticles modified with dodecanethiol [Fig. 7(c)], exhibited no propensity to form networks, and by TEM were seen as discrete structures. Furthermore, AFM images of unstained nanoparticles (0.36 mg mL^{-1}, drop cast in dichloromethane onto a silicon wafer) revealed roughly spherical nanoparticles (~60 nm diameter) and no worm-like networks [Fig. 7(d)]. Nanoparticle diameter determined

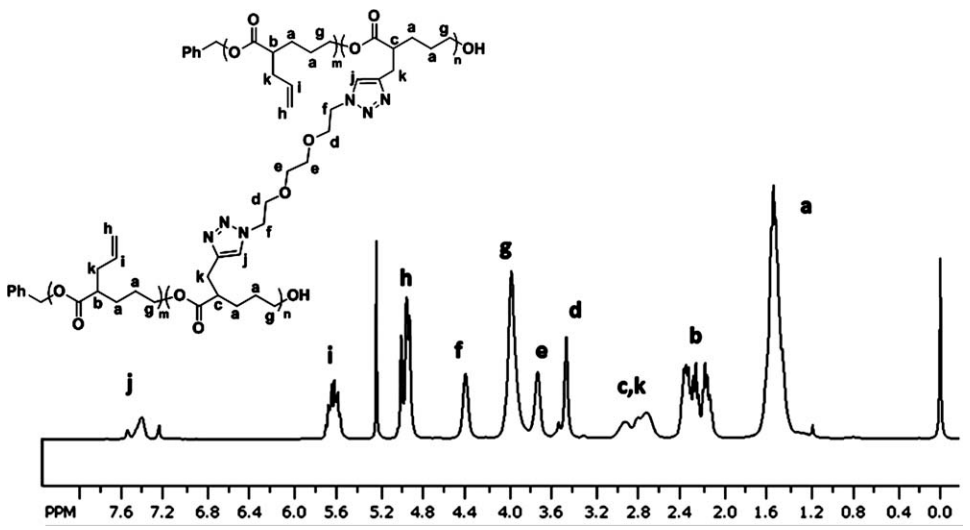


FIGURE 6 ^{1}H NMR spectrum of polyester nanoparticles obtained following click cycloaddition/crosslinking of *p*(AVL-*b*-PgVL) **5** with 1,8-diazide-3,6-dioxaoctane.

by AFM (60-nm diameter, 4-nm height) is larger than that observed by DLS (10–20 nm), which can be explained by a flattening of the structures on the substrate for these measurements.

The CuAAC crosslinking of *p*(AVL-*b*-PgVL) **5** yields polyester nanoparticles possessing available alkene groups. To examine the accessibility of the alkenes following crosslinking, a range of thiols (shown in Fig. 5) was tested for nanoparticle

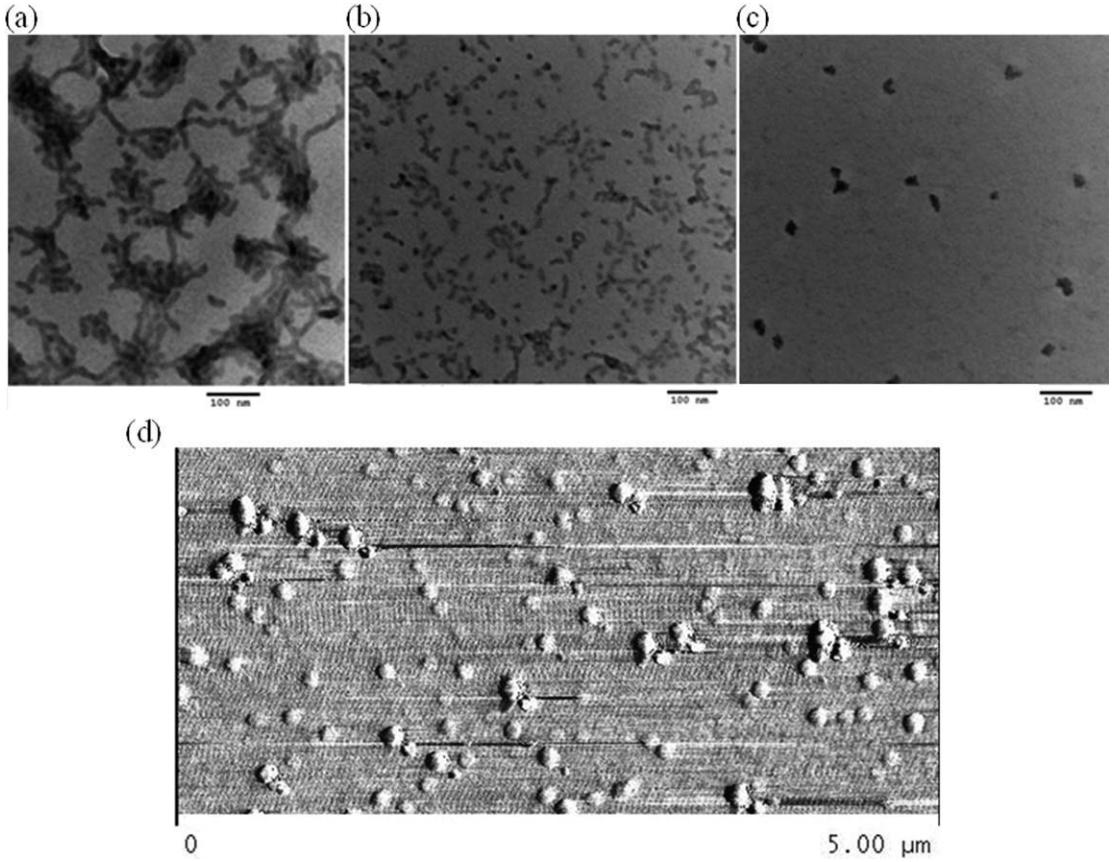


FIGURE 7 TEM images of crosslinked nanoparticles formed from (a) *p*(AVL-*b*-PgVL), 0.36 mg mL^{-1}; (b) *p*(AVL-*b*-PgVL), 0.18 mg mL^{-1}; (c) *p*(AVL-*b*-PgVL), and subsequently modified by dodecanethiol, 0.36 mg mL^{-1}; and (d) AFM image of crosslinked nanoparticles formed from *p*(AVL-*b*-PgVL), 0.36 mg mL^{-1}.

