Electronic Supplementary Material (ESI) for Polymer Chemistry.

Supplementary Information

On-demand shape transformation of polymer vesicles via site-specific isomerization of hydrazone photoswitches in monodisperse hydrophobic oligomers

Valene Wang,[1] Jiwon Kim,[1] Junyoung Kim,[1] Seul Woo Lee,[1] and Kyoung Taek Kim[1,*]

[1]Department of Chemistry, Seoul National University, Seoul 08826, Korea

*Correspondence to: ktkim72@snu.ac.kr

CONTENTS

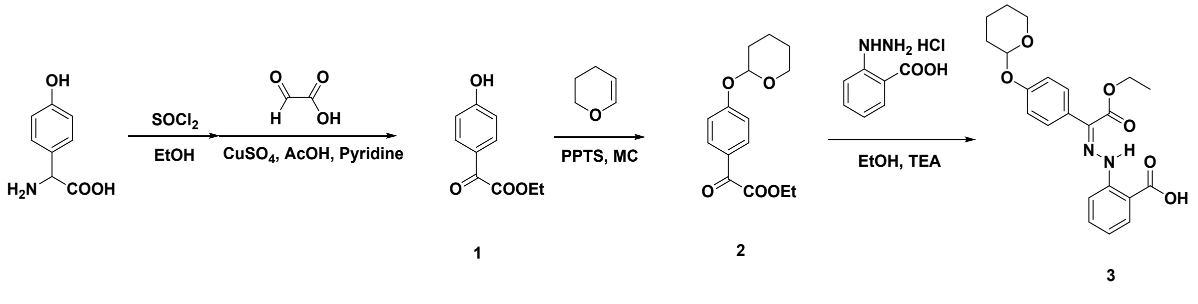
1. Materials and methods

General. Unless otherwise noted, all reagents and chemicals were purchased from Sigma Aldrich, Alfa Aesar and TCI and used as received. Dichloromethane (CH_2Cl_2) was distilled over CaH_2 under N_2. All reactions were performed under an inert atmosphere unless otherwise stated.

Methods. ^1H and ^{13}C NMR spectra were recorded on Agilent 500-MR DD2 Magnetic Resonance System and Varian/Oxford AS-500 using CD_2Cl_2 and $CDCl_3$ as solvents and internal standards. Molecular weights and dispersity Đ of polymers and block copolymers were measured by Agilent 1260 Infinity gel permeation chromatography (GPC) system equipped with a PL gel 5 µm MiniMIX-D column (Agilent Technologies) and differential refractive index detectors. THF was used as an eluent with a flow rate of 1 mL min^{-1} at 30 °C. A PS standard kit (Agilent Technologies) was used for calibration. Matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF-MS) was performed on Bruker Ultraflex II TOF/TOF mass spectrometer equipped with a nitrogen laser (335 nm). The analytical sample was prepared by mixing a THF solution of an analyte with a THF solution of 2-(4-Hydroxyphenylazo)benzoic acid (HABA) matrix. Cryogenic transmission electron microscopy (cryo-TEM) images were taken from JEM-1400 (JEOL) operating at 120 kV. The cryo-TEM experiments were performed with a thin film of aqueous sample solution (5 µL) transferred to a lacey supported grid (copper, 200 mesh, EM science) by the plunge-dipping method. The thin aqueous films were prepared at ambient temperature and with a humidity of 97–99% within custom-built environmental chamber in order to prevent water evaporation from the sample solution. The excess liquid was blotted with filter paper for 1–2 s, and the thin aqueous films were rapidly vitrified by plunging them into liquid ethane (cooled by liquid nitrogen) at its freezing point. Conventional TEM was performed on a Hitachi 7600 operating at 100 kV. Specimens were prepared by placing a drop of the sample solution on a carbon-coated Cu grid (200 mesh, EM science) and then air-drying the grid overnight. If necessary, specimens were prepared by premixing of dilute polymer solution (0.1 mg/mL) and phosphotungstic acid solution (2%) in a 10 : 1 volume ratio, and a drop of the premixed solution was placed on a carbon-coated Cu grid (200 mesh, EM Science). Dynamic light scattering (DLS) was performed on Malvern Zetasizer Nano-S. The dialyzed self-assembled polymer solution was diluted with water and an aliquot of 4 mL of the diluted solution was transferred into a plastic cuvette for measurement. Intensity data from each sample were collected in three replicates at 25 °C.

2. Preparation of hydrazone-based photo-switch

Hydrazone-based photo-switch (THP-H1-COOH) was synthesized by following the previously reported procedure.[1]



Scheme S1 Synthesis of hydrazone-based photo-switch.

THP-H1-COOH (3). It is synthesized in multi-gram quantity by following the literature methods.

^{1}H NMR (500 MHz, $CDCl_3$) δ 13.67 (s, 1H), 8.02 (dd, J=8.0, 1.5 Hz, 1H), 7.94 (d, J=8.0 Hz, 1H), 7.64 (d, J=9.0 Hz, 2H), 7.54 (t, J=8.5 Hz, 1H), 7.07 (d, J=9.0 Hz, 2H), 6.95 (t, J=8.0 Hz, 1H), 5.48-5.47 (m, 1H), 4.45 (q, J=7.0 Hz, 2H), 3.95-3.90 (m, 1H), 3.64-3.61 (m, 1H), 2.05-2.00 (m, 1H), 1.90-1.87 (m, 2H), 1.70-1.55 (m, 3H), 1.39 (t, J=7.0 Hz, 3H) ppm; ^{13}C NMR (125 MHz, CD_2Cl_2) δ 169.42, 162.97, 157.66, 147.26, 135.57, 132.74, 132.03, 130.08, 130.04(2C), 120.45, 117.49, 116.31(2C), 114.86, 96.84, 62.51, 61.92, 30.73, 25.64, 19.25, 14.41 ppm.

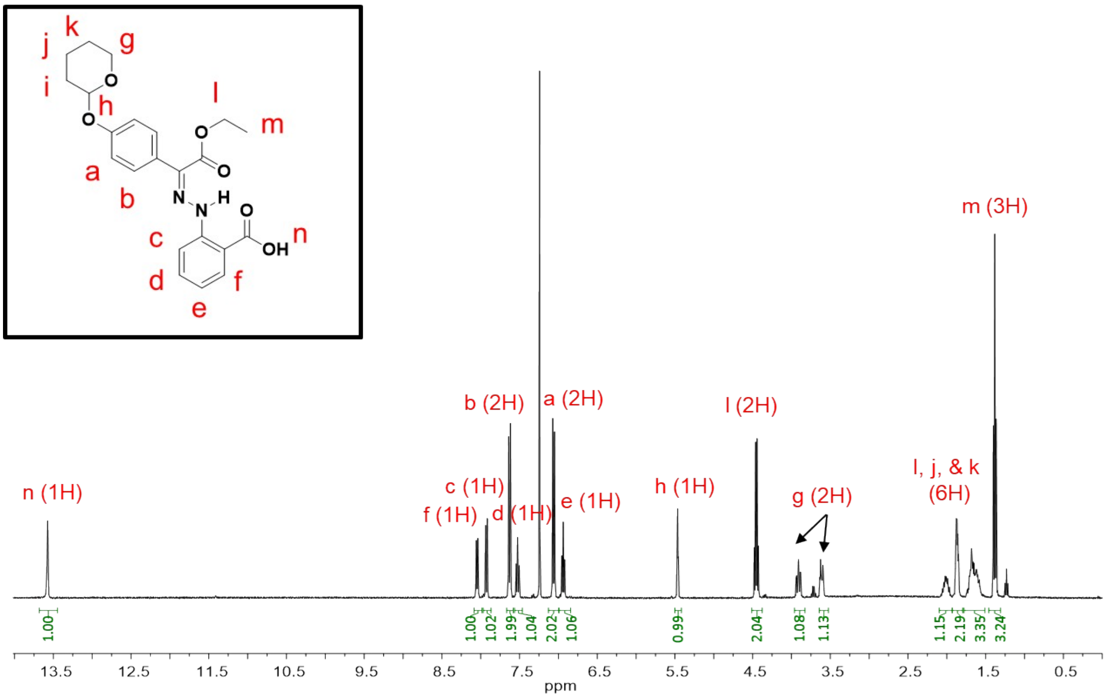


Fig. S1 ^{1}H NMR spectra of hydrazone-based photo-switch (THP-H1-COOH).

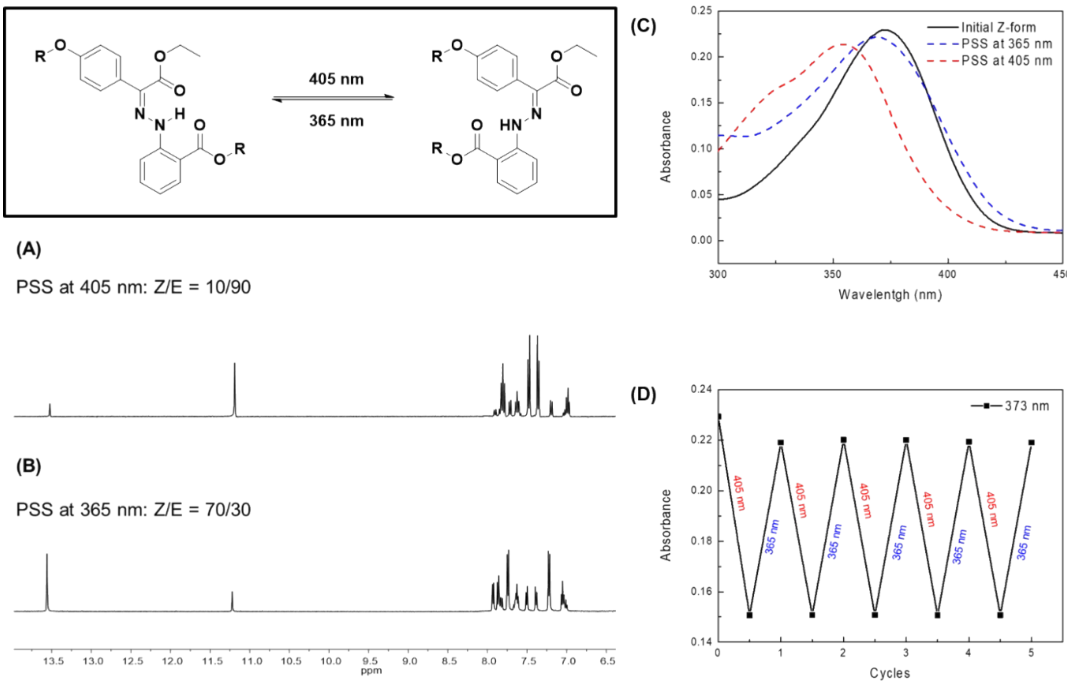
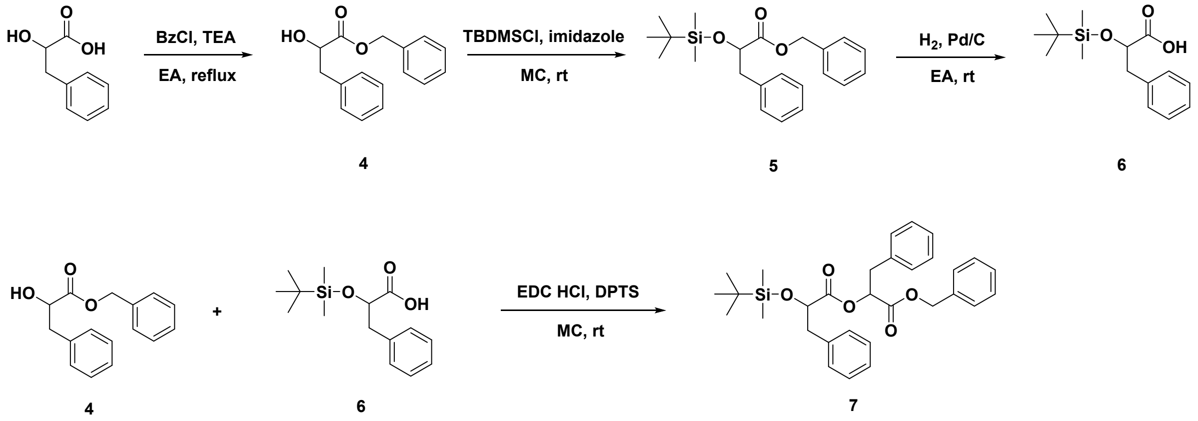
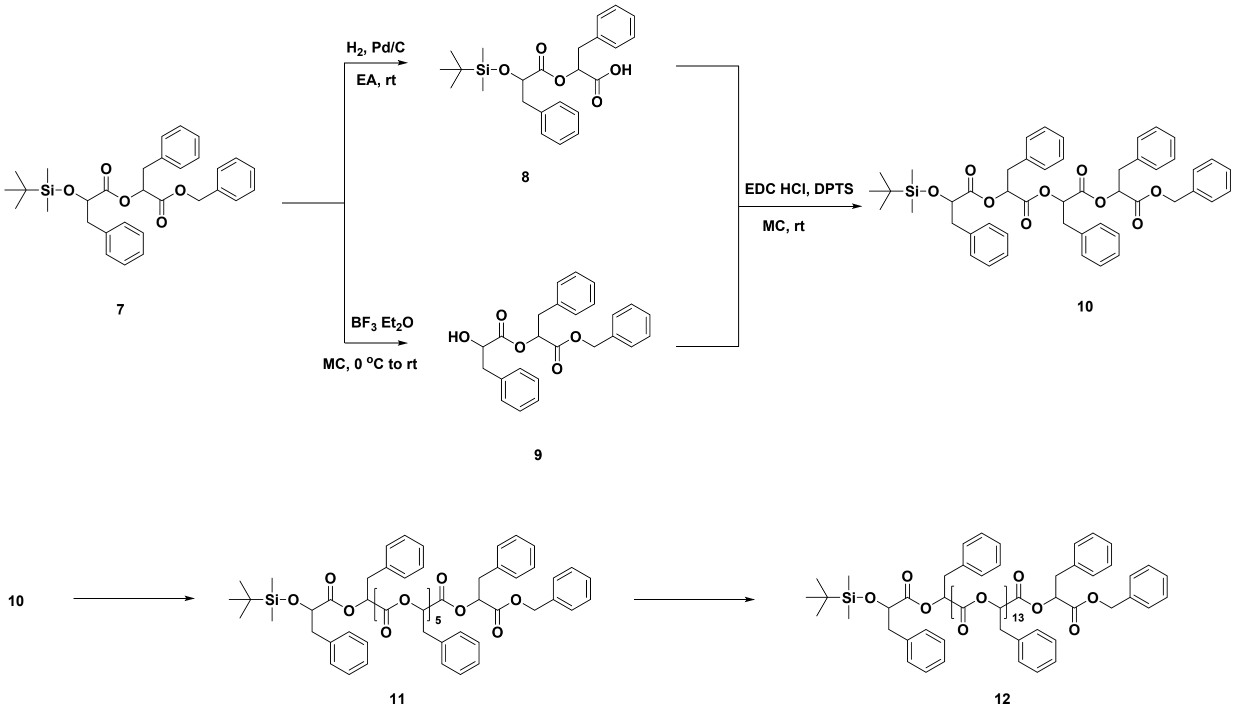


