Electronic Supplementary Information

Synthesis of Fully Degradable Cationic Polymers with Various Topological Structures via Postpolymerization Modification by Using Thio-Bromo "Click" Reaction

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Materials. α-bromo-ε-caprolactone (CL-Br) was prepared according to the literature procedure[1]. ε-Caprolactone (CL), Propargyl alcohol (PA), Benzyl alcohol (BnOH, 99%, Aladdin), *N,N*-Dimethylformamide (DMF) and toluene were dried over calcium hydride and then distilled under reduced pressure prior to use. Diphenyl phosphate (DPP, 97%, Energy Chemical), Stannous octoate ($Sn(Oct)_2$), 97%, Alfa Aesar), azidotrimethylsilane (TMS-N_3, 93%, Aladdin), Tetrabutylammonium fluoride (TBAF, 1.0M in THF, Aladdin), 2-(dimethylamino)ethanethiol hydrochloride (DMAET, 95%, acros), Triethylamine (TEA, 99.5%, Aladdin), Copper sulfate pentahydrate ($CuSO_4 \cdot 5H_2O$, 99.8%, Macklin), Ascorbic acid (99%, Aladdin) were used as received without further purification.

Characterization Methods

^{1}H-NMR spectra were recorded by Bruker AVANCE III 400 MHz system.

Size Exclusion Chromatography (SEC) measurements were carried out on an Agilent SEC system equipped with a refractive index (RI) detector and a multi-angle laser light scattering detector using N,N-dimethylformamide (DMF) with 10 mM LiBr (50 ℃) as eluent at a flow rate of 1 mL/min. Polystyrene standards were used for the calibration.

Fourier-transform infrared (FT-IR) spectroscopy was performed on a Thermo Nicolet Nexus 6700 spectrometer and the samples were dissolved in THF and casted on a KBr plate.

The dynamic light scattering (DLS) measurements were performed using a

Malvern ZetaSizer and repeated three times at 25 ℃ with a scattering angle (θ) of 173°.

Matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) measurement was performed on a Ultraflextreme MALDI-TOF/TOF instrument (Bruker Daltonics, Germany) equipped with a 355 nm Nd:YAG laser in positive reflection or linear mode. Matrix：DCTB (trans-2-[3-(4-tert-butylphenyl)2-methyl-2-propenylidene]malononitrile).

To prepare the samples for transmission electron microscope (TEM) analysis, a micelle solution was dropped onto a carbon-coated copper grid and left until dry. TEM images were obtained under JEM 1400PLUS TEM operated at an accelerating voltage of 120 kV. The images were recorded by a digital camera.

General Procedures for Synthesis

Synthesis of P(CL-Br). P(CL-Br) was synthesized via the ring opening polymerization (ROP) of CL-Br using BnOH as the initiator. Typically, CL-Br (1.0 g, 5.19 mmol), BnOH (18.6 mg, 0.17 mmol) and $Sn(Oct)_2$ (14.0 mg, 0.03 mmol) were dissolved in anhydrous toluene (5 mL) in a round bottom flask, reaction at 110 ℃ for 3 hours under nitrogen protection. The polymer was obtained by precipitating in excess cold methanol three times and dried to give 0.7 g of the product (yield 70.0%). The degree of polymerization (DP) was determined as $DP_{P(CL\text{-}Br)} = S_d/S_0 = 20$, where S_d and S_0 stand for the integrals of peak d and peak 0 at 3.56 ppm (the methylene protons adjacent to the hydroxyl group at polymer chain end) respectively in Figure 1B. ^{1}H-NMR ($CDCl_3$, ppm): 4.32-4.10 (-COCHBr- and -CH_2CH_2O-), 2.17-1.95 (-$CHBrCH_2CH_2$-), 1.78-1.30

(-$CH_2CH_2CH_2CH_2$-).

