SUPPORTING INFORMATION

Scalable Preparation of Cyclic Polymers from Ring-Closure Method Assisted by Continuous-Flow Technique

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Experimental

Materials

Bromobenzene, carbon disulfide (CS_2), 2,3-dimethyl anisole, copper sulfate pentahydrate, 4,4'-Azobis(4-cyanovaleric acid), styrene (St), sodium chloride, hydrochloric acid (HCl), alkaline alumina, magnesium sulphate ($MgSO_4$), acetonitrile, methanol, toluene, petroleum ether, ethyl acetate, dichloromethane (DCM), tetrahydrofuran (THF) and dimethylsuloxide (DMSO) were purchased as regent grade from Alfa Aesar, Aldrich, Acros, J&K Chemical, or Beijing Chemical Reagent Co. and used as received unless otherwise noted. St was dried over calcium hydride overnight and distilled under the reduced pressure. 2,2'-Azoisobutyronitrile (AIBN) was recrystallized from ethanol and stored at 4^{o}C. RAFT agent **1** was synthesized according to the previous literature.[1] A low-pressure fluorescent lamp (Philips UVB Broadband TL 20W/12) was used as the UV light source. A home-made coiled glass tubes were used as flow reactor having a coil diameter of 7.05 cm, a glass tube diameter of 1.15 cm, and varied volume of 100 mL and 200 mL.

Characterization

^{1}H-NMR spectra were recorded on a Bruker Fourier 300 spectrometer at room temperature.

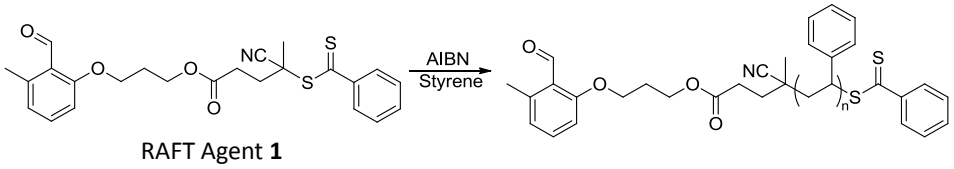
UV-VIS adsorption spectra were recorded using a TU-1901 Ultraviolet Spectrophotometer. The samples were dissolved in THF with a concentration of 5 x 10^{-5} mol/L. The spectra were measured from 200 to 400 nm with a resolution of 1 nm and slit width of 2 nm in a 1 cm UV cuvette.

Matrix-Assisted Laser Desorption/Ionization Time of Flight (MALDI-TOF) mass spectra were recorded on a Autoflex III MALDI-TOF mass spectrometer equipped with a 355 nm YAG laser.

It was operated at an accelerating potential of 20 kV in linear modes. The MALDI mass spectra represent averages over 256 consecutive laser shots (3 Hz repetition rate). The polystyrene were dissolved in THF with a concentration of 5 g/L. α-Cyano-4-hydroxycinnamic acid (CCA; 23 g/L in THF) was used as the matrix and NaCl (saturated in THF) was used as the cation source. The sample was prepared by mixing 10 μL of the polystyrene solution with 10 μL of the matrix solution and 2 μL of the NaCl solution. A 1 μL portion of the final solution was deposited onto the sample target and allowed to dry in air at 25°C. Internal standards (peptides or porphyrine derivatives) were used to calibrate the mass scale using the two-point calibration software 3.07.1 from Autoflex III systems.

Gel permeation chromatography (GPC) in THF was performed using four Waters Styragel columns (HT 2, HT 3, HT 4, and HT 5), a Waters 1515 isocratic HPLC pump, and a Waters 2414 RI detector. THF was used as the eluent at a flow rate of 1.0 mL/min. Polystyrene standards were used for the calibration.

Preparation of Linear PS



RAFT Agent **1**

St (25.0 g, 240.0 mmol), AIBN (10.8 mg, 0.07 mmol), and RAFT agent **1** (380 mg, 0.8 mmol) were mixed into a 50 mL Schlenk tube. After degassing through four freeze-evacuate-thaw cycles, the reaction was stirring for 13 h at 60 ^{o}C. Polymer was precipitated from an excess of methane three times. After drying overnight in a vacuum oven at room temperature, the light red product PS was obtained with a monomer conversion of 7.8% from ^{1}H-NMR.