Fig. S2 ^{1}H NMR spectra in DMSO of hydrazone-based photoswitches (A) after 405 nm, followed by (B) 365 nm photoirradiation to reach the PSS. (C) UV-Vis absorption spectra of hydrazone-based photoswitches in DMSO. (D) Switching cycles of hydrazone-based photoswitches in DMSO upon alternating irradiation using 405 nm and 365 nm light sources.

3. Procedure for the convergent growth of oligo(phenyl lactic acid)s



Scheme S2 Synthesis of phenyl lactic acid dimer (PLA$_2$).



Scheme S3 Synthesis of discrete oligo(phenyl lactic acid)s (OPLAs).

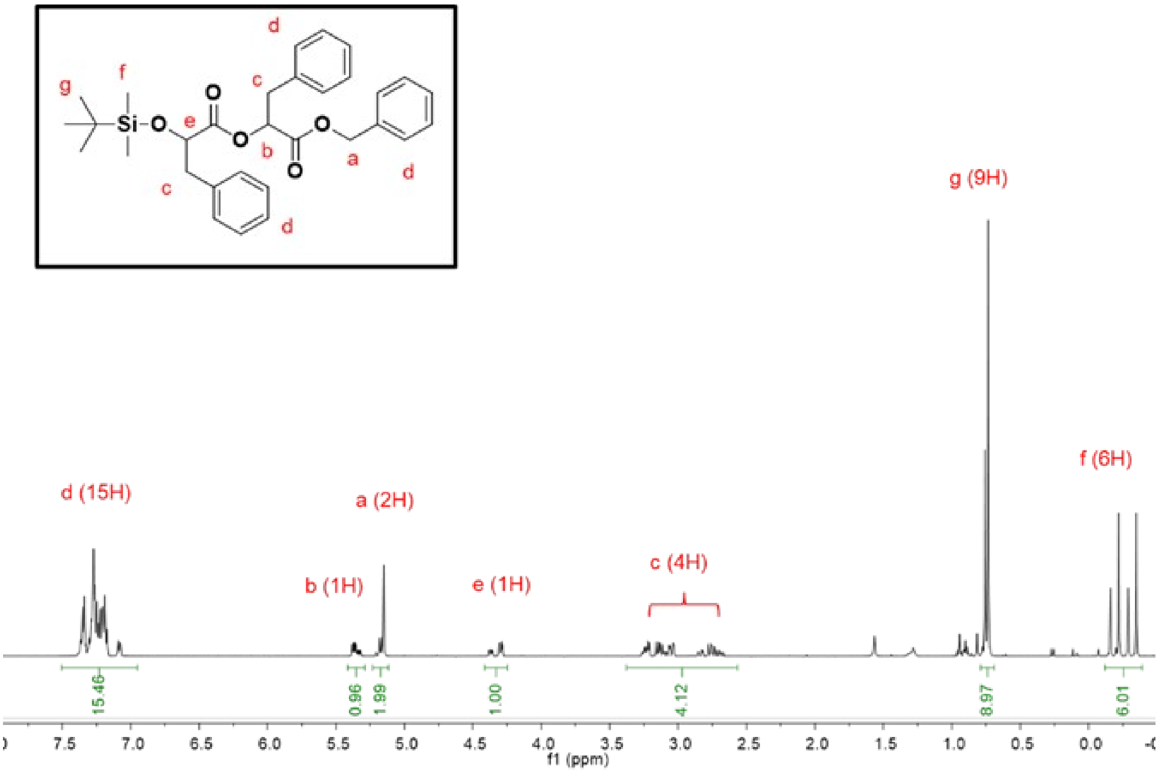


Fig. S3 ^{1}H NMR spectra of phenyl lactic acid dimer (PLA$_2$).

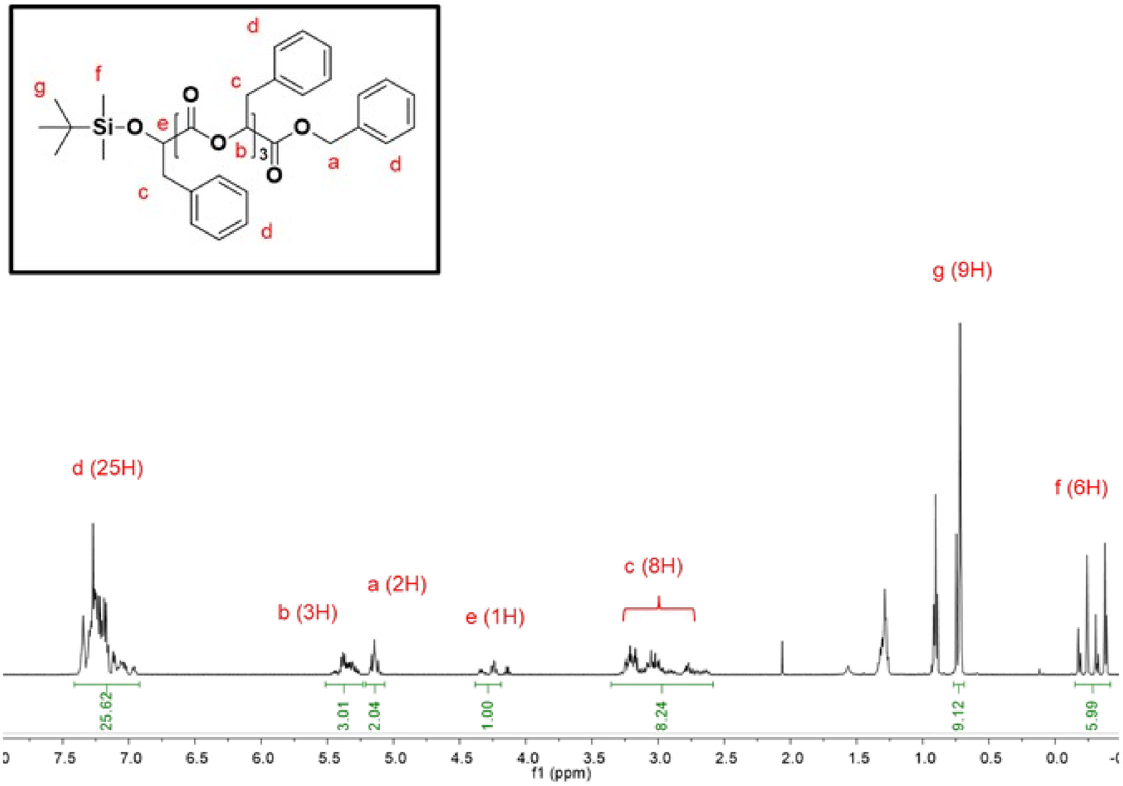


Fig. S4 ^{1}H NMR spectra of oligo(phenyl lactic acid) tetramer (OPLA$_4$).

