Supporting Information

for

Construction of a Reactive Diblock Copolymer, Polyphosphoester-*block*-Poly(L-lactide), as a Versatile Framework for Functional Materials that are Capable of Full Degradation and Nanoscopic Assembly Formation

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EXPERIMENTAL SECTION:

Materials

3-Bytyn-1-ol, 3-mercaptopropionic acid, 2-aminoethanethiol, 2,2-dimethoxy-2-phenylacetophenone (DMPA), dimethyl sulfoxide (DMSO), diethyl ether and benzoic acid were used as received from Sigma-Aldrich Co. 2-chloro-2-oxo-1,3,2-dioxaphospholane (COP, 95%) was used as received from Thermo Fisher Scientific Inc. Benzyl alcohol and 1,8-diazabicyclo[5,4,0]undec-7-ene (DBU) were purchased from Sigma-Aldrich Co. and distilled from calcium hydride prior to use. L-lactide (98%, Alfa Aesar) was purified and dried by azeotropic distillation in toluene three times. The dried L-lactides were stored in an argon-filled glove box. Tetrahydrofuran (THF) and dichloromethane (CH_2Cl_2) were dried through columns (J. C. Meyer Solvent Systems, Inc.). Spectra/Pro® membranes (MWCO 12−14 kDa, Spectrum Medical Industries, Inc. were used for dialysis.

Instrumentation

^1H, ^{13}C, and ^{31}P NMR spectra were recorded on Inova 300 MHz spectrometers interfaced to a UNIX computer using VnmrJ software. Chemical shifts were referenced to solvent resonance signals.

The DMF gel permeation chromatography (GPC) was conducted on a Waters Chromatography, Inc. (Milford, MA) system equipped with an isocratic pump model 1515, a differential refractometer model 2414, and a four-column set of 5 µm Guard (50 x 7.5 mm), Styragel HR 4 5 µm DMF (300 x 7.5 mm), Styragel HR 4E 5 µm DMF (300 x 7.5 mm), and Styragel HR 2 5 µm DMF (300 x 7.5 mm). The system was equilibrated at 70 °C in pre-filtered DMF containing 0.05 M of LiBr, which served as polymer solvent and eluent (flow rate set to 1.00 mL/min). Polymer solutions were prepared at a concentration of *ca.* 5 mg/mL and an injection volume of 200 µL was used. Data collection and analysis were performed with Empower 2 v. 6.10.01.00 software (Waters, Inc.). The system was calibrated with polystyrene standards (Polymer Laboratories, Amherst, MA) ranging from 615 to 442,800 Da.

Thermogravimetric analysis (TGA) was performed under N_2 atmosphere using a Mettler-Toledo model TGA/SDTA851e, with a heating rate of 10 °C/min and cooling rate of 5 °C/min. Measurements were analyzed using Mettler-Toledo Star^e v. 7.01 software.

Glass transition temperatures (T_g) were measured by differentia scanning calorimetry (DSC) on a Mettler-Toledo DSC822® (Mettler-Toledo, Inc., Columbus, OH), with a heating rate of 10 °C/min. Measurements were analyzed using Mettler-Toledo Star^e v. 7.01 software. The T_g was taken as the midpoint of the inflection tangent, upon the third heating scan.

Dynamic light scattering (DLS) measurements were conducted using Delsa Nano C (Beckman Coulter, Inc., Fullerton, CA) equipped with a laser diode operating at 658 nm. Size measurements were made in nanopure water (n = 1.3329, □ = 0.890 cP at 25 − 1 °C). Scattered light was detected at 165° angle and analyzed using a log correlator over 70 accumulations for a 3.0 mL sample in a glass sizing cell (4.0 mL capacity). The samples in the glass sizing cell were equilibrated for 30 min before measurements were made. The photomultiplier aperture and the attenuator were automatically adjusted to obtain a photon counting rate of *ca.* 10 kcps. Calculation of the particle size distribution and distribution averages was performed using COTIN particle size distribution analysis routines. The peak averages of histograms from number distributions out of 70 accumulations were reported as the average diameters of the particles.