Synthesis of diblock copolymer PCL-*b*-P(CL-Br). PCL-*b*-P(CL-Br) was synthesized by sequential ROP of CL and CL-Br using BnOH as the initiator. First, CL (3.0 g, 26.31 mmol), BnOH (56.8 mg, 0.52 mmol) and DPP (131.6 mg, 0.52 mmol) were dissolved in anhydrous toluene (8.8 mL) in a round bottom flask, reaction at room temperature for 5 hours under nitrogen protection. The polymer was obtained by precipitating in excess cold methanol three times and dried to give 2.51 g of the product (yield 83.6%). The DP was determined as $DP_{PCL} = S_c/S_0 = 36$, where S_c and S_0 stand for the integrals of peak c and peak 0 at 3.65 ppm (the methylene protons adjacent to the hydroxyl group at polymer chain end) respectively in Figure S4. Then, the synthesized PCL_{36} was used as macroinitiator to initiate the ROP of CL-Br. CL-Br (1.0 g, 5.2 mmol), PCL_{36} (1.1 g, 0.26 mmol) and $Sn(Oct)_2$ (21.0 mg, 0.05 mmol) were dissolved in anhydrous toluene (5.5 mL) in a round bottom flask, and the reaction was carried out at 110 °C for 3 hours under nitrogen protection. The polymer was obtained by precipitating in excess cold methanol three times and dried to give 1.91 g of the product (yield 81.0%). The DP of the P(CL-Br) block was determined as $DP_{P(CL\text{-}Br)} = S_g/S_0 = 38$, where S_g and S_0 stand for the integrals of peak g and peak 0 at 3.66 ppm (the methylene protons adjacent to the hydroxyl group at polymer chain end) respectively in Figure 2B. By changing the ratio of monomer to initiator and reaction time, copolymers with varied DPs of P(CL-Br) block were achieved. ^{1}H-NMR ($CDCl_3$, ppm): 4.30-4.12 (-COCHBr- in P(CL-Br) and -CH_2CH_2O- in P(CL-Br)), 4.12-4.02 (-CH_2CH_2OOC- in PCL), 2.36-2.27 (-$OOCCH_2CH_2$- in PCL), 2.17-1.95 (-$CHBrCH_2CH_2$- in P(CL-Br)), 1.82-1.24 (-

$CH_2CH_2CH_2CH_2CH_2O$- in PCL and -$CH_2CH_2CH_2CH_2$- in P(CL-Br)).

Synthesis of backbone P(CL-N_3). Firstly, CL-Br (2.0 g, 10.4 mmol), BnOH (5.6 mg, 0.05 mmol) and $Sn(Oct)_2$ (4.2 mg, 0.01 mmol) were dissolved in anhydrous toluene (4 mL) in a a pre-dried reaction tube. After three cycles of freeze-pump-thaw, the tube was sealed under vacuum and placed at 110 ℃ for 10 hours with continuous stirring. The polymer was obtained by precipitating in excess cold methanol three times and dried to give 1.80 g of the product. Similarly, the DP was determined to be 188 by ^{1}H-NMR. After purification, the resulting polymer (0.5 g, 2.6 mmol bromine group) was dissolved in 10 mL THF, TMS-N_3 (1.49 g, 12.9 mmol) was added. TBAF (13.0 mL, 1M in THF, 12.9 mmol,) was added drop-wise over 10 min at 0 ℃. The mixture was stirred at 0 ℃ for 1 hours and then heating to 50 ℃ for 24 hours. The polymer was obtained by precipitating in excess cold ether three times and dried to give 0.32 g of the product (yield 80.0%). ^{1}H-NMR analysis ($CDCl_3$, ppm): 4.25-4.07 (-CH_3CH_2O-), 3.87-3.74(-N_3CHCH_2-), 1.95-1.13 (-$N_3CHCH_2CH_2CH_2CH_2O$-).

Synthesis of side chain ay-PCL-*b*-P(CL-Br). ay-PCL-b-P(CL-Br) was synthesized by sequential ROP of CL and CL-Br using propargyl alcohol (PA) as the initiator. First, CL (3.0 g, 26.3 mmol), PA (73.7 mg, 1.3 mmol) and DPP (328.9 mg, 1.3 mmol) were dissolved in anhydrous toluene (6 mL) in a round bottom flask, reaction at room temperature for 2 hours under nitrogen protection. The polymer was obtained by precipitating in excess cold methanol three times and dried to give 2.82 g of the product (yield 94.0%). The DP was determined to be 17 by ^{1}H-NMR. Then, the synthesized ay-PCL_{17} was used as macroinitiator to initiate the ROP of CL-Br. CL-Br (3.0 g, 15.5

mmol), ay-PCL_{17} (1.0 g, 0.5 mmol) and $Sn(Oct)_2$ (42.0 mg, 0.1 mmol) were dissolved in anhydrous toluene (16 mL) in a round bottom flask, and the reaction was carried out at 110 °C for 4 hours under nitrogen protection. The copolymer was obtained by precipitating in excess cold methanol three times and dried to give 3.47 g of the product (yield 82.3%). Similarly, the DP of the P(CL-Br) block was determined to be 25 by ^{1}H-NMR. ^{1}H-NMR ($CDCl_3$, ppm): 4.71 (-CCH_2CO-), 4.30-4.12 (-COCHBr- in P(CL-Br) and -CH_2CH_2O- in P(CL-Br)), 4.12-4.02 (-CH_2CH_2OOC- in PCL), 2.36-2.27 (-$OOCCH_2CH_2$- in PCL), 2.17-1.95 (-$CHBrCH_2CH_2$- in P(CL-Br)), 1.82-1.24 (-$CH_2CH_2CH_2CH_2CH_2O$- in PCL and -$CH_2CH_2CH_2CH_2$- in P(CL-Br)).