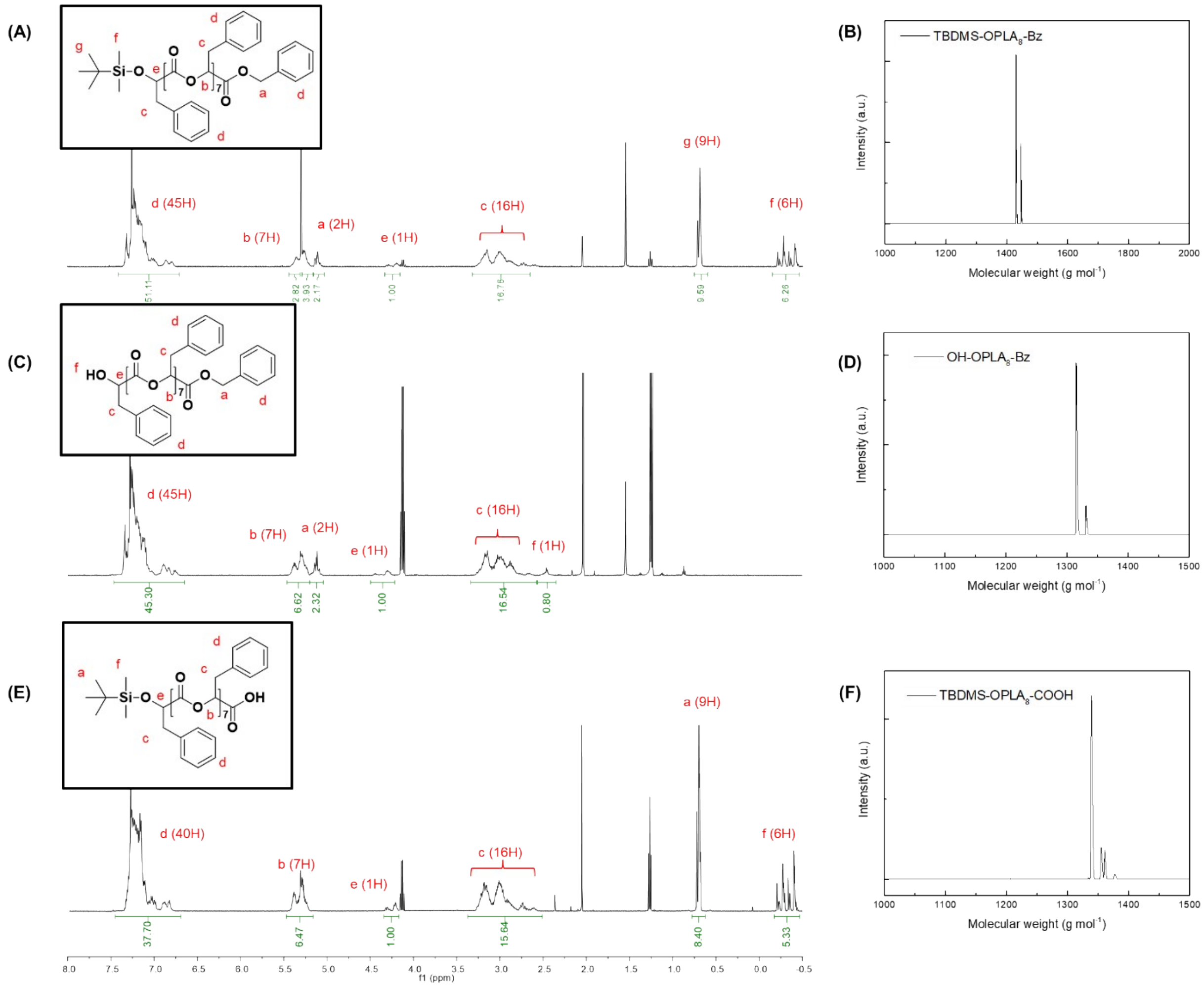


Fig. S5 (A, C and E) ^{1}H NMR spectra in $CDCl_3$ and (B, D and F) MALDI-TOF spectra of monodisperse hydrophobic block (TBDMS-OPLA$_8$-Bz), and deprotected (OH-OPLA$_8$-Bz) and (TBDMS-OPLA$_8$-COOH) compounds respectively.

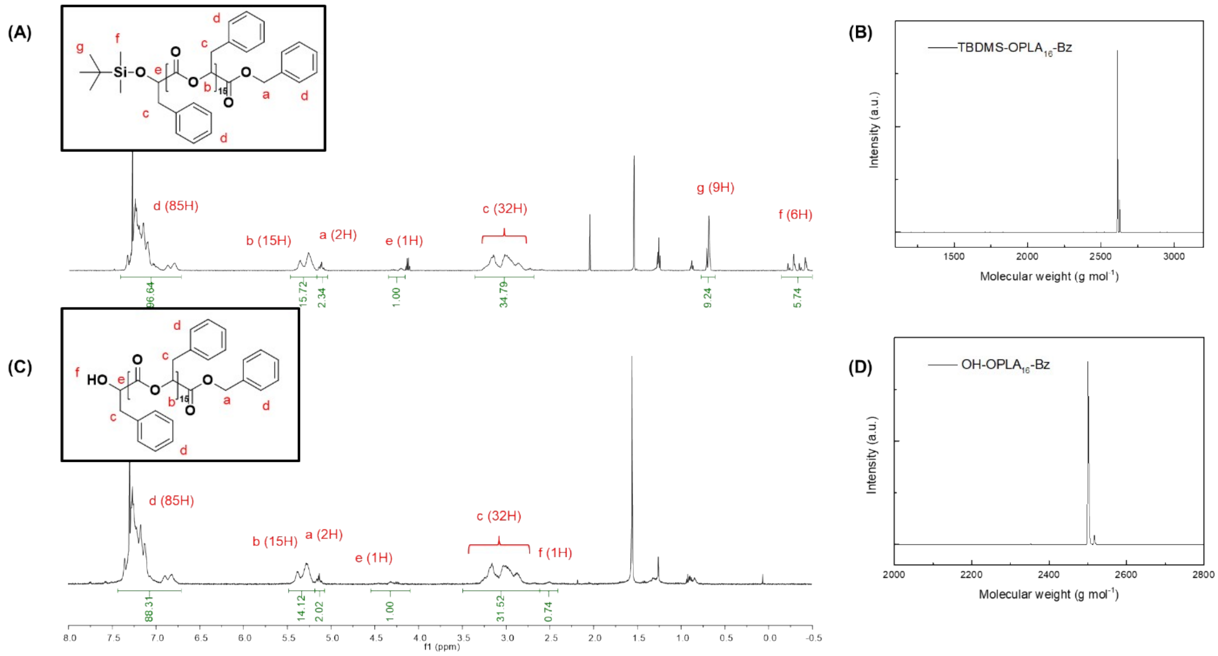
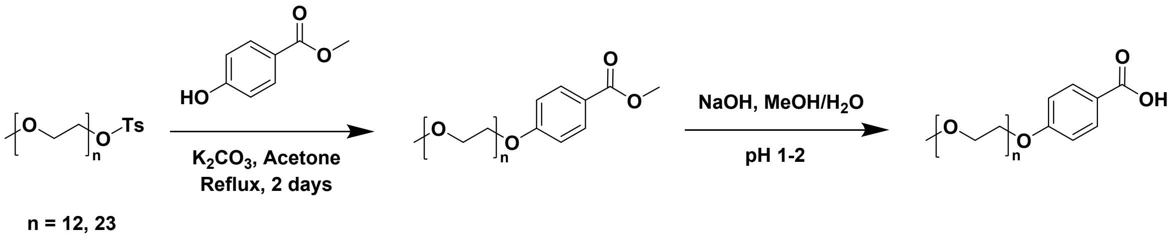


Fig. S6 (A and C) ^{1}H NMR spectra in $CDCl_3$ and (B and D) MALDI-TOF spectra of monodisperse hydrophobic block (TBDMS-$OPLA_{16}$-Bz), and deprotected (OH-$OPLA_{16}$-Bz) compound respectively.

$OPLA_{16}$ (12). It is synthesized in multi-gram quantity by following the literature methods.[2] ^{1}H NMR (500MHz, $CDCl_3$): 7.37-7.01 (m, 85H, Ph-H), 5.32 (m, 15H, COO-$CH(CH_3)C=O$), 5.14 (m, 2H, Ph-CH_2-O), 4.30 (ddd, J = 29.2, 9.2, 3.4 Hz, 1H, SiO-$CH(CH_2Ph)C=O$), 2.90 (m, 32H, Ph-CH_2-CH), 0.71 (d, J = 91. Hz, 9H, $(CH_3)_3C$-Si), -0.29 (dd, J = 51.5, 23.9 Hz, 6H, $(CH_3)_3C$-$Si(CH_3)$2-O) ppm.

4. Synthesis of hydrophilic polyethylene glycol chains

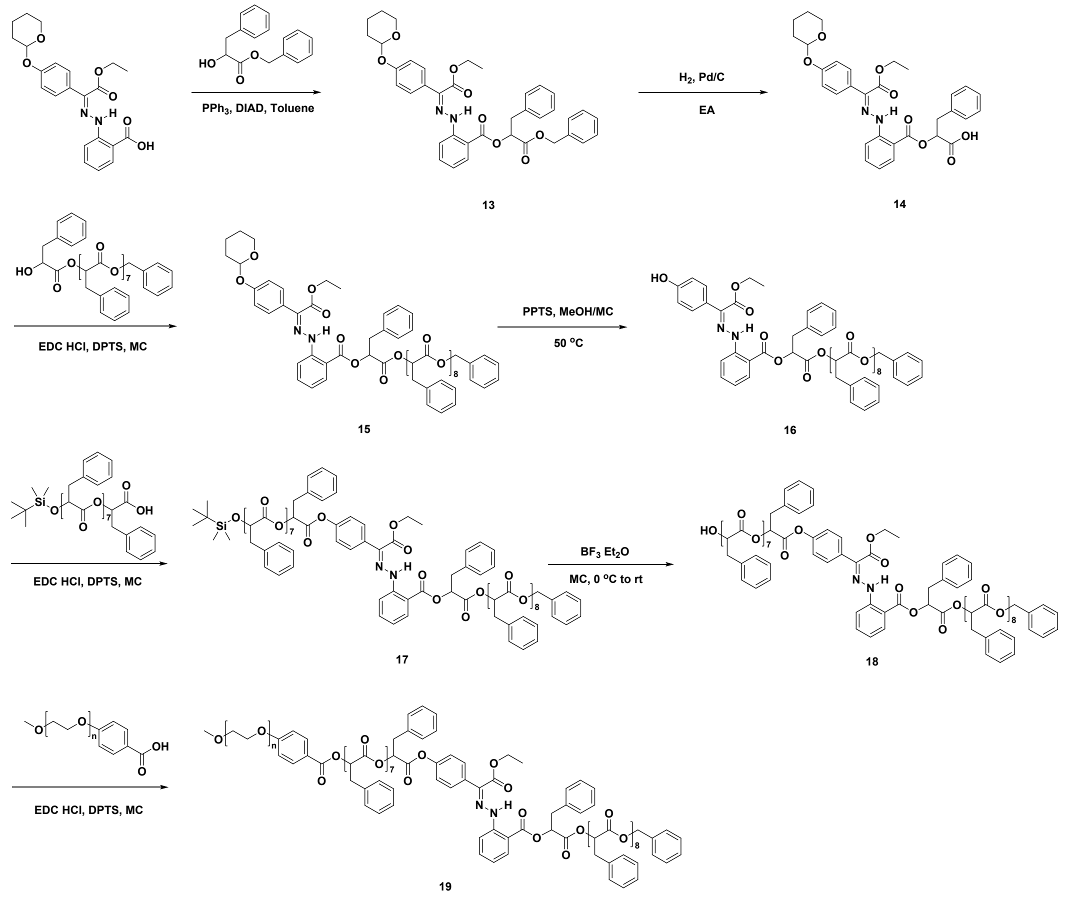


Scheme S4 Synthesis of PEG_n-COOH.

PEGn-COOH. It is synthesized in multi-gram quantity by following the literature methods.[3,4]

^{1}H NMR (400 MHz, $CDCl_3$) 8.01(d, J=8.4 Hz, 2H), 6.80(s, 2H), 4.11(s, 2H), 3.82(s, 3H), 3.76-3.50(m, $-CH_2CH_2O-$), 3.36(s, 4H) ppm.

5. Synthesis of block copolymers having hydrazone-based photo-switches



Scheme S5 Synthesis of block copolymer having hydrazone-based photo-switches (PEG-*b*-[$OPLA_8$-H1-$OPLA_9$]).

13: DIAD was added to a solution of hydrazone **3**, HO-PLA-Bz, and PPh_3 in toluene at 0 °C. The reaction was stirred at room temperature overnight. After removal of the solvent under vacuum, the product was purified by flash column chromatography affording a yellow oil.

14: Palladium on activated charcoal (10% Pd/C) was added to the solution of THP-H1-OPLA$_9$-Bz in EA. The suspension was purged with nitrogen for 15 min. The nitrogen atmosphere was then replaced with hydrogen atmosphere, and the reaction mixture was stirred at room temperature. Upon completion of the reaction, the suspension was filtered through a Celite cake to remove Pd/C. The product was obtained by removing the solvent from the filtrates under reduced pressure.