Transmission electron microscopy (TEM) images were collected on a JEOL 1200EX operating at 100 kV and micrographs were recorded at calibrated magnifications using a SIA-15C CCD camera. The samples as aqueous solutions (5 µL) were deposited onto carbon-coated copper grids. Excess sample was wicked off using filter paper and the grids were allowed to dry in air for 1 min. Following that, the grids were stained with 5 µL of a 2% uranyl acetate aqueous solution. Excess stain was wicked off using filter paper after 20 seconds. The sample grids were dried under vacuum overnight before analysis.

The zeta potential values of the nanoparticles were determined by Delsa Nano C particle analyzer (Beckman Coulter, Fullerton, CA) equipped with a 30 mW dual laser diode (658 nm). The zeta potential of the particles in suspension was obtained by measuring the electrophoretic movement of charged particles under an applied electric field. Scattered light was detected at a 30° angle at 25 °C. The zeta potential was measured at five regions in the flow cell and a weighted mean was calculated. These five measurements were used to correct for electroosmotic flow that was induced in the cell due to the surface charge of the cell wall. All determinations were repeated six times.

Synthesis of Butynyl Phospholane (BYP) Monomer

A solution of 2-chloro-2-oxo-1,3,2-dioxaphospholane (COP, 15.0 g, 105 mmol) in 50 mL of anhydrous THF was added dropwise to a stirred solution of 3-butyn-1-ol (8.12 g, 116 mmol) and triethylamine (11.7 g, 116 mmol) in 200 mL of anhydrous THF at 0 °C. The reaction mixture was allowed to stir for 11 h. The reaction mixture was filtered and the filtrate was concentrated vial rotary evaporator. The filtrate was distilled under reduced pressure to obtain a faint yellow and viscous liquid (110–120 °C, 0.5 mmHg) with a yield of 52.3%. IR: 3330–3170, 3050–2870, 1474, 1283, 1009, 926, 835, 756 cm^{-1}. ^{1}H NMR ($CDCl_3$, ppm): δ 4.50–4.31 (m, 4H, $POCH_2CH_2OP$), 4.21 (dt, *J* = 9.3 Hz, *J* = 6.9 Hz, 2H, $POCH_2CH_2C$), 2.59 (ddt, *J* = 6.9 Hz, 2.7 Hz, 0.3 Hz, 2H, $POCH_2CH_2C$), 2.02 (t, *J* = 2.7 Hz, 1H, $POCH_2CH_2CCH$). ^{13}C NMR ($CDCl_3$, ppm): δ 79.21, 70.58, 66.38, 66.12, 20.78. ^{31}P NMR ($CDCl_3$, ppm): δ 17.34. +ESI MS: calculated $[M+H]^+$ for $C_6H_9O_4P$: 177.0317, found: 177.0311.

General Procedure of Kinetic Study of Homopolymerization of BYP *via* ROP

In a glove box, a solution of BYP (0.608 g, 3.45 mmol) and benzyl alcohol (7.37 mg, 0.0682 mmol) in anhydrous CH_2Cl_2 (0.6 mL) was transferred into a 5 mL shell vial with a stir bar. DBU (20.8 mg, 0.137 mmol) was injected into the mixture solution. 0.05 mL of samples were extracted at 2, 3, 5, 7, 9 and 10 min and quenched by addition of solution of benzoic acid in CH_2Cl_2. Conversion of monomer to polymer was calculated by ^{31}P NMR spectroscopy.