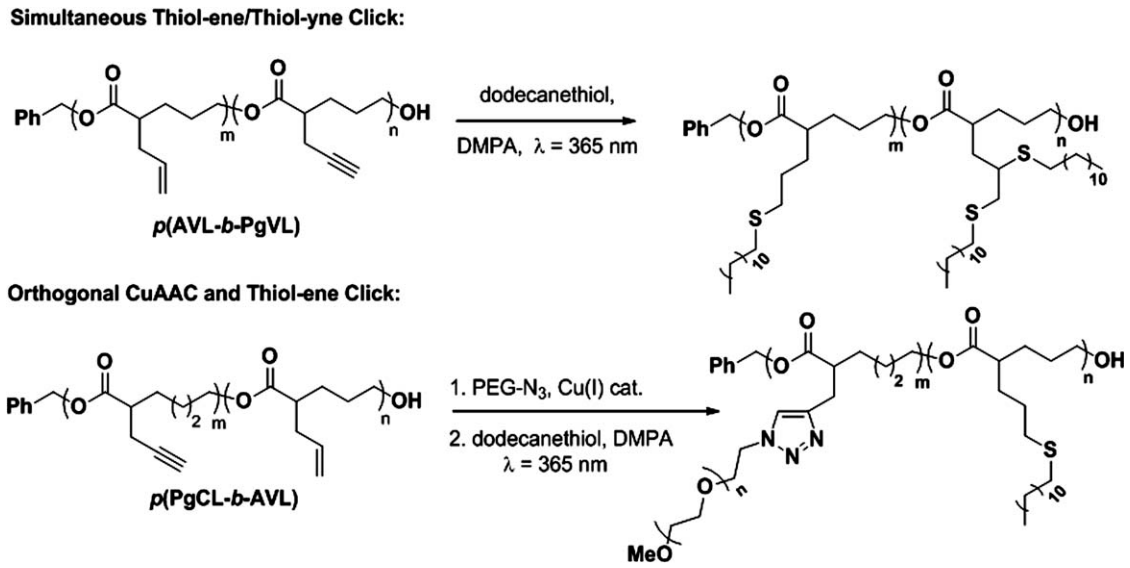


FIGURE 8 Schematic representation showing diblock polyesters differentiated using simultaneous thiol-ene/thiol-yne reactions [*p*(AVL-*b*-PgVL) **5**], or modified using sequential azide/alkyne and thiol-ene click chemistries orthogonally [*p*(PgCL-*b*-AVL)], yielding distinct diblock copolymers in both cases.

functionalization by thiol-ene coupling. We chose dodecanethiol **7** as a simple hydrophobic thiol, PC-terminated thiol (PC-thiol) **8** as a hydrophilic example, and rhodamaine thiol **9** as a fluorescent example. Both thermal and photoinitiated thiol-ene conditions[8] were tested. For dodecanethiol modification, 2,2′-azobisisobutyronitrile (AIBN; 0.5 equiv with respect to alkene) and *p*(AVL-*b*-PgVL) **5** with dodecanethiol (5.0 equiv) were stirred in degassed DMF at 80 °C for several hours, and the dodecane-modified nanoparticles were isolated by dialysis against CH_2Cl_2. ^{1}H NMR spectroscopy of the resulting nanoparticles showed no vinyl signals, indicating efficient alkene-to-dodecyl conversion. DLS measurements indicated an increase in nanoparticle size from 10 to 19 nm following dodecanethiol grafting. The thiol-ene reactions using PC-thiol **8** and rhodamine thiol **9** used 2,2-dimethoxy-2-phenylacetophenone (DMPA) as photoinitiator in degassed DMF (or DMF/MeOH in the case of PC-thiol grafting), with stirring at room temperature under a UVP Black Ray UV lamp emitting at ~365 nm. ^{1}H NMR spectroscopy showed loss of alkene and the appearance of signals stemming from the PC (from 2.9 to 4.2 ppm) or the rhodamine (from 6.2 to 7.9 ppm) moiety. DLS measurements indicated an increase in nanoparticle size following these grafting reactions, from 10 to 69 nm upon PC-thiol addition and from 11 to 23 nm with the addition of rhodamine-thiol. Whereas the polyester nanoparticles possessing unreacted alkenes were soluble only in organic solvents, such as CH_2Cl_2 (and not in methanol), the PC-modified nanoparticles were not soluble in CH_2Cl_2, and therefore, they are isolated by dialysis in methanol. PC-grafted nanoparticles were soluble in water when, as far as could be seen spectroscopically, most or all of the alkenes were converted to PC groups. The larger sizes observed with PC-grafted nanoparticles are likely due to swelling in the solvent (methanol) used for DLS-characterization of these structures.

Thiol-ene/yne Functionalization of *p*(AVL-*b*-PgVL)

Alkene-/alkyne-substituted diblock polyester copolymers also proved useful as precursors to highly functional polyesters, using (1) simultaneous (one-step) thiol-ene/yne grafting chemistry and (2) thiol-ene and CuAAC reactions performed in two steps. Thiol-ene/yne functionalization of *p*(AVL-*b*-PgVL) **5** provides a mechanism for grafting along the polyester backbone to afford polymer structures with twice the grafting density on the alkyne block (introducing 2 thiols per alkyne) relative to the alkene block [Fig. 8(a)]. To examine simultaneous thiol-ene/yne functionalization, *p*(AVL-*b*-PgVL) **5** was subjected to thermal thiol-ene reaction conditions with dodecanethiol **7** (5.0 equiv relative to total alkene/alkyne) and AIBN (0.5 equiv) in degassed DMF at 80 °C. After 3 h, a high conversion was indicated by complete disappearance of both the alkene (5.04 and 5.70 ppm) and the alkyne (2.01 ppm) proton peaks in the ^{1}H NMR spectrum, and GPC analysis of the final polymer indicated an increase in molecular weight (M_n; from 13,900 to 22,800 g mol^{-1}), although narrow PDI values (1.1–1.3) were maintained.