Synthesis of PCL-*g*-(PCL-*b*-P(CL-Br)) by CUAAC click chemistry. PCL-*g*-(PCL-*b*-P(CL-Br)) was prepared by coupling ay-PCL_{17}-*b*-$P(CL\text{-}Br)_{25}$ onto the above $P(CL\text{-}N_3)_{188}$ via a Cu-catalyzed alkyne-azide cycloaddition (CuAAC) coupling reaction. $P(CL\text{-}N_3)_{188}$ (11 mg, 0.066 mmol azide groups), ay-PCL_{17}-*b*-$P(CL\text{-}Br)_{25}$ (0.5 g, 0.073 mmol alkyne groups) and ascorbic acid (52.8 mg, 0.26 mmol) were dissolved in 5mL DMF in a Schlenk tube. Afterwards, 0.1 mL of toluene was added as an internal standard. Then the mixture was degassed by three cycles of freeze-pump-thaw followed by adding $CuSO_4 \cdot 5H_2O$ (6.7 mg, 0.026 mmol) quickly. The solution was frozen and another three pump-nitrogen cycles were carried out. After a reaction time of 15 hours at 50℃, SEC measurement was performed to determine the consumption of the side chains. The reaction mixture was passed through a neutral alumina column to remove the catalyst. The solution was concentrated and then fractionation was performed in mixture of diethyl ether and THF to remove excess side chains. The polymer was dried

to give 0.28 g of the product (yield 45.9%).

Modification of P(CL-Br) in copolymer by thio-bromo "click" reaction. A general procedure is given. $P(CL\text{-}Br)_{20}$ (0.5 g, 2.6 mmol bromine group), DMAET (0.54 g, 5.2 mmol) and TEA (0.52 g, 5.2 mmol) were dissolved in 10 mL DMF in a Schlenk tube, and the reaction mixture was degassed by three freeze-pump thaw cycles. The reaction mixture stirring under nitrogen protection for 30 min at room temperature and stopped by adding 20 mL dichloromethane into the flask. The filtrate was washed with saturated salt water (3 × 100 mL), dried over Na_2SO_4 , and the dichloromethane was removed by evaporation under reduced pressure. The product was dried at room temperature in a vacuum to give 0.38 g of product (yield 69.0%). The DP of P(CL-DMAET) is equal to that of P(CL-Br) because the reaction was quantitative. The same ratio of reactants (bromine group: DAETH: TEA = 1:2:2) and reaction time (0.5 h) were used for all polymer modifications. ^{1}H-NMR analysis ($CDCl_3$, ppm): 4.23-4.07 (-CH_2CH_2O-), 3.33-3.23 (-$SCHCH_2$-), 2.83-2.67 (-SCH_2CH_2N-), 2.61-2.48 (-SCH_2CH_2N-), 2.34-2.20 (-$CH_2N(CH_2)_2$), 1.99-1.85 (-$SCHCH_2CH_2$-), 1.70-1.24 (-$CH_2CH_2CH_2CH_2O$-).

Micelle preparation of PCL-*b*-P(CL-DMAET) diblock copolymer. 10 mg PCL-*b*-P(CL-DMAET) was dissolved in 1 ml DMF solution, and 10 ml neutral aqueous solution was added slowly with stirring. The mixed solution was allowed to stand for 30 min to stabilize after full emulsification, it was then transferred into a dialysis bag (Mw = 3500 Da) and dialyzed in neutral aqueous solution for 24 hours. The nanoparticles were characterized by DLS and TEM.