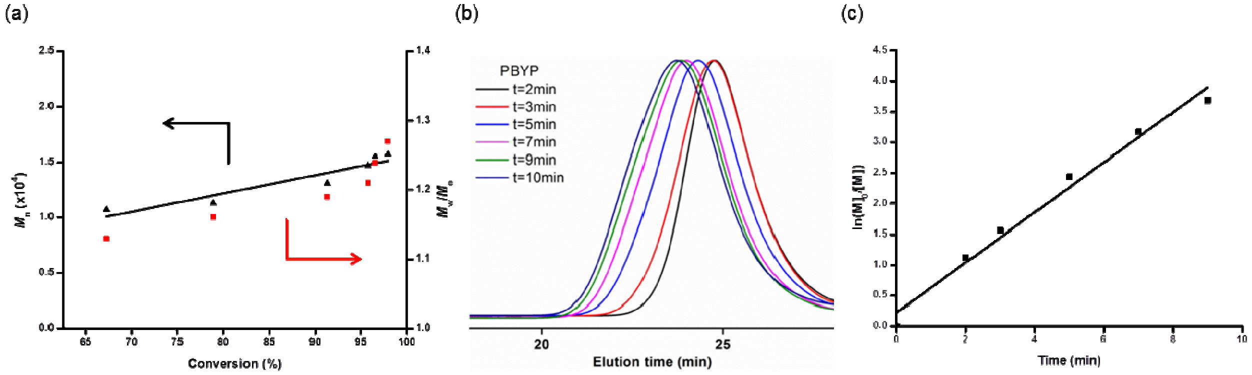

Figure S1. (a) Kinetic plots of M_n and M_w/M_n *vs.* monomer conversion in ROP of BYP, obtained from GPC analysis. (b) GPC traces as a function of polymerization time. (c) Pseudo-first-order kinetic plots of $\ln([M]_0/[M])$ *vs.* time, obtained from ^{31}P NMR spectroscopy data. Conditions: [BYP] = 5.7 M in CH_2Cl_2, [BYP] : [BnOH] : [DBU] = 50 : 1. : 2.

General Procedure of Kinetic Study of Second-block (PLLA) Polymerization *via* ROP

In a glove box, a solution of BYP (0.504 g, 2.86 mmol) and benzyl alcohol (6.14 mg, 0.0568 mmol) in anhydrous CH_2Cl_2 (0.5 mL) was transferred into a 20 mL vial with a stir bar. DBU (17.3 mg, 0.114 mmol) was injected into the mixture solution. After stirring for 7 min of polymerization, a solution of LLA (409 mg, 2.86 mmol) in anhydrous CH_2Cl_2 (3.5 mL) was added into the mixture solution. Then, 0.1 mL of samples were extracted at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, and 4 min and quenched by addition of solution of benzoic acid in CH_2Cl_2. Conversion of monomer, LLA, to polymer was calculated by ^{1}H NMR spectroscopy.

One-pot Sequential Block Copolymerization of BYP and LLA, $PBYP_{49}$-*b*-$PLLA_{44}$

In a glove box, a solution of BYP (3.02 g, 17.2 mmol) and benzyl alcohol (37.0 mg, 0.340 mmol) in anhydrous CH_2Cl_2 (3.0 mL) was transferred into a vial with a stir bar. DBU (104 mg, 0.682 mmol) was injected into the mixture solution. After stirring for 7 min, a solution of LLA (2.46 g, 17.0 mmol) in anhydrous CH_2Cl_2 (21 mL) was added into the mixture solution. After 4 min, the reaction was quenched by addition of solution of benzoic acid in CH_2Cl_2. The product was precipitated in diethyl ether three times and dried overnight in vacuum. 4.9787 g (97.6% yield). GPC: M_n = 21,900 g/mol, PDI = 1.17. IR: 3350–3150, 3050–2850, 1757, 1456, 1271, 1211, 1184, 1130, 1074, 1009, 970, 804 cm^{-1}. ^{1}H NMR (CD_2Cl_2, ppm): δ 7.42–7.30 (m, 5H, aromatic ring), 5.16 (broad q, *J* = 7.2 Hz, 100H, $ArCH_2OP$ and $OCCH(O)CH_3$), 4.34–4.22 (b, 196H, $POCH_2CH_2O$), 4.22–4.08 (b, 98H, $POCH_2CH_2CCH$), 2.67–2.56 (b, 98H, $POCH_2CH_2CCH$), 2.28–2.09 (b, 49H, OCH_2CH_2CCH), 1.55 (broad d, *J* = 7.2 Hz, 264H, $CH_3CH(O)CO$). ^{13}C NMR (CD_2Cl_2, ppm): δ 170.02, 130.07, 129.16, 128.57, 80.28, 71.00, 69.53, 67.00, 66.27, 21.06, 17.02. ^{31}P NMR (CD_2Cl_2, ppm): δ -1.60. DSC: (T_g) = -33.23 °C. TGA in N_2: 190-290 °C, 40% mass loss; 290–370 °C, 42% mass loss; 12% mass remaining above 370 °C.