The orthogonality of CuAAC and thiol-ene chemistries was demonstrated for *p*(PgCL-*b*-AVL), using α,ω-PEG-750-monomethyl ether azide (m-PEG_{750}-N_3) and dodecanethiol **7** in sequential grafting reactions to yield amphiphilic block copolyesters [Fig. 8(b)], with the azide/alkyne reaction performed first to prevent the unwanted radical thiol-yne chemistry. CuAAC coupling of α-methoxy-ω-azido PEG (PEG-azide)[16] with the diblock precursor was performed first in a water/THF (1:4) mixture using copper(II) sulfate and sodium ascorbate and stirring the reaction for 15 h at 80 °C. Excess m-PEG_{750}-N_3 was removed by dialysis, and trace copper was removed using Cuprisorb^{TM}, giving the PEGylated polyester as a hygroscopic solid in 90% yield after lyopholization. Triazole and PEG protons were observed in the ^{1}H

NMR spectrum, and the allyl group remained intact as supported by the unchanged integration ratio between the alkene protons at 5.04 and 5.70 ppm, and the oxymethylene protons of the polymer backbone at 4.00 ppm. The disappearance of the terminal alkyne peak at 2.05 ppm indicated complete consumption of alkyne. Furthermore, the ^{13}C NMR spectrum showed the appearance of the triazole carbons at 144.94 and 122.70 ppm, as well as the methylene carbons connecting the triazole to PEG (69.6 and 50.1 ppm). An increase in molecular weight (M_n) was observed by GPC (from 12,500 to 24,800 g mol^{-1}), with significant deviation from the theoretical molecular weight of 56,000 g mol^{-1} explained by the extensive branching (grafting) of the structure. The PDI value of the final polymer remained low ($\sim$1.1) owing to the mild CuAAC conditions that allow functionalization in the absence of substantial polyester degradation. Typically, trace amounts m-PEG$_{750}$-N$_3$ remained following the initial purification (by dialysis or precipitation), as seen by the presence of a small peak at long retention time by GPC (Supporting Information). Dodecanethiol was then attached to the PEGylated polyester by thiol-ene grafting using DMPA as photoinitiator. PEGylated *p*(AVL-*b*-PgVL) was dissolved in a DMF solution containing dodecanethiol **7** and DMPA, and the solution was degassed by three freeze–pump–thaw cycles, then irradiated at 365 nm for 8 h. The product was collected by precipitation into cold hexane and obtained as a slightly yellow, waxy solid in 80% yield. High alkene conversion was achieved, as seen by ^{1}H NMR spectroscopy, noting the disappearance of the vinyl peaks at 5.04 and 5.70 ppm. The ^{13}C NMR spectrum further supported the absence of olefin in the product. The originally overlapping carbonyl signals of PEGylated *p*(AVL-*b*-PgVL) became two distinct peaks, in accord with the block structure derived from the parent copolyester, and characterization by GPC revealed an increase in molecular weight (M_n; from 24,800 to 29,000 g mol^{-1}).

In summary, we demonstrated ready synthetic access to highly functional aliphatic polyesters and the efficient modification of these structures using orthogonal CuAAC and thiol-ene chemistries. TBD-catalyzed ROP of alkene- and alkyne-substituted lactone monomers proved useful for the preparation of the corresponding aliphatic polyesters in excellent yield and with low PDI. Diblock copolymers prepared in this way were suitable for orthogonal chemistries, crosslinking the polymers by CuAAC to give polyester nanoparticulate materials that were amenable to further functionalization by thiol-ene chemistry. Functionalities ranging from hydrophilic solubilizing groups to fluorescent moieties were introduced successfully to the nanoparticles, showing the modular nature of this approach. Taken together, this work opens new routes to functional, biodegradable polyesters of interest for tailored delivery and controlled release applications, and that considerably extend the tool box of structures available for such applications.

EXPERIMENTAL

Materials

Benzyl alcohol, calcium hydride, copper(I) bromide (CuBr, 98%), PMDETA, 99%, TBD (98%), *N*-ethyl-*N*′-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC; >98%), DMAP (99%), sodium azide (98%), rhodamine B (dye content $\sim$95%), 3-bromopropylamine hydrobromide (98%), potassium thioacetate (>98%), dimethylamine (40 wt % solution in water), 1-dodecanethiol ($\geq$98%), 11-bromoundecanol ($\sim$98%), DMPA (99%), trimethylamine (99%), triethylamine (>99%), AIBN (98%), and PTA were purchased from Sigma–Aldrich. δ-Valerolactone (99%) was purchased from Acros Organics. Copper(II) sulfate pentahydrate (99.6%) was purchased from Fisher Scientific. Ethylene chlorophosphate (95%) was purchased from Alpha Aesar and distilled prior to use. Dialysis tubing (Spectra/Por® Membrane molecular weight cutoff, MWCO = 6000–8000) was purchased from VWR International. Carbon-coated copper grids were purchased from Electron Microscopy Sciences. Sodium ascorbate (Source Naturals) and Cuprisorb™ (Marine Depot) were used as received. δ-Valerolactone, benzyl alcohol, triethylamine, and methylene chloride were dried and distilled over calcium hydride. THF and toluene were distilled over sodium/benzophenone ketyl. AIBN was recrystallized from methanol. All other materials were used without further purification. PEG-azide was synthesized using a literature procedure.[6]

Instrumentation

NMR spectra were recorded using a Bruker DPX300 or Bruker Avance400 spectrometer with the residual solvent signal as calibration. Molecular weight and PDI values were determined by GPC, eluting in THF, and estimated relative to polystyrene standards [from Scientific Polymer Products; peak-average molecular weight (M_p) 503, 700, 1306, 2300, 4760, 12,400, 196,700, and 556,000 g mol^{-1}]. The GPC was equipped with a three-column set (Polymer Laboratories 300 $\times$ 7.5 mm, 2 Mixed-D, 50 Å) and a refractive-index detector (Waters R4010); or with three PL Gel 5 μm MIXED-D 300 $\times$ 7.5 mm^2 columns and a multiangle light scattering detector (DAWN EOS), viscometer (Viscostar), and refractive index detector (Optilab rEX) with a flow rate of 0.75 mL min^{-1}. UV/vis absorbance was recorded on a Perkin-Elmer Lambda 25 UV/vis spectrometer. IR data was recorded on a Perkin-Elmer Spectrum One FTIR spectrometer equipped with a universal attenuated total reflection sampling accessory. AFM imaging was carried out in air with the tapping mode using a Nanoscope III Dimension 3000 microscope (Veeco Digital Instruments) with silicon probe cantilevers. DLS measurements were made using a Nano-ZS instrument, model ZEN3600 (Malvern Instruments, UK). TEM was performed on a JEOL 2000 FX MARK II 200 keV microscope.