15: EDC was added to a solution of THP-H1-PLA-COOH (14), HO-OPLA$_8$-Bz, and DPTS in MC at 0 ^{o}C. The mixture was stirred at room temperature overnight. After removal of the solvent under vacuum, the product was purified by flash column chromatography affording a yellow oil.

16: A mixture of THP-H1-OPLA$_9$-Bz (15) and PPTS in MC/MeOH was heated to 50 ^{o}C and then stirred for 4 h. After removal of the solvent under vacuum, the product was purified by flash column chromatography to afford the *Z*-isomer product.

17: EDC was added to a solution of TBDMS-OPLA$_8$-COOH, HO-H1-OPLA$_9$-Bz, and DPTS in MC at 0 ^{o}C. The mixture was stirred at room temperature overnight. After removal of the solvent under vacuum, the product was purified by flash column chromatography affording a yellow oil.

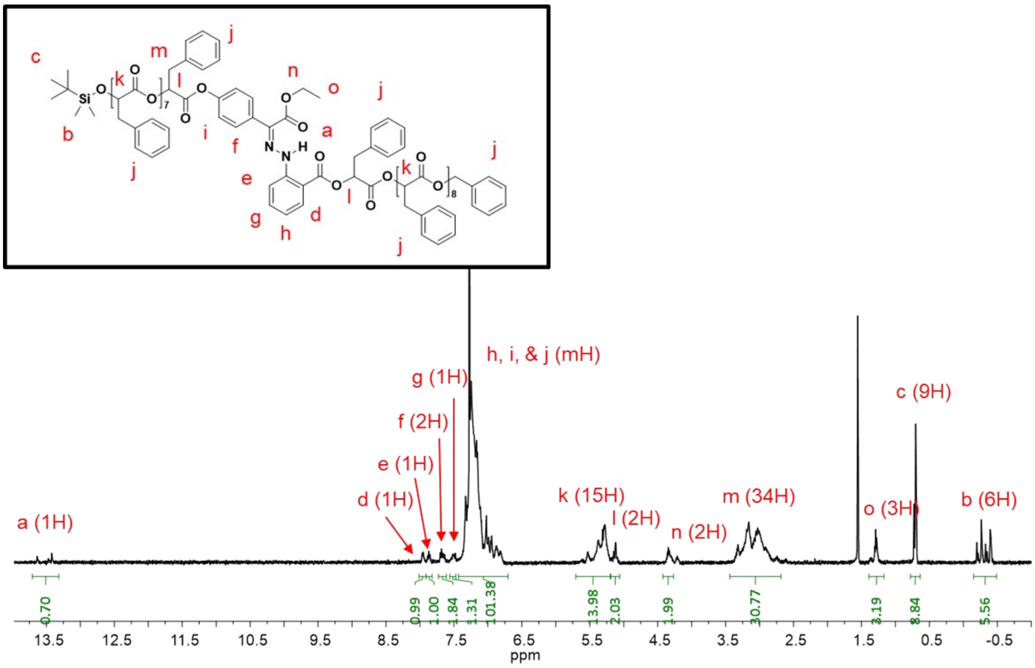


Fig. S7 ^{1}H NMR spectra of hydrophobic block (TBDMS-OPLA$_8$-H1-OPLA$_9$-Bz).

18: The hydrophobic chain, TBDMS-OPLA$_8$-H1-OPLA$_9$-Bz (17), was dissolved in dry MC. The solution was cooled to 0 °C on an ice bath, and boron trifluoride diethyl etherate (BF$_3$ Et$_2$O) was added dropwise. The reaction mixture stirred at room temperature for 4 h. Upon completion of the reaction, the reaction was quenched with saturated NaHCO$_3$ followed by dilution with water. The organic layer was separated and washed with brine. The combined organic layer was dried over MgSO$_4$, and the solvent was removed under reduced pressure. The crude product was purified by column chromatography affording a yellow viscous oil.

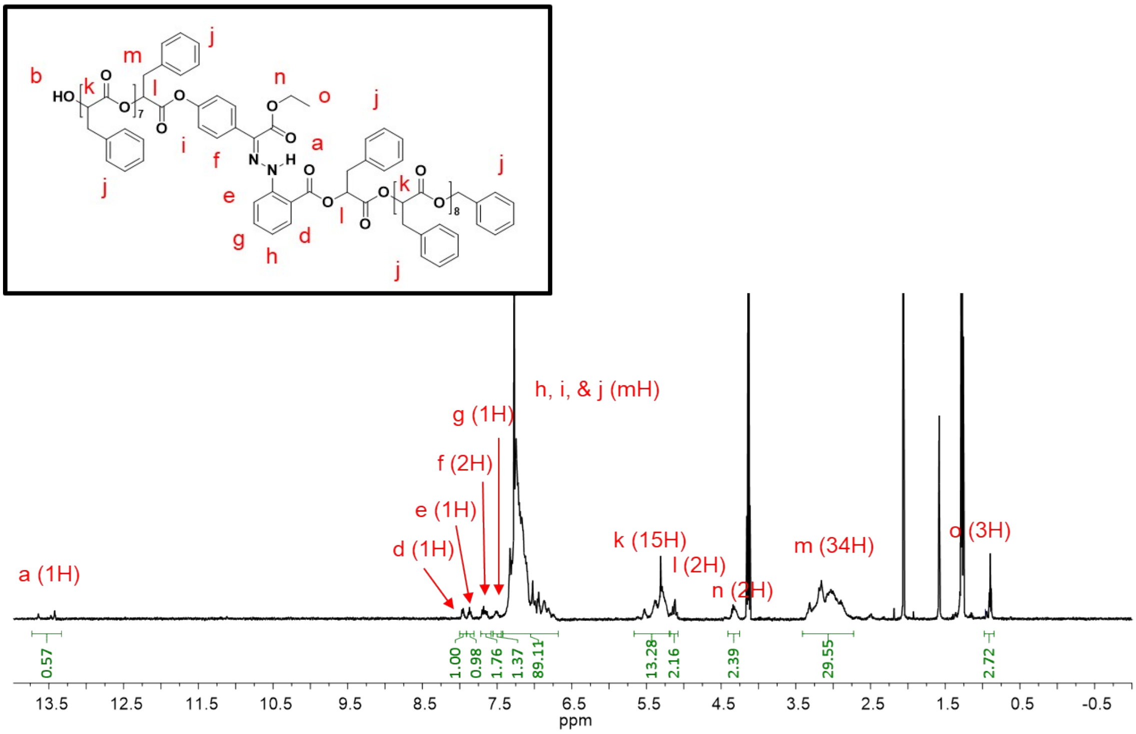


Fig. S8 ^{1}H NMR spectra of hydrophobic block (HO-OPLA$_8$-H1-OPLA$_9$-Bz).

19: The deprotected hydrophobic block, HO-OPLA$_8$-H1-OPLA$_9$-Bz (18), and the hydrophilic block, PEG-COOH, were dissolved in dry MC. The mixture was cooled to 0 °C on an ice bath. To the mixture, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC HCl) and DPTS were added. The reaction mixture was stirred overnight at room temperature. Upon completion of the reaction, the reaction mixture was washed with water and brine. The combined organic layer was dried over $MgSO_4$, and the solvent was removed under reduced pressure. The crude product was purified by column chromatography affording a yellow viscous oil.

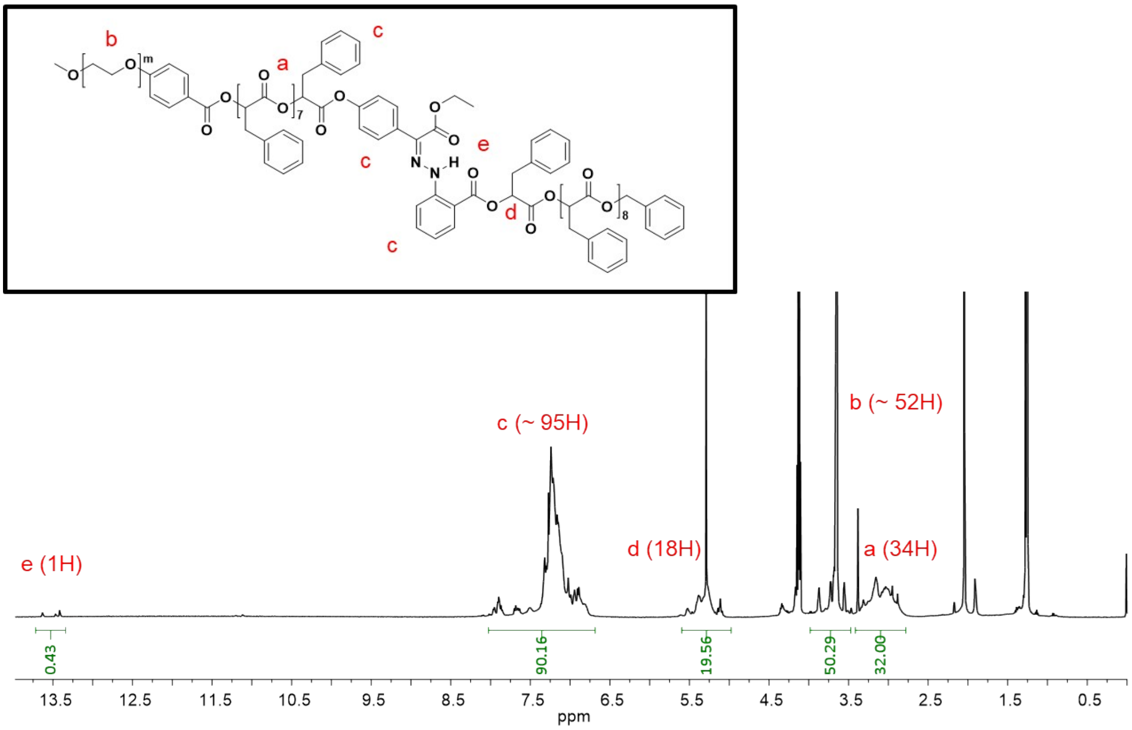
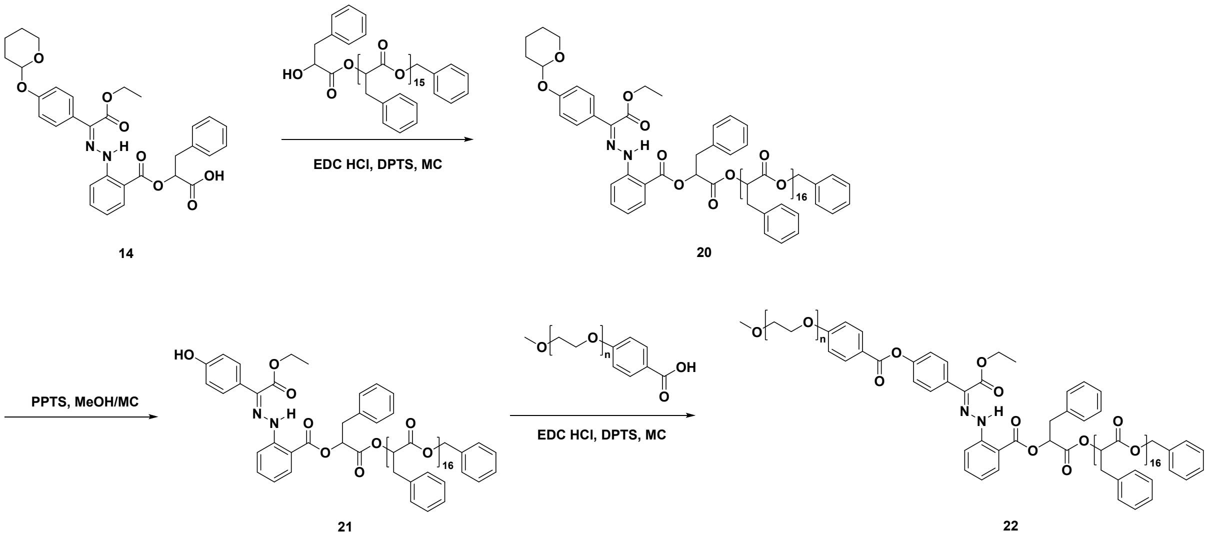


Fig. S9 ^{1}H NMR spectra of amphiphilic block copolymer (PEG-*b*-[OPLA_8-H1-OPLA_9]).