Thiol-yne "Click" Reaction of PBYP Block of PBYP$_{49}$-*b*-PLLA$_{44}$ with 3-Mercaptopropionic Acid

A solution of block copolymer, PBYP$_{49}$-*b*-PLLA$_{44}$ (149 mg, 0.00990 mmol), 3-mercaptopropionic acid (524 mg, 4.93 mmol), and 2,2-dimethoxy-2-phenylacetophenone (215 mg, 0.840 mmol) in 7.5 mL of dimethyl sulfoxide was irradiated under UV irradiation (365 nm, 6 W) for 90 min while stirring. The reaction mixture was purified by precipitated in diethyl ether three times, dialyzed in nanopure water and freeze-dried overnight to give a white solid. (189 mg, 75.1% yield). IR: 3675–2760, 2700–2430, 1757, 1715, 1452, 1408, 1385, 1184, 1130, 1086, 1016, 982, 802, 754 cm^{-1}. ^{1}H NMR (DMSO, ppm): δ 13.2–11.9 (b, $\mathrm{SCH_2CH_2C(O)O}\mathit{H}$), 7.44–7.26 (m, 5H, aromatic ring), 5.46 (d, *J* = 6.9 Hz, 2H, $\mathrm{OC}\mathit{H}_2\mathrm{Ar}$), 5.20 (broad q, *J* = 7.2 Hz, 88H, $\mathrm{OCC}\mathit{H}\mathrm{(O)CH_3}$), 4.35–3.80 (b, 294H, $\mathrm{POC}\mathit{H}_2\mathrm{C}\mathit{H}_2\mathrm{O}$ and $\mathrm{POC}\mathit{H}_2\mathrm{CH_2CH}$), 3.00–2.80 (b, 196H, $\mathrm{SCH_2C}\mathit{H}_2\mathrm{COOH}$), 2.80–2.62 (b, 245H, $\mathrm{SC}\mathit{H}_2\mathrm{CH_2COOH}$ and $\mathrm{SC}\mathit{H}\mathrm{(CH_2)CH_2CH_2}$), 2.60–2.50 (b, 98H, $\mathrm{SC}\mathit{H}_2\mathrm{CHS}$), 2.25–2.05 and 1.85–1.57 (b, 98H, $\mathrm{POCH_2C}\mathit{H}_2\mathrm{CH}$), 1.46 (broad d, *J* = 7.2 Hz, 264H, $\mathrm{OCCH(O)C}\mathit{H}_3$). ^{13}C NMR (DMSO, ppm): δ 173.05, 172.19, 169.27, 68.72, 66.25, 65.34, 44.05, 42.91, 41.67, 38.19, 37.54, 34.73, 34.18, 33.53, 29.71, 27.18, 26.09, 25.22, 16.53. ^{31}P NMR (DMSO, ppm): δ -1.19. DSC: (T_g) = 6.34 °C. TGA in N_2: 105–190 °C, 13% mass loss; 190–280 °C, 40% mass loss; 280–350 °C, 25% mass loss; 22% mass remaining above 350 °C.