TEM Images

TEM images were obtained using a JEOL 2000FX microscope operating at an accelerating voltage of 200 keV. Polymer solutions (0.5 mg in 1 mL of 2-propanol and 0.4 mL of acetonitrile) were mixed with five drops of 3 wt% PTA solution in 2-propanol for a negative stain and sonicated for 5 min. Samples were prepared by slowly dipping the carbon-coated copper grid into the polymer solution three times and drying at room temperature.

AFM Images

Polymer solutions (0.36 mg mL^{-1}) were drop cast onto a silicon surface. AFM images were taken on a Digital Instruments Dimension 3100 microscope operated in tapping mode using standard silicon nitride probes. Height and phase images were taken at scanning speeds of 6 μm s^{-1}.

DLS Measurements

DLS was performed on a Nano-ZS instrument, model ZEN3600 (Malvern Instruments, UK). Samples were dissolved in dichloromethane or methanol and filtered through a 0.45-μm filter prior to each measurement. Values reported are size distribution by volume.

Monomer Synthesis

Allyl-valerolactone,[16] propargyl-valerolactone,[6] TMS-protected propargyl-valerolactone,[14] and propargyl-caprolactone[17] were synthesized as reported previously.

Homopolymer Synthesis

Polymerizations were carried out at room temperature under nitrogen in a flame-dried Schlenk flask. Benzyl alcohol was added to a toluene solution of TBD (0.04 M) and stirred for 30 min prior to introducing monomer at a monomer-to-initiator ratio of 140:1. The monomer concentration was 2 M in toluene, while TBD was 2 mol % relative to monomer. Polymerizations were terminated by precipitation into cold methanol. Residual catalyst and unreacted monomer were removed from the isolated polymer by repeated precipitation into cold methanol. Aliquots of the final crude reaction mixtures were obtained just prior to precipitation and quenched by a 1 M benzoic acid solution in $CDCl_3$, followed by determination of percent monomer conversion using ^{1}H NMR spectroscopy.

Example Homopolymer Synthesis: pVL

To a previously incubated solution of benzyl alcohol (5.5 μL, 5.31×10^{-2} mmol) and TBD (0.04 M in toluene, 3.7 mL, 0.148 mmol), VL (0.69 mL, 7.4 mmol) was added, and the mixture was stirred at room temperature, under nitrogen, for 5 min. The polymerization was then quenched by precipitation into cold methanol, and *p*VL was isolated as colorless oil.

Synthesis of pAVL

Synthesis of *p*AVL was performed following the general procedure for all homopolymers, with a reaction time of 40 min, before precipitating into methanol.

Synthesis of pPgVL

Synthesis of *p*-PgVL was performed following the general procedure for all homopolymers, with a reaction time of 20 min, followed by precipitation into methanol.

Synthesis of p(TMS-PgVL)

Synthesis of *p*(TMS-PgVL) was performed following the general procedure for all homopolymers, with a reaction time of 20 min, followed by precipitation into methanol.

Synthesis of pPgCL

*p*PgCL was prepared following the general procedure for all homopolymers, with a reaction time of 2 h and 45 min, followed by precipitation into methanol.

Copolymer Synthesis

Copolymer syntheses were carried out following a procedure similar to that for the homopolymers. All polymerizations were conducted at room temperature under nitrogen, in a flame-dried two-neck Schlenk flask sealed with a rubber septum. Benzyl alcohol was added to a TBD solution (0.04 M) in toluene and stirred for 20 min, at a monomer-to-initiator ratio of 140:1, relative to the first monomer added (in the case of the diblock copolymers) or to the total number of moles of monomer (for the random copolymer). For the diblock copolymers, the monomer with the faster rate of homopolymerization was added first and allowed to reach ~80% conversion; then, the second monomer was added and polymerized to 80% conversion. For the random copolymer synthesis, the two monomers were added simultaneously. In all cases, the total monomer concentration was 2 M in toluene, while the amount of TBD used was 2 mol % relative to the first monomer added (for diblock copolymers) or to the total number of moles of monomer (for random copolymers). Polymerizations were terminated by precipitation into cold methanol. Residual catalyst and unreacted monomers were removed from the isolated copolymers by repeated precipitation into cold methanol. Aliquots of the final crude reaction mixture were characterized before precipitation, as well as before addition of the second monomer, in the case of the diblock copolymer, to determine percent conversion using ^{1}H NMR. Aliquots were quenched using a 1M benzoic acid solution in $CDCl_3$.