Supporting Figures

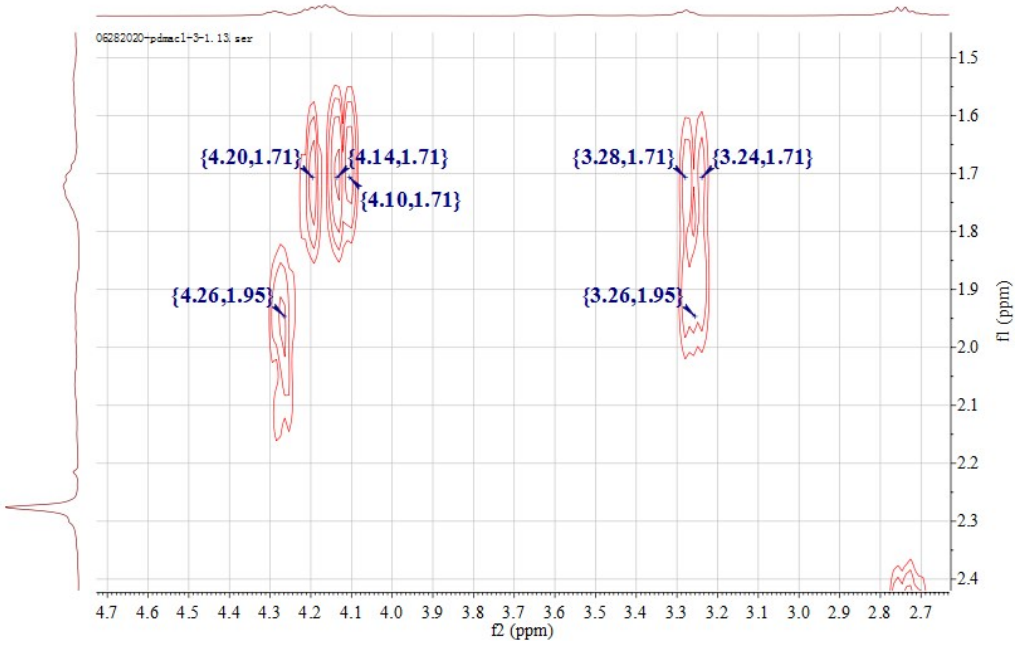


Figure S1. H-H correlation spectroscopy of P(CL-DMAET)$_{20}$. $CDCl_3$ was used as solvent for test.

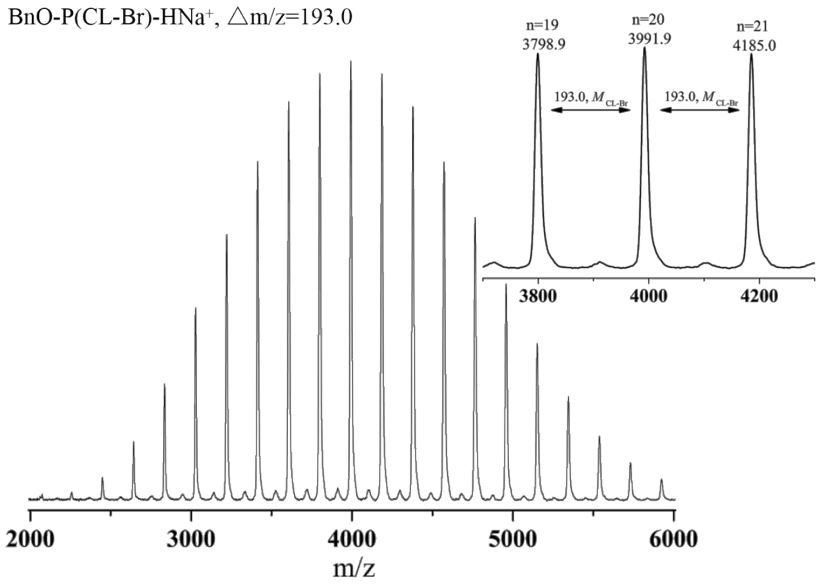


Figure S2. MALDI-TOF mass spectrum of P(CL-Br)$_{20}$. For example, the observed value *m/z* = 3991.9 agrees with the theoretical value of P(CL-Br) at DP of 20, 3991.9 = 193.04($M_{CL\text{-}Br}$)×20 + 108.14(M_{BnOH}) + 22.99(M_{Na^+}).

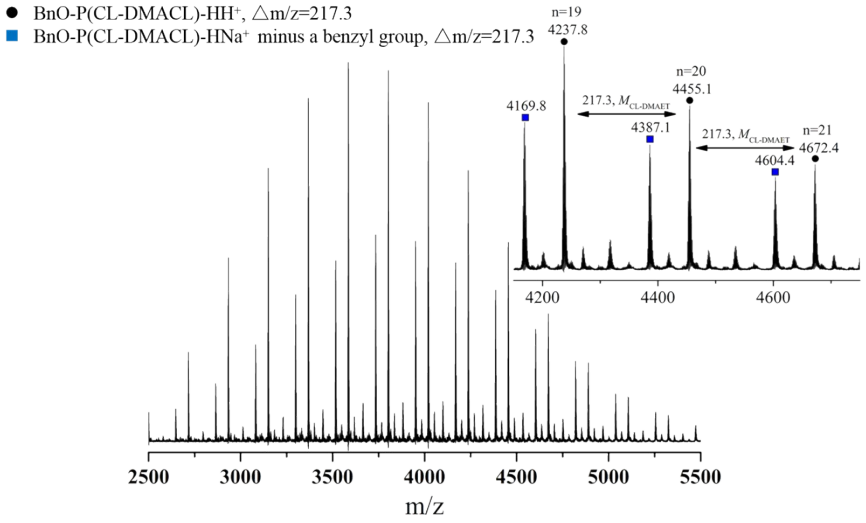


Figure S3. MALDI-TOF mass spectrum of $P(CL\text{-}DMAET)_{20}$. For example, the observed value $m/z = 4455.1$ agrees with the theoretical value of P(CL-DMAET) at DP of 20, $4455.1 = 217.3(M_{CL\text{-}DMAET}) \times 20 + 108.14(M_{BnOH}) + 1.00(M_{H^+})$, and $m/z = 4387.1$ corresponds to P(CL-DMAET) at DP of 20 with benzyl group cleaved off, $4387.1 = 217.3(M_{CL\text{-}DMAET}) \times 20 + 108.14(M_{BnOH}) - 91.1(M_{Benzyl}) + 1.00(M_H) + 22.99(M_{Na^+})$.