Scheme S6 Synthesis of block copolymer having hydrazone-based photo-switches (PEG-*b*-[H1-OPLA_{17}]).

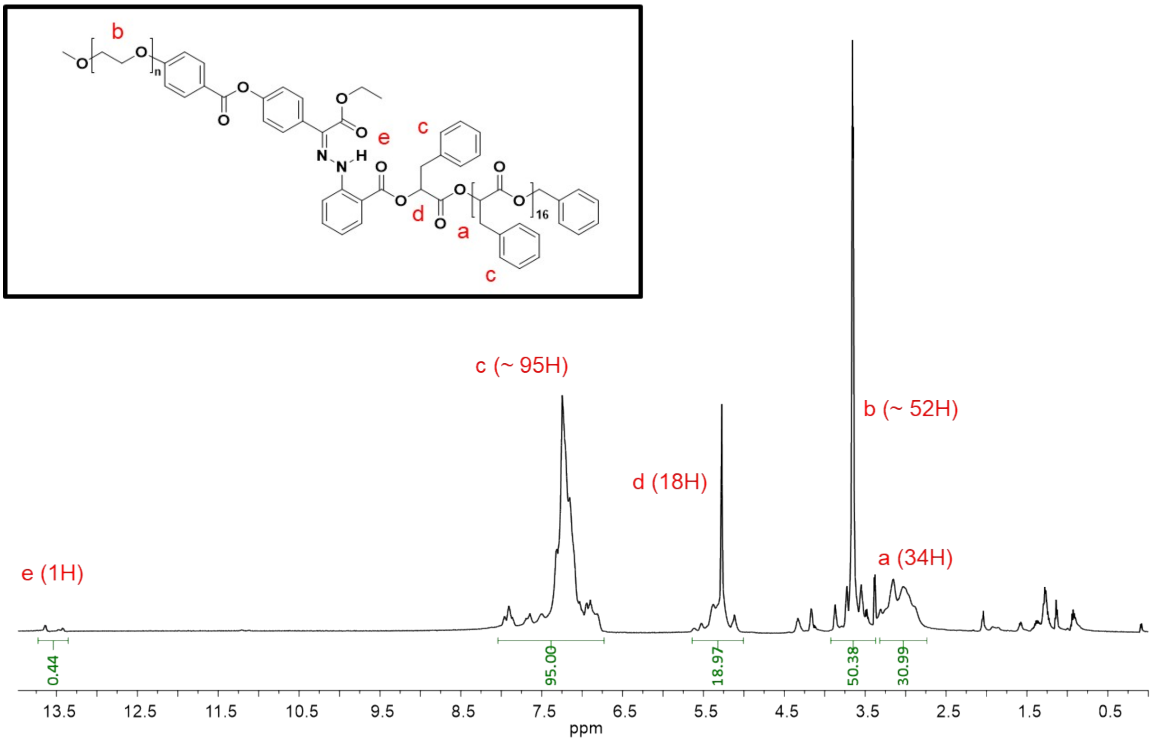


Fig. S10 ^{1}H NMR spectra of amphiphilic block copolymer (PEG-*b*-[H1-OPLA$_{17}$]).

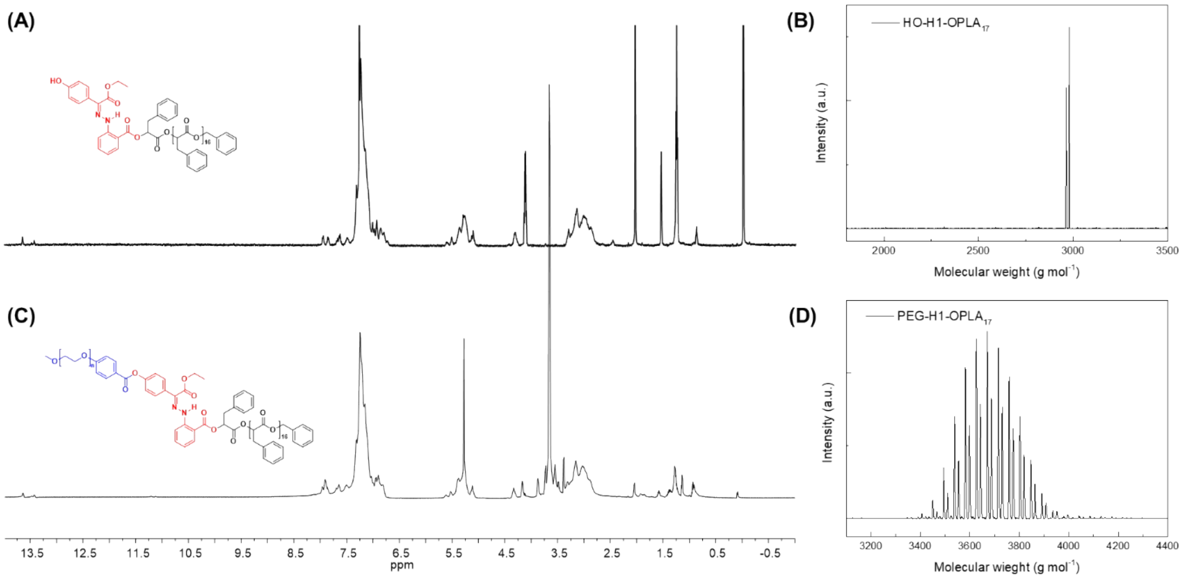


Fig. S11 (A and C) ^{1}H NMR spectra in $CDCl_3$ and (B and D) MALDI-TOF spectra of monodisperse hydrophobic block (HO-H1-OPLA$_{17}$) and amphiphilic block copolymer (PEG550-*b*-[H1-OPLA$_{17}$]) respectively.

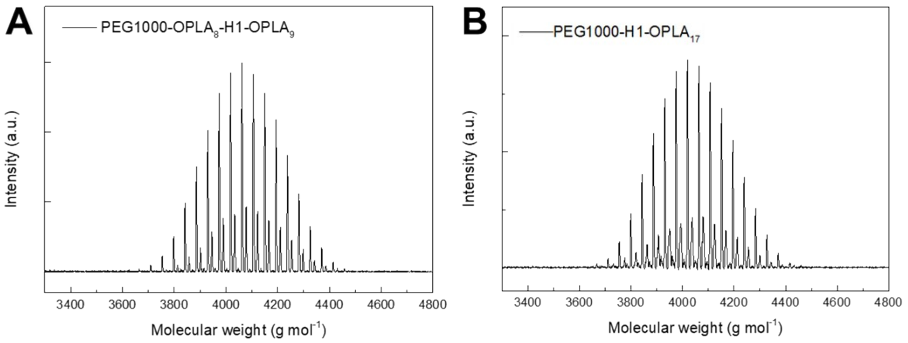


Fig. S12 MALDI-TOF spectra of amphiphilic block copolymers (PEG-*b*-[OPLA$_8$-H1-OPLA$_9$] and PEG-*b*-[H1-OPLA$_{17}$]) containing polydisperse hydrophilic block (M_n = 1000).

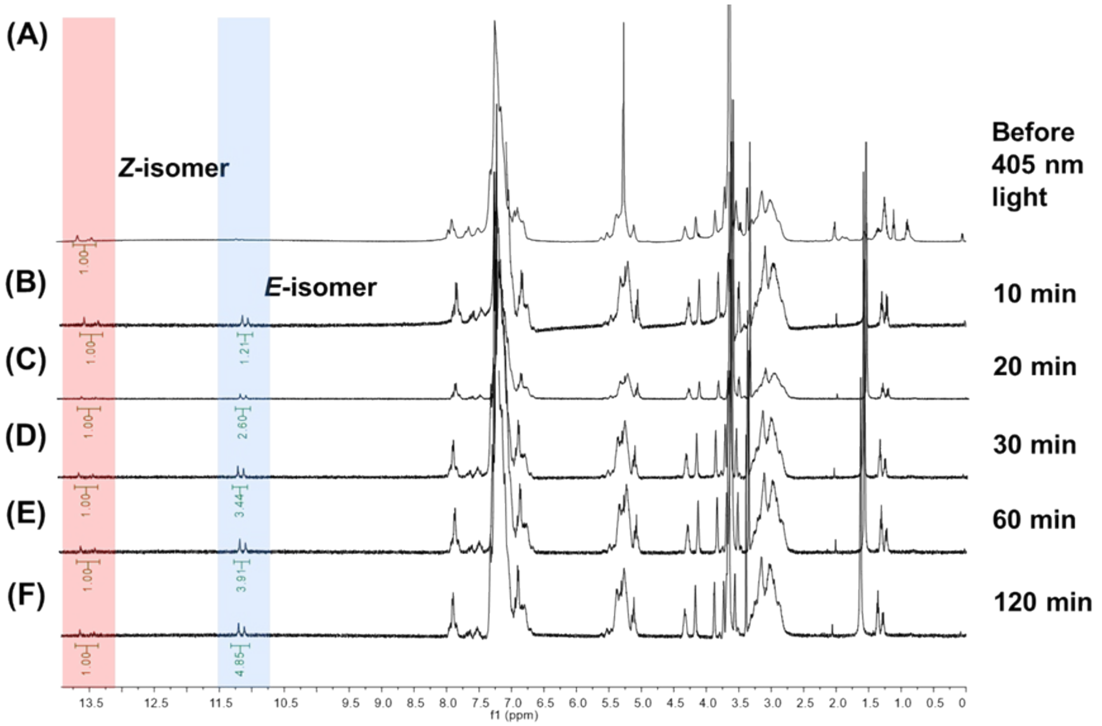


Fig. S13 Time-dependent ^{1}H NMR analyses of amphiphilic block copolymer containing hydrazone-based photoswitches (A) before and (B to F) after 405 nm light irradiation.

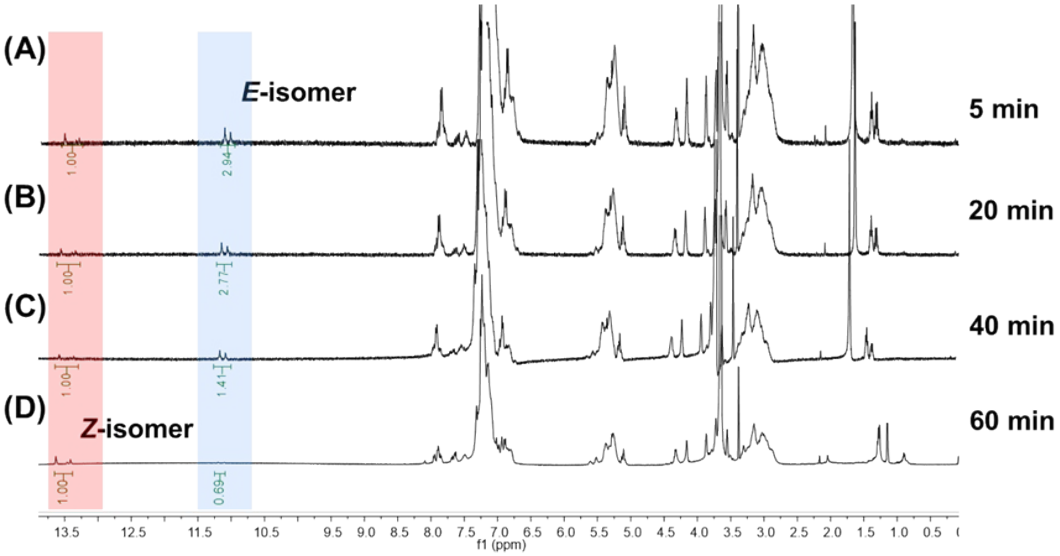


Fig. S14 Time-dependent ^{1}H NMR analyses of amphiphilic block copolymer containing hydrazone-based photoswitches (A to D) after 365 nm light irradiation.