Example Diblock Synthesis: p(AVL-b-PgVL) 5

To a previously incubated solution of benzyl alcohol (5.27 μL, 5.1×10^{-2} mmol) and TBD (0.04 M in toluene, 3.58 mL, 0.143 mmol), AVL **1** (1.0 g, 7.14 mmol) was added, and the reaction mixture was stirred at room temperature, under nitrogen, for 40 min. An aliquot was taken and quenched with a 1 M benzoic acid solution in $CDCl_3$. PgVL **2** was added (0.98 g, 7.1 mmol), and the reaction mixture was stirred at room temperature for 20 min. The polymerization was then quenched by precipitation into cold methanol, and *p*(AVL-*b*-PgVL) was isolated as a colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ ($CHCl_3$ = 7.26 ppm), 5.70 (m, 1H, CH_2=C*H*), 5.04 (m, 2H, CH_2=CH), 4.08 (m, 4H, CH_2OC=O), 2.2–2.6 (br m, 6H, C*H*C=O + CH_2C≡CH + CH_2CH=CH_2), 2.05 (s, 1H, C≡C*H*), 1.66 (m, 8H, CHCH_2CH_2CH_2O AVL + CHCH_2CH_2CH_2O PgVL). ^{13}C NMR ($CDCl_3$, 75 MHz): δ ($CHCl_3$ = 77.16 ppm) 175.2 (*C*=O_{AVL}), 173.8 (*C*=O_{PgVL}), 135.2 (*C*H=CH_{2AVL}), 117.1 (CH=*C*H_{2AVL}), 80.9 (C≡*C*H_{PgVL}), 70.3 (*C*≡CH_{PgVL}), 64.1 (CH_2O_{AVL}), 64.0 (CH_2O_{PgVL}), 44.8 (*C*HC=O_{AVL}), 44.0 (*C*HC=O_{PgVL}), 36.5 (*C*H_2CH=CH_{2AVL}), 28.1 ($CH_2CH_2CH_{2AVL}$), 27.4 ($CH_2CH_2CH_{2PgVL}$), 26.5 (CH*C*H_2CH_{2AVL}), 26.1 (CH*C*H_2CH_{2PgVL}), 21.1 (*C*H_2C≡C_{PgVL}).

Synthesis of p(PgCL-b-AVL)

To a stirred solution of TBD (0.04 M in toluene, 3.6 mL, 0.060 mmol) and benzyl alcohol (11 μL, 0.106 mmol), PgCL **4** (1.13 g, 7.43 mmol) was added, and the mixture was stirred for 1.5 h. An aliquot (~50 μL) was taken for GPC and ^{1}H NMR analyses. AVL **1** (1.04 g, 7.43 mmol) was added, and the reaction mixture was stirred for 70 min. The

polymerization was terminated by adding benzoic acid, and the polymer was isolated by precipitation into cold methanol and hexane to afford 1.67 g (93%) of a colorless viscous liquid. The overall monomer conversion was 83% and the composition of final polymer was found to be the same as feed ratio in accord with conversion determined for each block. ^{1}H NMR ($CDCl_3$, 300 MHz): δ ($CHCl_3$ = 7.26 ppm) 5.71 (m, 1H, CH_2=C*H*), 5.03 (m, 2H, CH_2=CH), 4.04 (m, 4H, CH_2O), 2.15–2.6 (br m, 6H, C*H*C=O + CH_2C≡CH + CH_2CH=CH_2), 2.0 (s, 1H, C≡C*H*), 1.66 (m, 8H, CHCH_2C$H_2$$CH_2O$ AVL + CHC$H_2$$CH_2CH_2$$CH_2O$ PgCL), 1.37 (m, 2H, $CHCH_2$C$H_2$$CH_2$$CH_2O$ PgCL). ^{13}C NMR ($CDCl_3$, 75 MHz): δ ($CHCl_3$=77.16 ppm) 175.2 (C=O_{AVL}), 174.2 (C=O_{PgCL}), 135.2 (C=C_{AVL}), 117.1 (C=C_{AVL}), 81.3 (*C*≡CH_{PgCL}), 70.2(C≡*C*H_{PgCL}), 64.4(CH_2O_{PgCL}), 64.0 (CH_2O_{AVL}), 44.8 (*C*HC=O_{AVL}), 44.4 (*C*HC=O_{PgCL}), 36.5 (*C*H_2C=C), 28.4 (*C*$H_2CH_2O_{PgCL}$), 28.0 (CH*C*H_{2AVL}), 26.5 ($CHCH_2$*C*H_{2AVL}), 24.6 (C=OCH*C*H_{2PgCL}), 23.4 (C=OCHCH_2-*C*H_{2PgCL}), 21.1 (*C*H_2C≡C_{PgCL}).

Synthesis of p[(TMS-PgVL)-b-PgVL] 6

p-(TMS-PgVL)-*b*-PgVL **6** was synthesized following the general procedure given above, with TMS-PgVL **3** added first, stirring for 23 min, then addition of PgVL **2**, with continued stirring for 20 min.

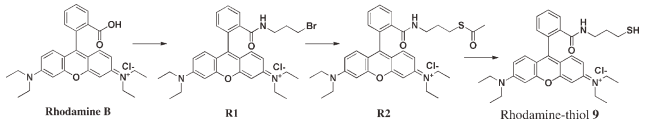
Synthesis of p(PgVL-co-VL)

p-PgVL-*co*-VL was synthesized by simultaneous addition of PgVL **2** and VL to an incubated solution of benzyl alcohol and TBD and stirred for 23 min.

Synthesis of 1,8-Diazido-3,6-dioxaoctane

To a solution of 1,2-bis(2-chloroethoxy) ethane (0.90 g, 4.81 mmol) in water/acetone (1:1) was added sodium azide (1.90 g, 28.9 mmol) and a trace of sodium iodide. The reaction mixture was stirred at 50 °C overnight, then diluted with water, filtered over Celite, and extracted with dichloromethane. The combined organic layers were dried over magnesium sulfate and concentrated on a rotary evaporator to yield 1,8-diazido-3,6-dioxaoctane as a clear, slightly yellow oil in 86% yield. IR: 2100 cm^{-1}. Note: For safety considerations, due to the relatively low (C + O):N ratio of 1.33:1, this reaction was performed at <1 g of 1,8-diazido-3,6-dioxaoctane, and the compound was stored as a solution in dichloromethane.