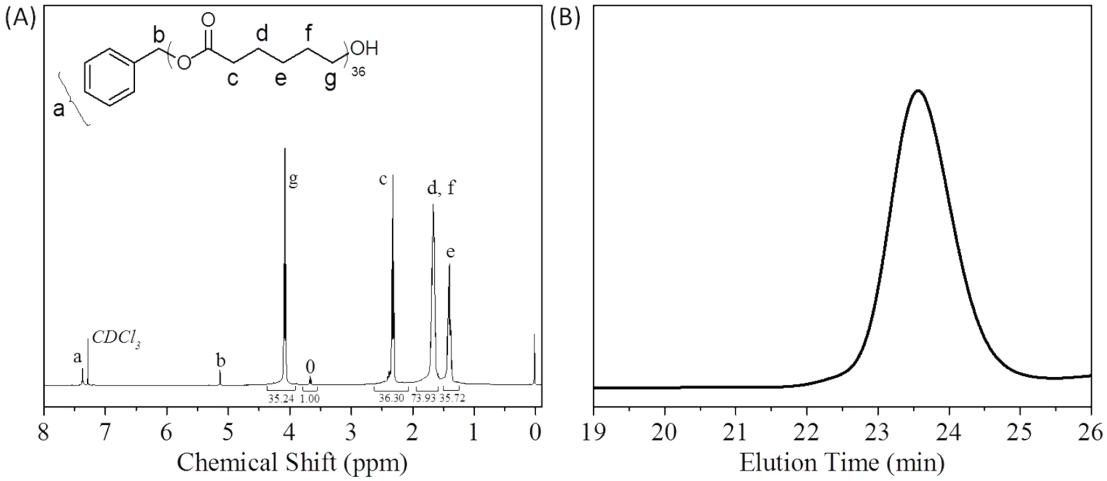


Figure S4. SEC traces (A) and ^1H NMR spectra (B) of PCL_{36}. Peak 0 corresponds to the methylene protons adjacent to the hydroxyl group at polymer chain end. $CDCl_3$ was used as solvent for ^1H NMR test, and DMF was used as eluent for SEC measurement (polystyrene as standard).

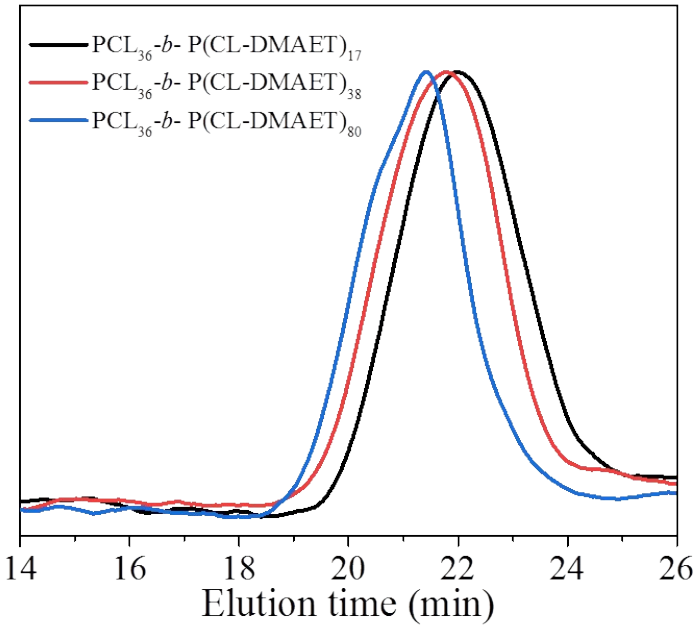


Figure S5. SEC traces of PCL_{36}-*b*-P(CL-DMAET)$_{17}$ (black line), PCL_{36}-*b*-P(CL-DMAET)$_{38}$ (red line) and PCL_{36}-*b*-P(CL-DMAET)$_{80}$ (blue line), DMF was used as eluent for SEC measurement (polystyrene as standard).