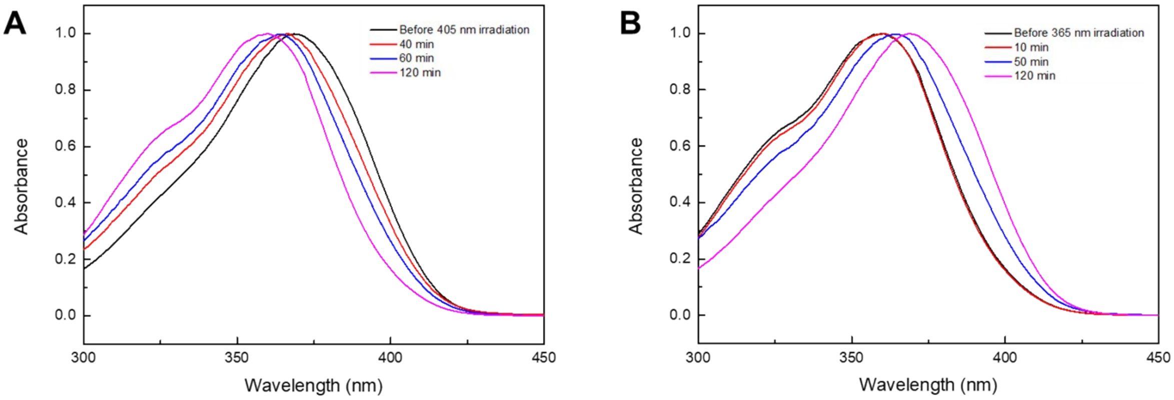
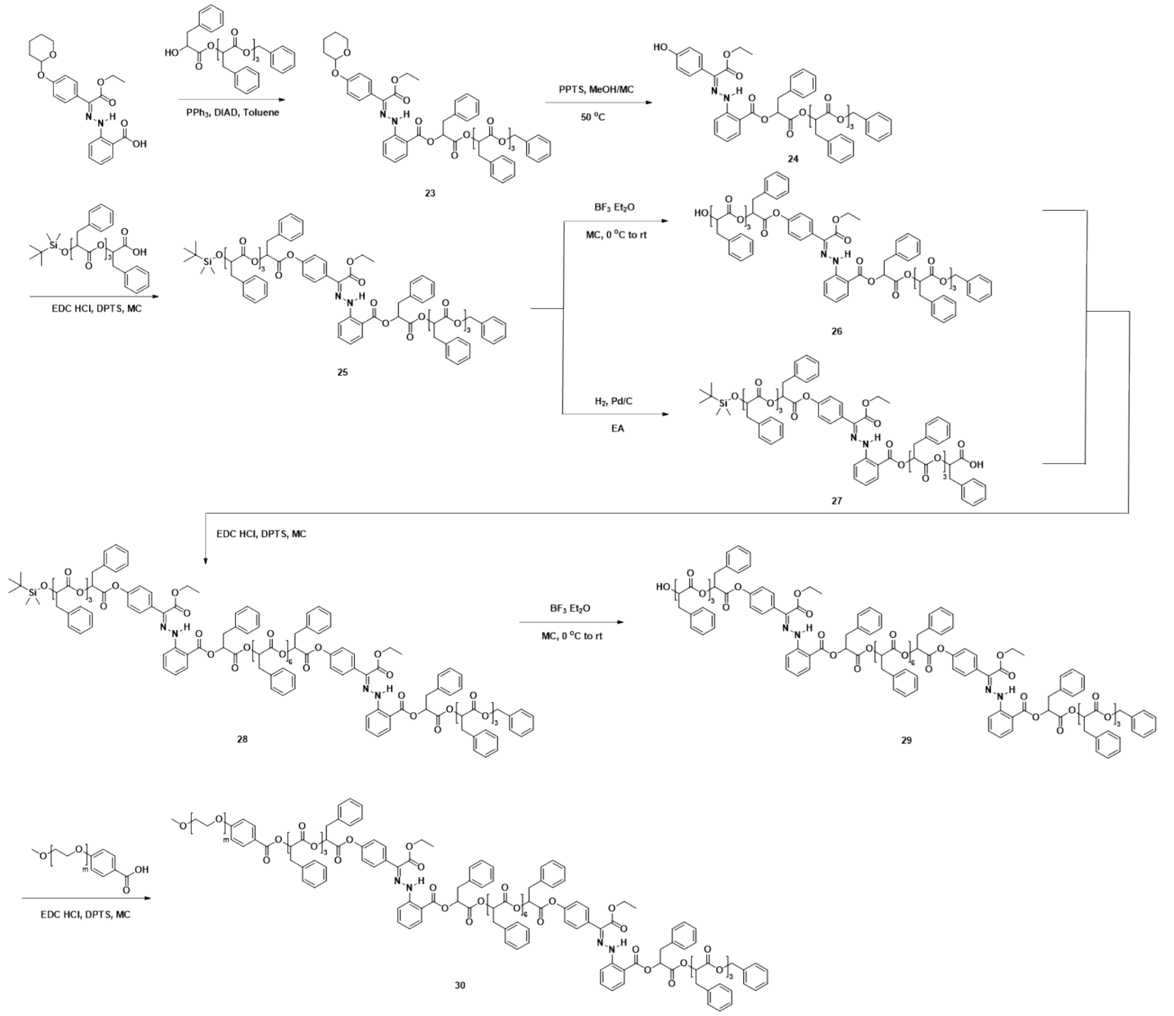


Fig. S15 Time-dependent UV-Vis absorption spectra of self-assembled amphiphilic block copolymer containing hydrazone-based photoswitches (A) after 405 nm, followed by (B) 365 nm light irradiation.



Scheme S7 Synthesis of block copolymer having multiple hydrazone-based photo-switches (PEG-*b*-[OPLA_4-H1-OPLA_8-H1-OPLA_4]).

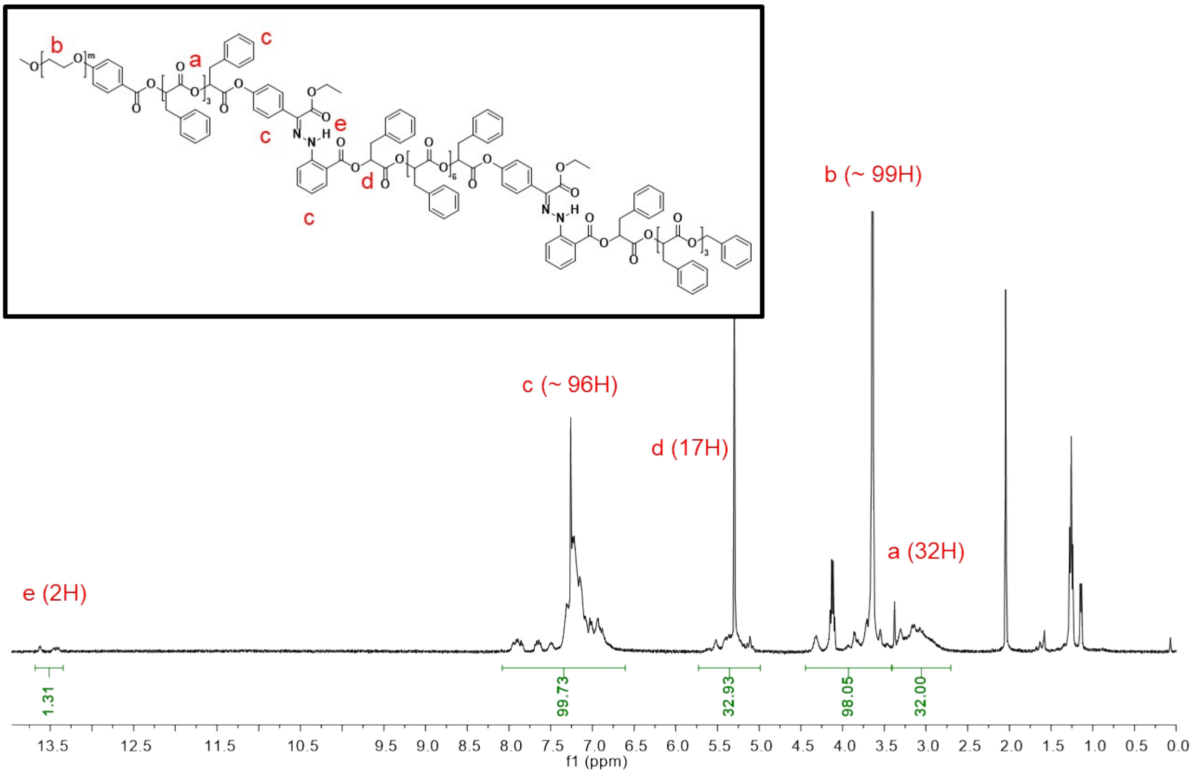


Fig. S16 ^{1}H NMR spectra of amphiphilic block copolymer (PEG-*b*-[OPLA$_4$-H1-OPLA$_8$-H1-OPLA$_4$]).

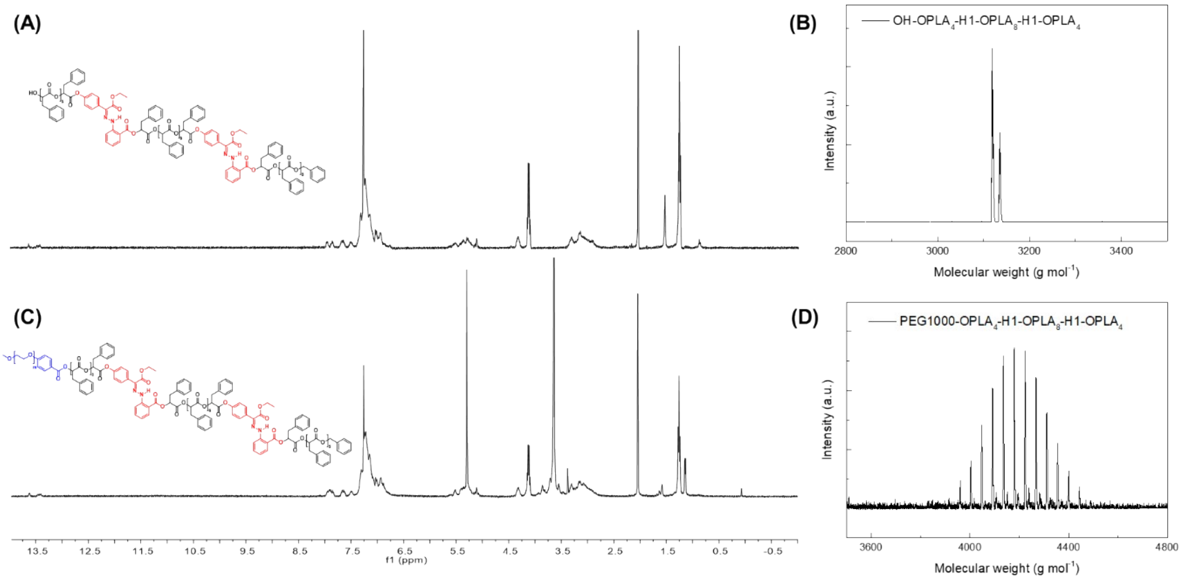


Fig. S17 (A and C) ^{1}H NMR spectra in $CDCl_3$ and (B and D) MALDI-TOF spectra of monodisperse hydrophobic block (HO-OPLA$_4$-H1-OPLA$_8$-H1-OPLA$_4$) and amphiphilic block copolymer (PEG1000-*b*-[OPLA$_4$-H1-OPLA$_8$-H1-OPLA$_4$]) respectively.