Synthesis of Rhodamine-Thiol 9



Rhodamine B (0.40 g, 0.85 mmol), 3-bromopropylamine hydrobromide (0.186 g, 0.851 mmol), EDC (0.198 g, 1.28 mmol), and DMAP (0.311 g, 2.55 mmol) were added to dry dichloromethane (~50 mL) and stirred at room temperature overnight. The organic layer was washed with saturated sodium bicarbonate solution (3×), 1 M hydrochloric acid (1×), and brine (3×), dried over magnesium sulfate, and concentrated on a rotary evaporator to yield **R1** as a pink oil in 65% yield. ^{1}H NMR and mass spectrometry confirmed the identity of the product. ^{1}H NMR ($CDCl_3$, 300 MHz): δ ($CHCl_3$ = 7.26 ppm) 8.24 (1H, d), 7.88 (1H, m), 7.82 ppm (1H, m), 7.47 (1H, d), 7.10 (2H, d), 7.03 (2H, d), 6.98 (2H, d), 3.65 (8H, q), 3.30 (2H, t), 3.10 (2H, t), 1.67 (2H, m) 1.21 (12H, t). low resolution mass spectrometry FAB: (*m/z*): $[M+H]^+$ calculated from $C_{31}H_{37}BrN_3O_2$ 562.2; found 562.5. To a solution of **R1** (0.326 g, 0.553 mmol) in anhydrous DMF (~5mL), potassium thioacetate (0.0630 g, 0.553 mmol) was added, and the resulting solution was stirred at 60 °C for 6 h. After cooling to room temperature, the reaction mixture was diluted with dichloromethane and washed exhaustively with water and brine to remove DMF. The organic layer was dried over magnesium sulfate and concentrated on a rotary evaporator to yield **R2** as a pink oil in 80% yield. ^{1}H NMR and mass spectrometry confirmed the identity of the product. ^{1}H NMR ($CDCl_3$, 300 MHz): δ ($CHCl_3$ = 7.26 ppm) 8.24 (1H, d), 7.88 (1H, m), 7.82 ppm (1H, m), 7.47 (1H, d), 7.10 (2H, d), 7.03 (2H, d), 6.98 (2H, d), 3.65 (8H, q), 3.15 (2H, t), 2.65 (2H, t), 2.34 (3H, s), 1.45 (2H, m), 1.21 (12H, t). low resolution mass spectrometry FAB: (*m/z*): $[M+H]^+$ calculated from $C_{33}H_{40}N_3O_3S$ 558.3; found 558.6. To a solution of **R2** (0.26 g, 0.44 mmol) in THF (~3 mL), dimethylamine (40 wt % solution in water; 19.9 mg, 0.442 mmol) was added, and the mixture was stirred at room temperature, under a nitrogen atmosphere, overnight. The mixture was diluted with dichloromethane and the organic layer was washed with water (3×) and brine (3×), dried over magnesium sulfate and concentrated on a rotary evaporator to yield rhodamine-thiol **9** as an odorous pink oil in 70% yield. ^{1}H NMR and MS confirmed the identity of the product.

^{1}H NMR ($CDCl_3$, 300 MHz): δ ($CHCl_3$ = 7.26 ppm) 8.24 (1H, d), 7.88 (1H, m), 7.82 ppm (1H, m), 7.47 (1H, d), 7.10 (2H, d), 7.03 (2H, d), 6.98 (2H, d), 3.65 (8H, q), 3.15 (2H, t), 2.65 (2H, t), 1.45 (2H, m), 1.21 (12H, t). LRMS FAB: (*m/z*): $[M+H]^+$ calculated from $C_{31}H_{41}N_3O_2S$ 516.3; found 514.0 and 1029.0 (disulfide-linked dimer).

Synthesis of PC-Thiol 8

To a solution of 11-bromoundecanol (3.00 g, 26.3 mmol) in DMF, potassium thioacetate (5.60 g, 21.9 mmol) was added, and the reaction mixture was stirred at room temperature for 3 h. The reaction mixture was diluted with dichloromethane and washed with water. The combined organic layers were dried over magnesium sulfate and concentrated on a rotary evaporator to yield 11-thioacetylundecanol as an off-white powder. In a flame-dried two-neck round bottom flask, a solution of 11-thioacetylundecanol (1.85 g, 8.2 mmol) and triethylamine (1.3 mL, 9.08 mmol) in anhydrous THF (20 mL) was added; the flask was equipped with septum, stir bar, and nitrogen inlet. Ethylene chlorophosphate (0.84 mL, 9.1 mmol) was added dropwise, and the resulting mixture allowed to warm to room temperature, followed by continued stirring for 1 h. The formed solid was removed by vacuum filtration over Celite, using a blanket of nitrogen, then the volatiles were removed by rotary evaporation, and the isolated product taken to the next step without further purification. The crude product was dissolved in anhydrous

acetonitrile (22 mL) and cooled to 0 °C in a glass pressure vessel. Trimethylamine (3.6 mL, 38 mmol) was added, and the mixture was heated at 70 °C overnight. The reaction mixture was slowly cooled to precipitate the product, which was isolated by filtration to yield thioacetyl-PC as a brown, oily solid. Thioacetyl-PC (1.84 g, 4.48 mmol) was dissolved in methanol (5 mL), diluted with THF (20 mL), and stirred under nitrogen. To this solution, a 40 wt % solution of dimethylamine was added dropwise in water (5.66 mL, 44.8 mmol), and the reaction mixture was stirred at room temperature overnight. Volatiles were removed under vacuum, and residual water was removed by lyophilization to give PC-thiol **8** as a brown solid in 66% yield.

^{1}H NMR ($CDCl_3$, 300 MHz): δ ($CHCl_3$ = 7.26 ppm) 4.24 (2H, m), 3.83 (2H, m), 3.67 (2H, m), 3.25 (9H, s), 2.67 (2H, m), 1.64 (4H, m), 1.30 (16H, m).

Nanoparticle Formation using Azide-Alkyne Cycloaddition with 1,8-Diazido-3,6-dioxaoctane and p(AVL-b-PgVL) 5

Nanoparticles were obtained using three concentrations of alkyne in the reaction mixture: 0.00362, 0.0544, and 0.215 M. The general procedure was as follows: *p*(AVL-*b*-PgVL) **5** and 1,8-diazide-3,6-dioxaoctane (0.5 equiv with respect to alkyne) were dissolved in dry, degassed dichloromethane. Copper(I) bromide (1.0 equiv with respect to alkyne) and PMDETA (2.0 equiv with respect to alkyne) were added, and the solution is stirred at room temperature, under a nitrogen atmosphere, overnight. The nanoparticles were isolated by dialysis in dichloromethane/MeOH (1:1 v/v; MWCO = 6000–8000).