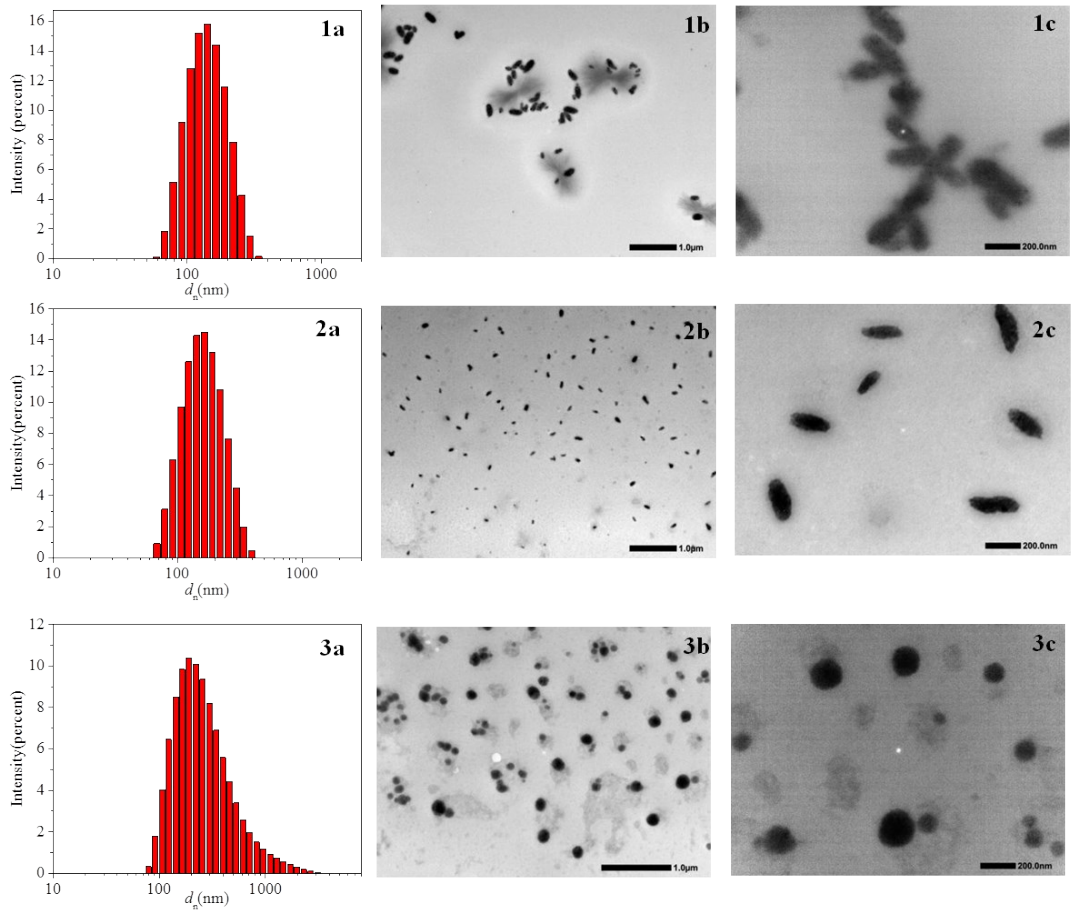


Figure S6. Size distribution measured by DLS: 1a, PCL_{36}-*b*-$P(CL\text{-}DMAET)_{17}$; 2a, PCL_{36}-*b*-$P(CL\text{-}DMAET)_{38}$; 3a, PCL_{36}-*b*-$P(CL\text{-}DMAET)_{80}$. TEM images of different micelles: PCL_{36}-*b*-$P(CL\text{-}DMAET)_{17}$, 1b (bar: 1.0 μm), 1c (bar: 200.0 nm); PCL_{36}-*b*-$P(CL\text{-}DMAET)_{38}$, 2b (bar: 1.0 μm), 2c (bar: 200.0 nm); PCL_{36}-*b*-$P(CL\text{-}DMAET)_{80}$, 3b (bar: 1.0 μm), 3c (bar: 200.0 nm).

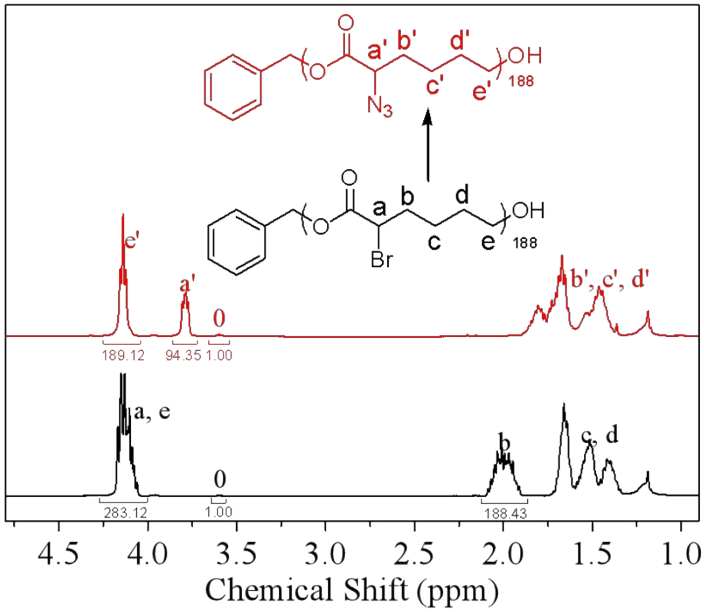


Figure S7. ^{1}H-NMR spectra of P(CL-Br)$_{188}$ (bottom, black line) and P(CL-N$_3$)$_{188}$ (top, red line). Peak 0 corresponds to the methylene protons adjacent to the hydroxyl group at polymer chain end. $CDCl_3$ was used as solvent for ^{1}H NMR test.