6. Solution self-assemblies of BCPs via co-solvent method

5 mg of BCPs was dissolved in acetone (1 mL) in a 20 mL capped vial with magnetic stirrer. The solution was stirred for 1 h at room temperature (860 rpm). A syringe pump was calibrated to inject water at a speed of 0.5 mL/h. The vial cap was replaced with a rubber septum, and water was added to the polymer solution over 2 h using a syringe pump with a 6-mL syringe equipped with a steel needle. However, water was added to the polymer solution over 1 h for **BCP5** only. The resulting suspension was subjected to dialysis (molecular weight cutoff 12-14 kDa (SpectraPor, Rancho Dominguez, CA)) against water for 24 h.

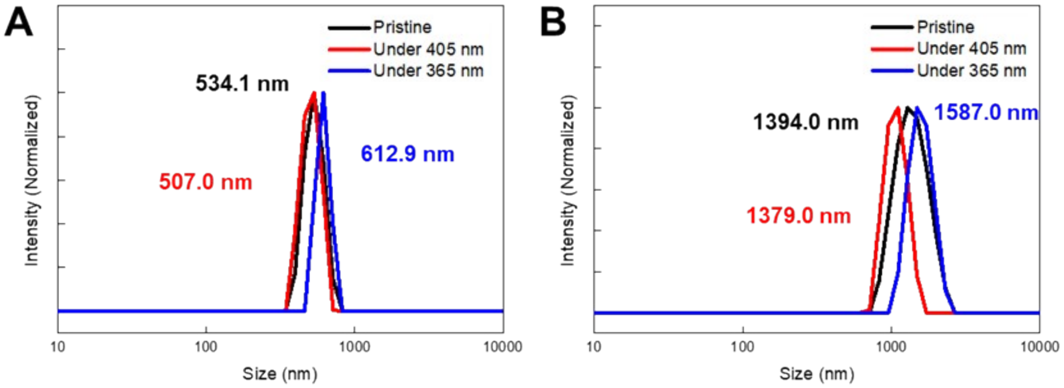


Fig. S18 Dynamic light scattering (DLS) analysis of self-assembled structures of (A) PEG550-*b*-[OPLA$_8$-H1-OPLA$_9$] and (B) PEG550-*b*-[H1-OPLA$_{17}$] under different light sources.

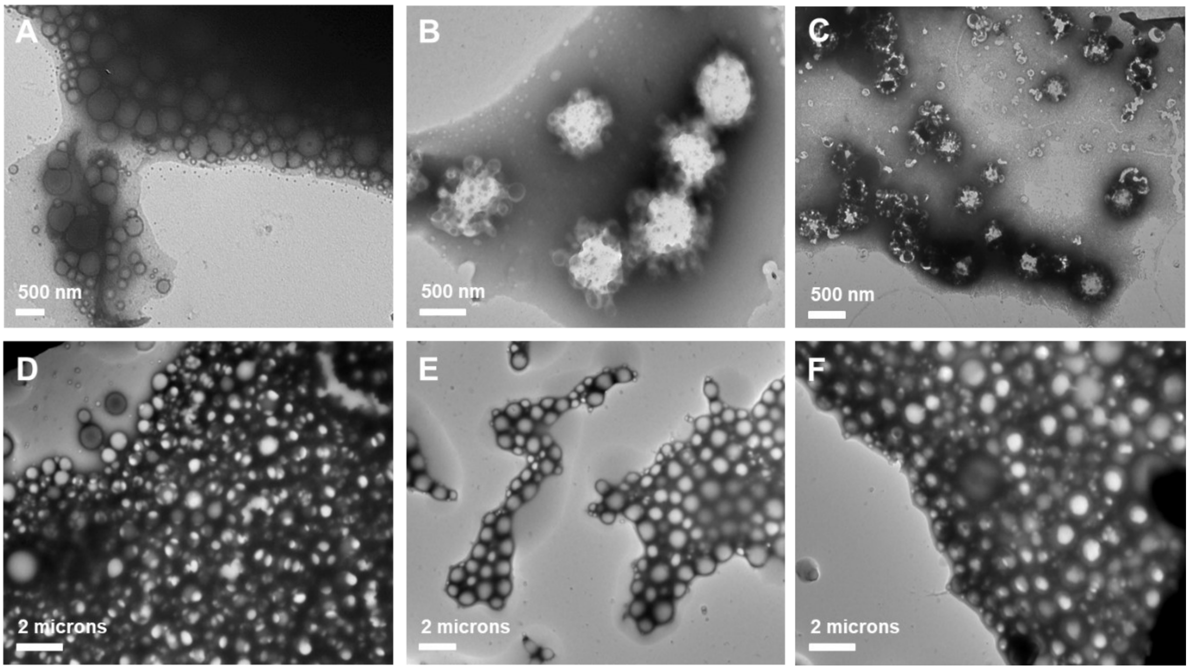


Fig. S19 TEM images of self-assembled structures of (A−C) PEG550-*b*-[$OPLA_8$-H1-$OPLA_9$] (D−F) PEG550-*b*-[H1-$OPLA_{17}$] under different light sources. The morphologies were observed (A and D) before and (B and E) after blue-light irradiation, followed by (C and F) UV light irradiation.

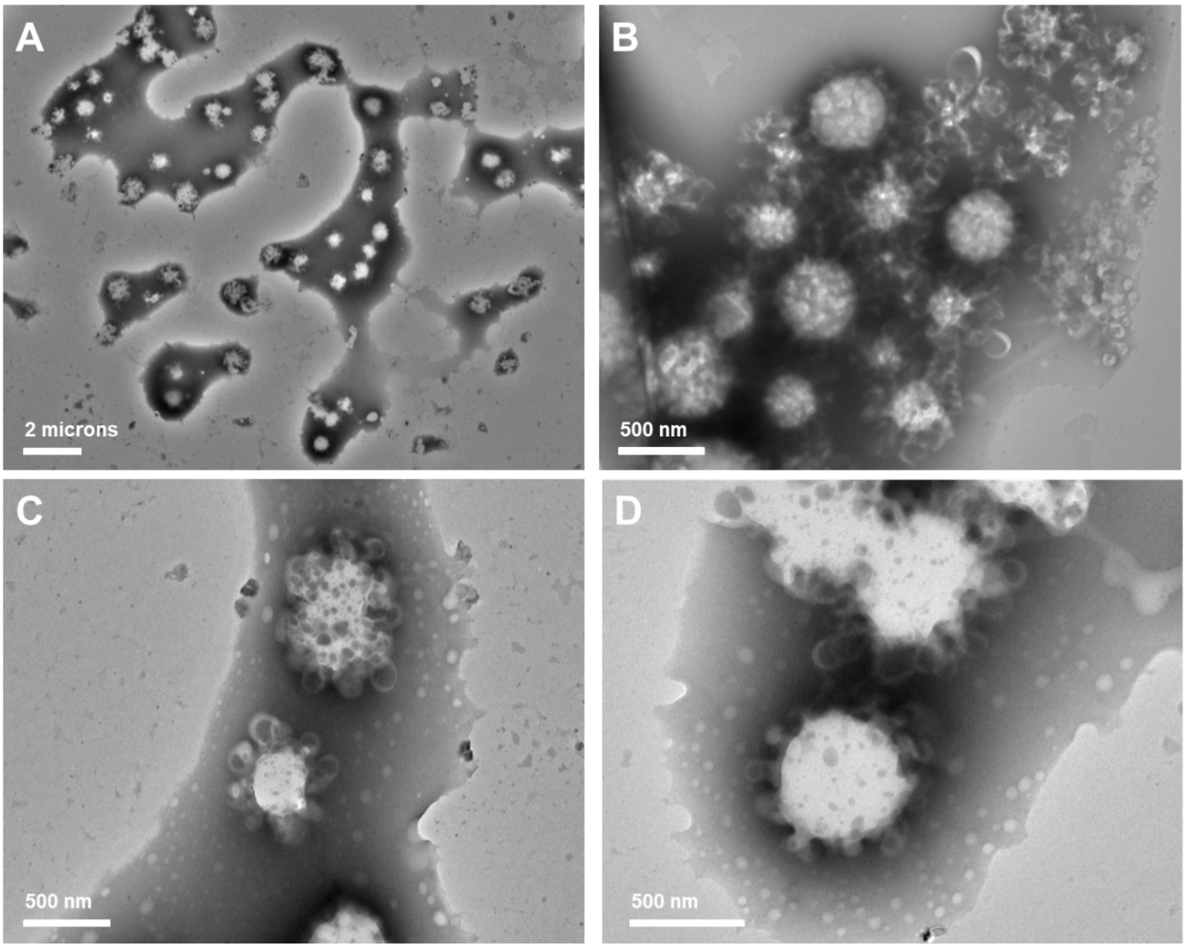


Fig. S20 TEM images with different resolutions of flower-like structures. The structures were prepared via the shape transformation of the self-assembled structures of PEG550-*b*-[OPLA$_8$-H1-OPLA$_9$] after blue-light irradiation for 2 h.

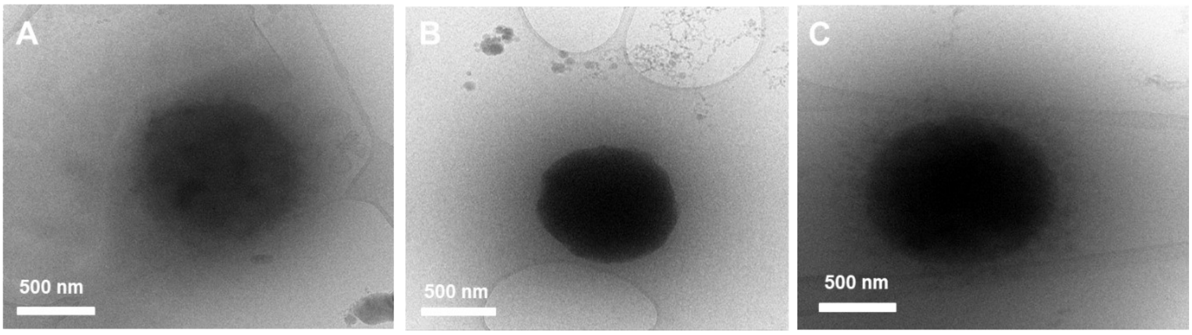


Fig. S21 Cryo-TEM images of self-assembled structures of PEG550-*b*-[H1-OPLA$_{17}$] under different light sources. The morphologies were observed (A) before and (B) after blue-light irradiation, followed by (C) UV light irradiation.