^{1}H NMR ($CDCl_3$, 300 MHz): δ ($CHCl_3$ = 7.26 ppm) 7.45 (1H, br m), 5.70 (1H, m), 5.04 (2H, m), 4.49 (4H, m), 4.06 (2H, br m), 3.62 (4H, m), 3.54 (4H, m), 2.80 (3 H, br m), 2.36 (1H, br m), 1.61 (22H, m).

Thiol-ene Modification of Nanoparticles

Both thermal and photoinitiated thiol-ene reactions[8] were used to further modify the *p*(AVL-*b*-PgVL) crosslinked nanoparticles. Thermal reactions were carried out in the presence of AIBN at 80 °C in DMF. Photoinitiated reactions used DMPA as the initiator and were conducted at room temperature, irradiating at 365 nm in DMF.

Dodecanethiol Addition. To a degassed solution of *p*(AVL-*b*-PgVL) nanoparticles in anhydrous DMF (just enough to dissolve the polymer), dodecanethiol (5.0 equiv with respect to alkene) and AIBN (0.5 equiv with respect to alkene) were added, and the mixture was stirred at 80 °C overnight. The reaction mixture was transferred to a Spectra/Por® dialysis membrane (MWCO = 6000–8000) and dialyzed against dichloromethane/MeOH (1:1 v/v) overnight.

^{1}H NMR ($CDCl_3$, 300 MHz): δ ($CHCl_3$ = 7.26 ppm) 7.45 (1H, br m), 5.70 (1H, m), 5.04 (2H, m), 4.49 (4H, m), 4.06 (2H, br m), 3.62 (4H, m), 3.54 (4H, m), 2.80 (3 H, br m), 2.51 (2H, t), 2.36 (1H, br m), 1.61 (22H, m), 0.883 (3H, s).

PC-Thiol Reactions. To a degassed solution of *p*(AVL-*b*-PgVL) nanoparticles in anhydrous DMF (just enough to dissolve), PC-thiol (1.57 equiv with respect to alkene) was added in a small amount of degassed methanol (just enough to dissolve) and DMPA (0.2 equiv with respect to alkene), and the mixture was stirred overnight at room temperature under a UVP Black Ray UV bench lamp, which emits at ~365 nm. The crude reaction mixture was transferred to a Spectra/Por® dialysis membrane (MWCO = 6000–8000) and dialyzed against methanol overnight.

^{1}H NMR ($CDCl_3$, 300 MHz): δ ($CHCl_3$=7.26 ppm) 7.45 (1H, br m), 5.70 (1H, m), 5.04 (2H, m), 4.49 (4H, m), 4.24 (2H, m), 4.06 (2H, br m), 3.83 (2H, m), 3.62 (4H, m), 3.67 (2H, m), 3.54 (4H, m), 3.25 (9H, s), 2.80 (3 H, br m), 2.67 (2H, m), 2.36 (1H, br m), 1.61 (26H, m), 1.30 (16H, m).

Rhodamine Thiol Reactions. To a degassed solution of *p*(AVL-*b*-PgVL) nanoparticles in anhydrous DMF (just enough to dissolve the polymer), rhodamine thiol and DMPA (0.2 equiv with respect to alkene) were added, and the mixture was stirred overnight at room temperature under a UVP Black Ray UV bench lamp, which emits at ~365 nm. The crude reaction mixture was transferred to a Spectra/Por® dialysis membrane (MWCO = 6000–8000 g mol^{-1}) and dialyzed against dichloromethane/MeOH (1:1 v/v) overnight.

Orthogonal CuAAC and Thiol-ene Reactions on p(PgCL-b-AVL)

CuAAC: *p*(PgCL-*b*-AVL) and m-PEG$_{750}$-N$_3$. Diblock copolyester *p*(PgCL-*b*-AVL) (430 mg, 1.57 mmol alkyne) and m-PEG750-azide (0.889 g, 1.15 mmol) were suspended in a solution of water/THF (1:4 v/v, 10 mL). Sodium ascorbate (79 mg, 0.40 mmol) and copper(II) sulfate (50 mg, 0.20 mmol) were added and the reaction mixture was stirred at 80 °C for 15 h under N_2. The organic solvent was removed under reduced pressure. Excess *m-PEG$_{750}$-N$_3$* was removed by dialyzing against dichloromethane for 3 days (MWCO 10 kDa). To remove trace copper, the crude product was suspended in 20 mL deionized water and treated with Cuprisorb™ until the suspension become light yellow. The product was isolated by lyophilization as a slightly yellow, hydroscopic powder (1.11g, 90.6%).

GPC (THF, polystyrene standard) M_n = 2.48 × 10^4 g mol^{-1}; PDI = 1.09. ^{1}H NMR ($CDCl_3$, 300 MHz): δ ($CHCl_3$ = 7.26 ppm) 7.44 (s, 1H, R_2C=C*H* triazole), 5.66 (m, 1H, CH_2=C*H*), 4.98 (m, 2H, C*H*$_2$=CH), 4.43 (m, 2H, R_2NCH_2), 3.95 (m, 4H, CH_2OC=O, lactones), 3.78 (m, 2H, $R_2NCH_2CH_2$), 3.58 (br m, 70H, $CH_2CH_2O_{PEG}$), 3.32 (s, 3H, CH_{3PEG}), 2.92 (m, 1H, $CHC=O_{PgCL}$), 2.76 (m, 2H, $CH_2C=C_{PgCL}$), 2.10–2.45 (m, 3H, $CHC=O_{AVL}$ + $CH_2C=CH_2$), 1.56 (m, 8H, $CH_2CH_2CH_2O_{PgCL}$ + $CH_2CH_2O_{AVL}$), 1.28 (br m, 2H, $CH_2CH_2CH_2O_{PgCL}$). ^{13}C NMR ($CDCl_3$, 75MHz) δ ($CHCl_3$ = 77.16 ppm) 175.11 (*C*=O), 144.95 (triazole R_2C=CR), 135.11 (*C*=CH_2), 122.70 (R_2C=*C*R triazole), 117.07 (C=*C*H$_2$), 71.9 (*C*H$_2$O$_{PEG}$CH$_3$), 70.6 (*C*H$_2$CH$_2$O$_{PEG}$), 69.6 ($R_2NCH_2CH_2O$), 64.2 (*C*H$_2$O$_{PgCL}$), 64.0 (*C*H$_2$O$_{AVL}$), 59.0 (*C*H$_{3PEG}$), 50.1 ($R_2NCH_2CH_2O$), 45.4 (*C*HC=O$_{PgCL}$), 44.8 (*C*HC=O$_{AVL}$), 36.5 (*C*H$_2$C=C), 31.5 (*C*H$_2$CR=CR$_{2PgCL}$), 28.5 (*C*H$_2$CH$_2$CO$_{PgCL}$), 28.0 (CH*C*H$_{2AVL}$), 26.5 (CHCH$_2$*C*H$_{2AVL}$), 23.5 (C=OCHCH$_2$*C*H$_{2PgCL}$).