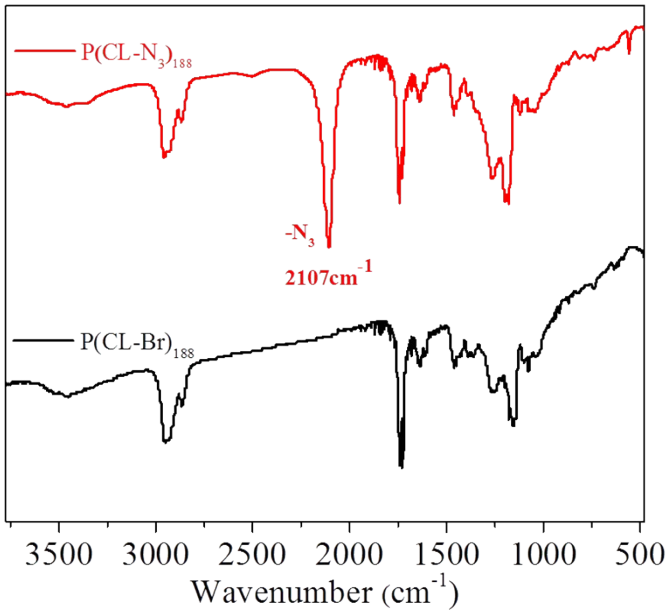


Figure S8. FT-IR spectra of P(CL-Br)$_{188}$ (bottom, black line) and P(CL-N$_3$)$_{188}$ (top, red line).

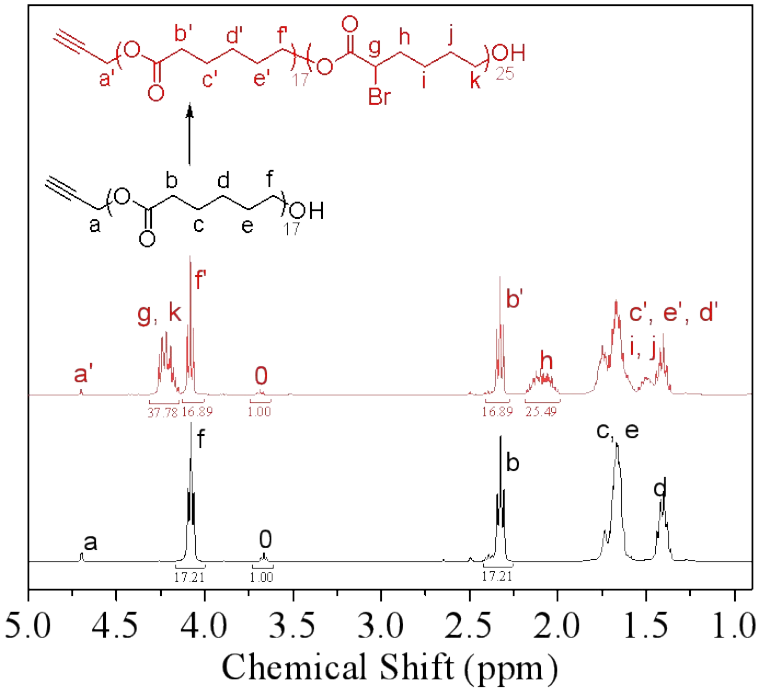


Figure S9. ^{1}H-NMR spectra of ay-PCL$_{17}$ (bottom, black line) and ay-PCL$_{17}$-*b*-P(CL-Br)$_{25}$ (top, red line). Peak 0 corresponds to the methylene protons adjacent to the hydroxyl group at polymer chain end. $CDCl_3$ was used as solvent for ^{1}H NMR test.

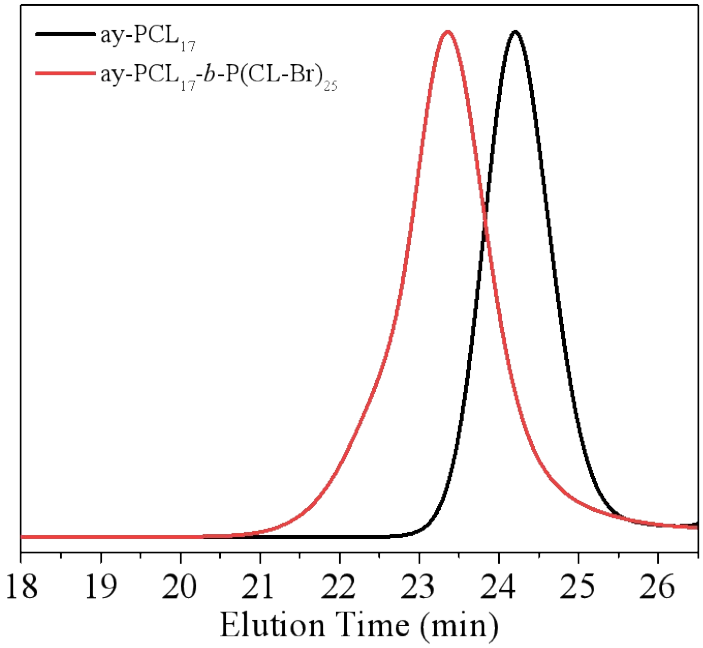


Figure S10. SEC traces of ay-PCL$_{17}$ (black line) and ay-PCL$_{17}$-*b*-P(CL-Br)$_{25}$ (red line), DMF was used as eluent for SEC measurement, polystyrene as standard.