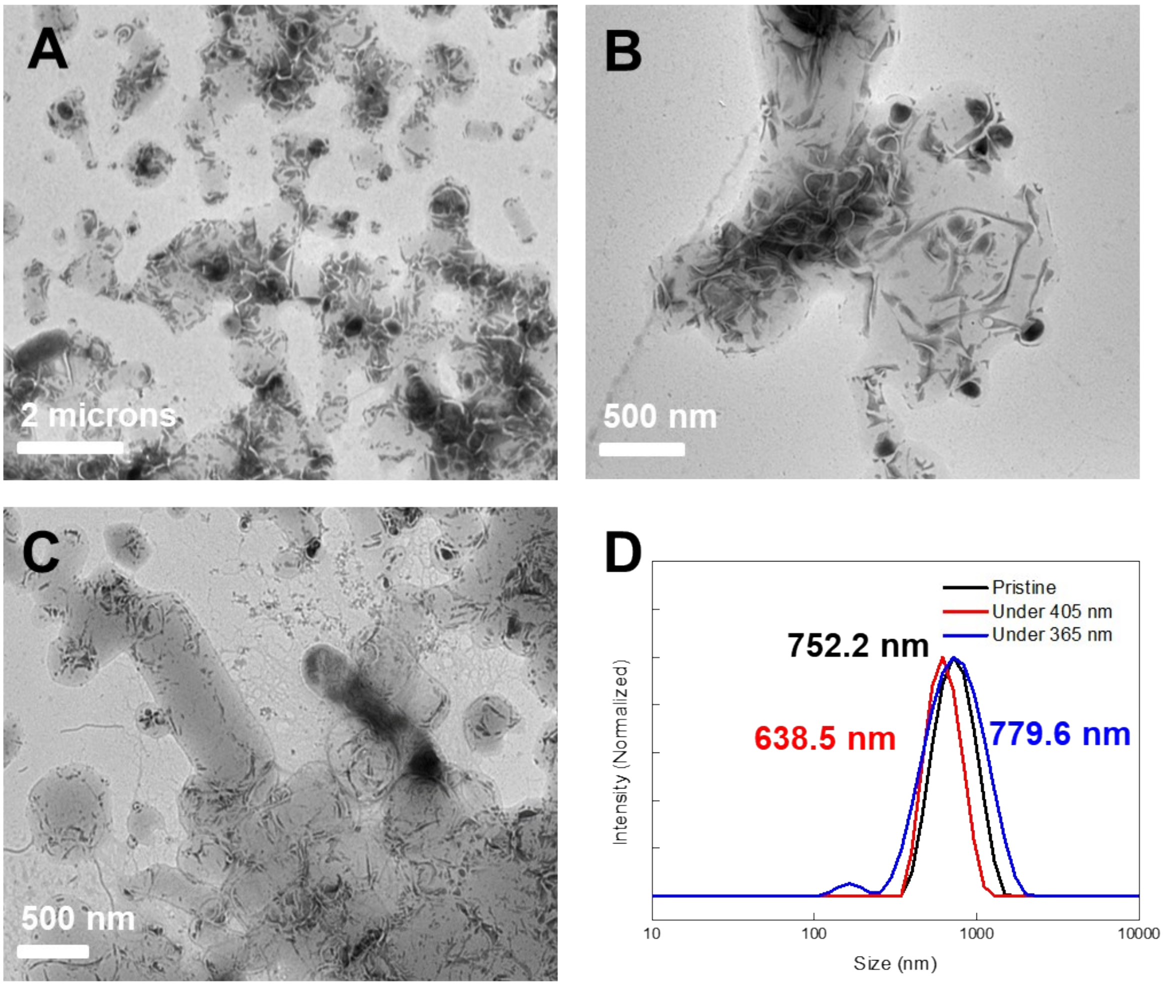


Fig. S22 (A−C) TEM images and (D) dynamic light scattering (DLS) analysis of self-assembled structures of PEG1000-*b*-[OPLA$_8$-H1-OPLA$_9$] under different light sources. The morphologies were observed (A) before and (B) after blue-light irradiation, followed by (C) UV light irradiation.

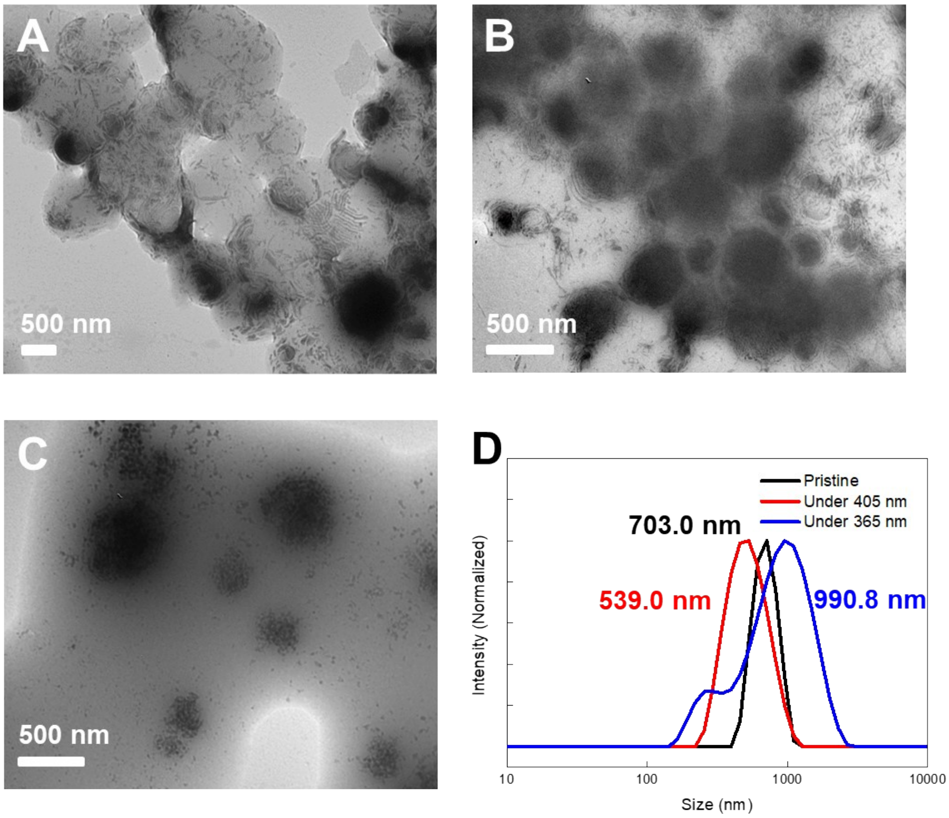


Fig. S23 (A−C) TEM images and (D) dynamic light scattering (DLS) analysis of self-assembled structures of PEG1000-*b*-[H1-OPLA$_{17}$] under different light sources. The morphologies were observed (A) before and (B) after blue-light irradiation, followed by (C) UV light irradiation.

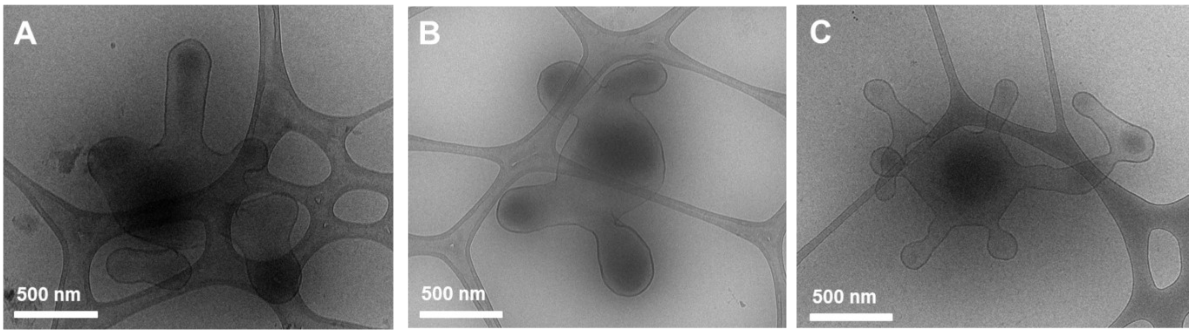


Fig. S24 Cryo-TEM images of urchin-like structures of PEG1000-*b*-[OPLA$_8$-H1-OPLA$_9$] after blue-light irradiation.

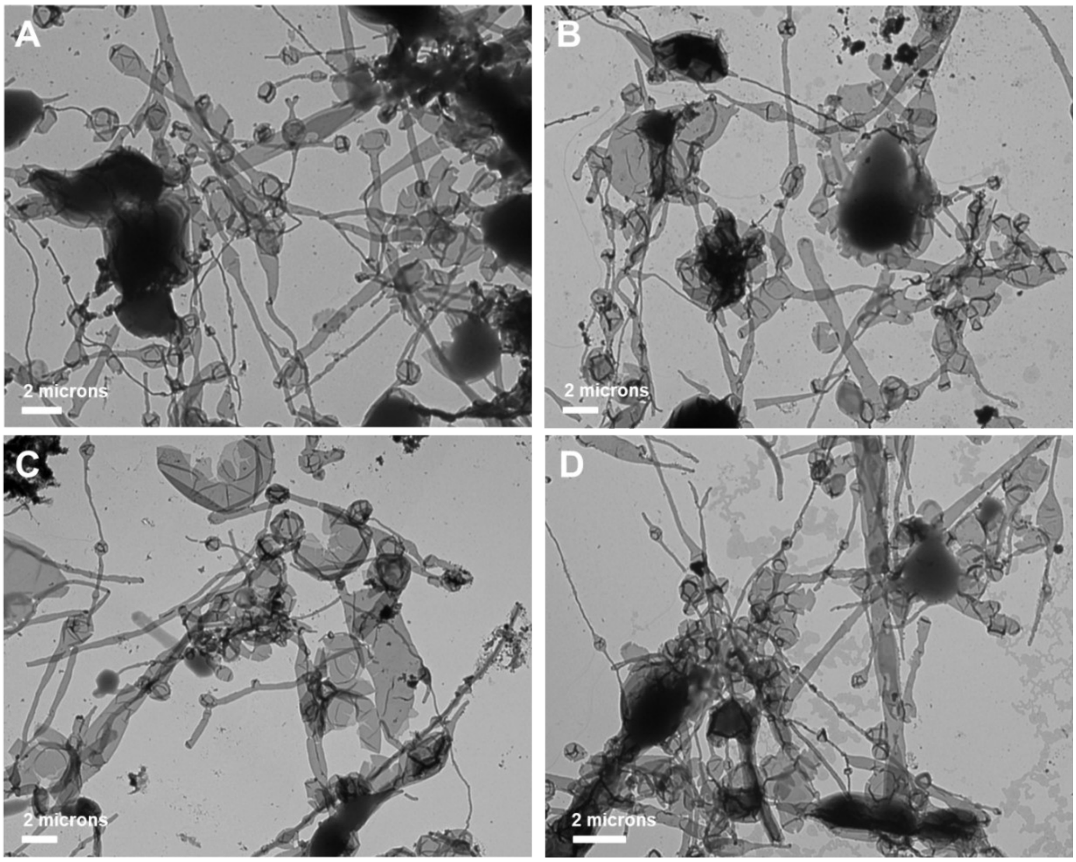


Fig. S25 TEM images of elongated structures. The structures were prepared via the shape transformation of the self-assembled structures of PEG1000-*b*-[OPLA$_4$-H1-OPLA$_8$-H1-OPLA$_4$] after blue-light irradiation for 2 h. The structures of PEG1000-*b*-[OPLA$_4$-H1-OPLA$_8$-H1-OPLA$_4$] (A−D) were treated with phosphotungstic acid solution for negative staining.

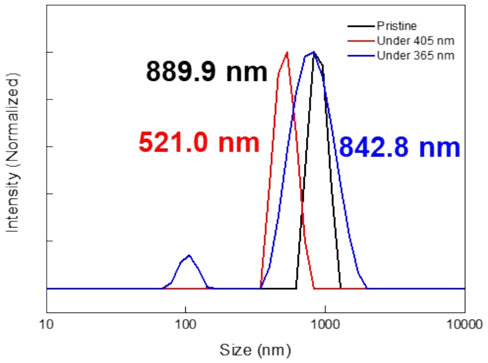


Fig. S26 Dynamic light scattering (DLS) analysis of self-assembled structures of PEG1000-*b*-[OPLA$_4$-H1-OPLA$_8$-H1-OPLA$_4$] under different light sources.

7. References

1 A. Ryabchun, Q. Li, F. Lancia, I. Aprahamian and N. Katsonis, *J. Am. Chem. Soc.,* 2019, **141,** 1196−1200.

2 J. M. Lee, M. B. Koo, S. W. Lee, H. Lee, J. Kwon, Y. H. Shim, S. Y. Kim and K. T. Kim, *Nat. Commun.,* 2020, **11,** 56.

3 M. G. Jeong, J. C. M. van Hest and K. T. Kim, *Chem. Comm.,* 2012, **48,** 3590−3592.

4 Y. La, C. Park, T. J. Shin, S. H. Joo, S. Kang and K. T. Kim, *Nat. Chem.,* 2014, **6,** 534−541.