Thiol-yne "Click" Reaction of PBYP Block of PBYP$_{49}$-*b*-PLLA$_{44}$ with 2-Aminoethanethiol

A solution of block copolymer, PBYP$_{49}$-*b*-PLLA$_{44}$ (150 mg, 0.0995 mmol), 2-aminoethanethiol (0.554 g, 4.88 mmol), and 2,2-Dimethoxy-2-phenylacetophenone (250 mg, 0.975 mmol) in 7.5 mL of dimethyl sulfoxide was irradiated under UV irradiation (365 nm, 6 W) for 90 min. The reaction mixture was purified by precipitated in diethyl ether four times, dialyzed in nanopure water at pH 3 and freeze-dried overnight to give a white solid. (220 mg, 83.8% yield). IR: 3600–3300, 3250–2470, 1755, 1604, 1454, 1250, 1184, 1084, 1013, 806, 754 cm^{-1}. ^{1}H NMR (DMSO, ppm): δ 8.60–7.95 (b, $\mathrm{SCH_2CH_2N}\mathit{H}_3^+$), 7.46–7.42 (m, 5H, aromatic ring), 5.46 (d, *J* = 6.9, 2H, $\mathrm{OC}\mathit{H}_2\mathrm{Ar}$), 5.20 (broad q, *J* = 7.2 Hz, 88H, $\mathrm{OCC}\mathit{H}\mathrm{(O)CH_3}$), 4.40–3.85 (b, 294H, $\mathrm{POC}\mathit{H}_2\mathrm{C}\mathit{H}_2\mathrm{O}$ and $\mathrm{POC}\mathit{H}_2\mathrm{CH_2CH}$), 3.45–3.33 (b, 196H, $\mathrm{SCH_2C}\mathit{H}_2\mathrm{NH_3^+}$), 3.20–2.75 (b, 343H, $\mathrm{SC}\mathit{H}_2\mathrm{C}\mathit{H}\mathrm{SC}\mathit{H}_2\mathrm{CH_2NH_3^+}$), 2.30–2.15 and 1.90–1.66 (b, 98H, $\mathrm{POCH_2C}\mathit{H}_2\mathrm{CHS}$), 1.46 (broad d, *J* = 7.2 Hz, 264H, $\mathrm{OCCH(O)C}\mathit{H}_3$). ^{13}C NMR (DMSO, ppm): δ 169.21, 164.54, 68.69, 66.45, 65.16, 41.36, 36.96, 33.91, 33.39, 28.64, 26.79, 16.49. ^{31}P NMR (DMSO, ppm): δ -1.26. DSC: (T_g) = -7.49 °C. TGA in N_2: 190–350 °C, 74% mass loss; 26% mass remaining above 350 °C.

General Procedure for Self-assembly of Functional Diblock Copolymers

The functional anionic and cationic diblock copolymers (1.0 mg) were suspended into MOPS buffer (150 mM) at pH 7.4 and acetate buffer (150 mM) at pH 5.0.

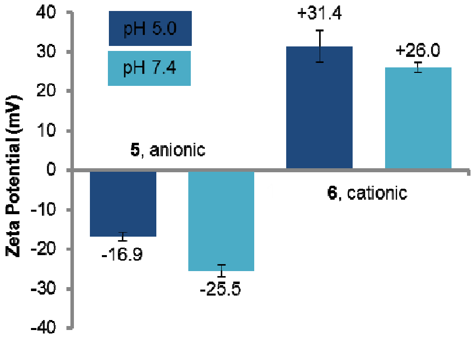

Figure S2. Zeta potential values of micelles, **5** and **6**, in MOPS buffer at pH 7.4 and acetate buffer at pH 5.0. The average values and their standard deviations were made from six-time measurements.