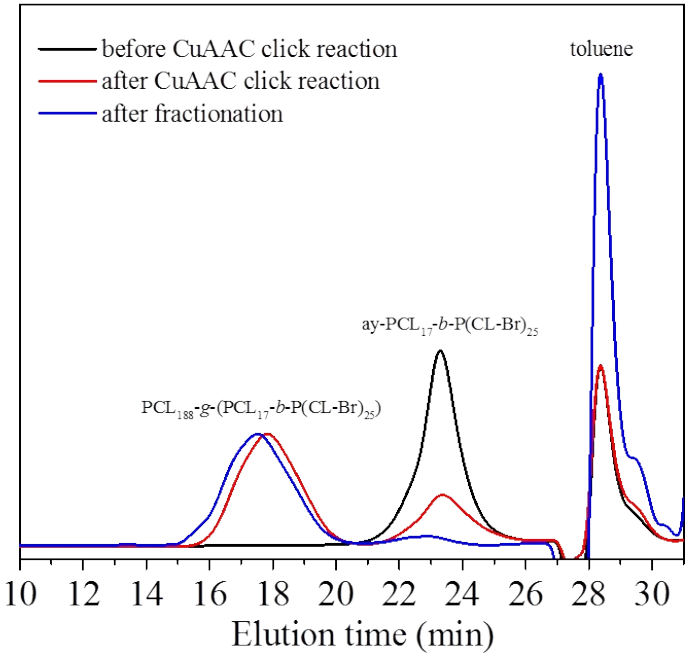
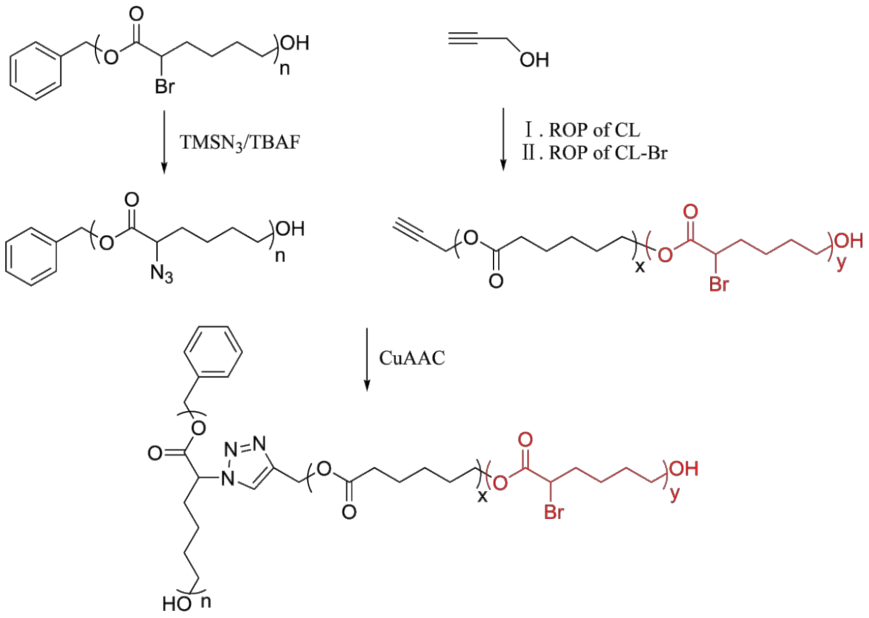


Figure S11. SEC traces recorded for (black line) before CuAAC "click" reaction, (red line) after click reaction between P(CL-N_3), ay-PCL-*b*-P(CL-Br) and (blue line) the coupling product after purification and (green line) the molecular brush was modified by DMAET. DMF was used as eluent for SEC measurement (polystyrene as standard).

Scheme S1. Synthesis of core-shell molecular bottlebrush PCL-*g*-(PCL-*b*-P(CL-Br)).



References

(1) Wang, G.; Shi, Y.; Fu, Z.; Yang, W.; Huang, Q.; Zhang, Y., Controlled synthesis of poly(ε-caprolactone)-graft-polystyrene by atom transfer radical polymerization with poly(ε-caprolactone-co-α-bromo-ε-caprolactone) copolymer as macroinitiator. *Polymer* **2005**, *46*, 10601-10606.