Thiol-ene Addition of Dodecanthiol to *p*[(PgCL-*g*-PEG$_{750}$)-*b*-(AVL)]. *p*[(PgCL-*g*-PEG$_{750}$)-*b*-(AVL)] (310 mg, 0.260 mmol alkene), 2,2′-dimethoxy-2-phenylacetonphenone (7.4 mg, 0.029 mmol), and dodecanethiol (0.14 mL, 0.58 mmol) were added to a vial equipped with a magnetic stir bar. DMF (0.58 mL) was added, and the vial was sealed with a rubber septum. The reaction mixture was degassed via four freeze–pump–thaw cycles and irradiated at 365 nm for 8 h at room temperature. The reaction mixture was precipitated into hexane. Upon the removal of solvent and drying under vacuum overnight, the modified polymer (300 mg, 82%) was isolated as a slightly yellow, waxy solid.

GPC (THF, Psty standard) $M_n = 4.11 \times 10^4$ g mol^{-1}; PDI = 1.17. ^{1}H NMR ($CDCl_3$, 300 MHz): δ ($CHCl_3$ = 7.26 ppm) 7.43 (s, 1H, $R_2C{=}CH$ triazole), 4.45 (m, 2H, R_2NCH_2), 3.98 (m, 4H, $CH_2OC{=}O$, lactones), 3.81 (m, 2H, $R_2NCH_2CH_2$), 3.60 (br m, 70H, $CH_2CH_2O_{PEG}$), 3.34 (s, 3H, CH_{3PEG}), 2.92 (m, 1H, $CHC{=}O_{PgCL}$), 2.76 (m, 2H, $CH_2C{=}C$), 2.44 (br m, 4H, $CH_2CH_2SCH_2(CH_2)_{11}CH_3$), 2.31 (br m, 1H, $CHC{=}O_{AVL}$), 1.4–1.9 (m, 14H, $CH_2CH_2CH_2SCH_2CH_2(CH_2)_9CH_3$ + $CH_2CH_2CH_2$-O_{PC} + $CH_2CH_2O_{AVL}$), 1.28 (br, 20H, $CH_2CH_2CH_2O_{PgCL}$ + $SCH_2CH_2(CH_2)_9CH_3$), 0.80 (br, 3H, $SCH_2CH_2(CH_2)_9CH_3$). ^{13}C NMR $CDCl_3$, 75 MHz) δ ($CHCl_3$ = 77.16 ppm) 175.2 ($C{=}O_{AVL}$), 175.1 ($C{=}O_{PgCL}$), 144.9 ($R_2C{=}CR$), 122.70 ($R_2C{=}CR$), 71.9 ($CH_2O_{PEG}CH_3$) , 70.6 ($CH_2CH_2O_{PEG}$), 69.6 ($R_2NCH_2CH_2O$), 64.2 (CH_2O_{PgCL}), 64.0 (CH_2O_{AVL}), 59.0 (CH_{3PEG}), 50.1 ($R_2NCH_2CH_2O$), 45.4 ($CHC{=}O_{PgCL}$), 44.8 ($CHC{=}O_{AVL}$), 32.2 (CH_2SCH_2), 32.1 (CH_2SCH_2), 31.9 ($S(CH_2)_9CH_2CH_2CH_3$), 31.5 ($CH_2CR{=}CR_{2PgCL}$), 29.6 ($S(CH_2)_3(CH_2)_5(CH_2)_3CH_3$), 29.6 ($CH_2(CH_2)_2S(CH_2)_{11}CH_3$), 29.4 ($S(CH_2)_2CH_2(CH_2)_5CH_2(CH_2)_2CH3$), 29.0 ($SCH_2CH_2(CH_2)_9$-$CH_3$), 28.6 ($CH_2CH_2CO_{PgCL}$), 28.0 ($CHCH_{2AVL}$), 27.3 ($CH_2CH_2$-$S(CH_2)_{11}CH_3$), 26.6 ($CHCH_2CH_{2AVL}$), 23.5 ($C{=}OCHCH_2CH_{2PgCL}$), 22.7 ($S(CH_2)_{10}CH_2CH_3$), 14.14 ($S(CH_2)_{11}CH_3$).

Simultaneous Thiol-ene/yne: p(AVL-b-PgVL) 5 and Dodecanethiol

To a solution of *p*(AVL-*b*-PgVL) **5** (0.50 g, 3.6 mmol alkyne + alkene) in degassed dimethylformamide (30 mL), dodecanethiol (3.64 g, 18.0 mmol) and AIBN (0.29 g, 1.80mmol) were added, and the mixture was heated at 80 °C for 3 h. The crude reaction mixture was transferred to a dialysis membrane (MWCO = 6000–8000) and dialyzed against dichloromethane for 2 days to yield the product as a slightly yellow oil.

^{1}H NMR ($CDCl_3$, 300 MHz): δ ($CHCl_3$ = 7.26 ppm), 4.08 (m, 4H, $CH_2OC{=}O$), 2.48 (t, 2H, dodecanethiol), 2.2–2.6 (br m, 6H, $CHC{=}O$ + $CH_2C{\equiv}CH$ + $CH_2CH{=}CH_2$), 1.66 (m, 10H, $CHCH_2CH_2CH_2O$ AVL + $CHCH_2CH_2CH_2O$ PgVL + dodecanethiol), 1.25 (m, 20H, dodecanethiol), 0.874 (t, 3H, dodecanethiol).

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