Preparation of Cyclic PS in Batch Condition

A representative protocol was shown as follows. Linear PS (4.3 mg) was dissolved in mixed solvents (75 mL) of acetonitrile/dichloromethane (v/v = 2/1) to achieve a molar concentration of 2×10^{-5} M. A round bottom flask (100 mL) was used as the batch reactor. The reaction solution was stirred under UV irradiation (7.5 mW/cm^2) for 30 min at room temperature. The cyclic PS was then conveniently collected by evaporation of the solvents.

Preparation of Cyclic PS in Continuous-Flow Condition

A representative protocol was shown as follows. Linear PS (1 g) was dissolved in mixed solvents (17.3 L) of acetonitrile/dichloromethane (v/v = 2/1) to achieve a molar concentration of 2×10^{-5} M. A home-made coiled glass tubes were used as flow reactor having a coil diameter of 7.05 cm, a glass tube diameter of 1.15 cm, and a reaction volume of 200 mL. With a 100 mL/min flow rate, 2 min UV irradiation was achieved for the ring-closing reaction in flow reactor. At this condition, 3h was required for handling 17.3L reaction volume to ring-close 1g linear PS. The resultant cyclic PS was then conveniently collected by evaporation of the solvents.

Optimization of Ring-Closing Reaction Concentration

To achieve a high purity of cyclic topology, ring-closure strategy required a highly diluted ring-closing reaction solution (10^{-5} M level) to selectively achieve intra-molecular coupling but avoid inter-molecular coupling side reaction. Although continuous-flow technique could handle the unlimited volume of reaction solution, the diluted solvents should be used as less as possible considering the production efficiency. As a resultant, ring-closing reaction concentration should be optimized for the formation of cyclic polymer in large scale, by considering the dilemma between avoiding intermolecular side coupling reaction and handling minimum reaction volume

for a reasonable production efficiency.

For the linear PS with a degree of polymerization of 32, a molar concentration of 1×10^{-5} M was used as start point for optimizing the ring-closing reaction concentration. Figure S1A shows the GPC curves of the cyclic PS produced at batch reaction condition with different UV irradiation time, where a round bottom flask (100 mL) was used as the batch reactor containing 2.0 mg linear PS in 70 mL mixed solvents of acetonitrile/dichloromethane (v/v = 2/1) (1×10^{-5} M). The ring-closing reaction could be finished in 10 min UV irradiation, which was indicated by the overlapped GPC curves of the resultant cyclic PS with 10 min (red) and 30 min (blue) UV irradiation. This was again indicated by the complete disappearance of characteristic UV-VIS adsorption peak (305 nm, Figure S1B red and blue curves) of dithioester and ^{1}H NMR signal (10.66 ppm, Figure S2 B and C) of orthoquinodimethane end groups, comparing to those of linear counterparts. Two peak distributions were observed from the GPC curves (red and blue) of the resultant cyclic PS. The minor (< 7%) broad distribution at shorter elution time (< 33.73 min) was formed by the intermolecular coupling byproducts with high molecular weight. The major symmetrical and narrow peak distribution (> 93%) at longer elution time (> 33.73 min) was contributed by the well-defined PS monocycles. Compared to that (black curve) of linear precursor, the peak position of PS monocycles shifted completely to the lower molecular direction indicating a smaller hydrodynamic radius of the resultant cyclic polymer topology. With the ring-closing reaction concentration of 1×10^{-5} M, preparation of 1g cyclic PS requires to handle around 35 L solvents.

The ring-closing reactions were then performed at higher linear PS concentrations to minimize the volume of used solvents for a higher production efficiency. Figure S3A shows the GPC curves of the cyclic PS produced at same batch reaction condition only with different ring-

closing reaction concentrations of 1×10^{-5} M, 2×10^{-5} M, 3×10^{-5} M, and 5×10^{-5} M, in which a round bottom flask (100 mL) was used as the batch reactor and UV irradiation time was used as 30 min. Figure S3B and Figure S4 show the corresponding UV-VIS and ^{1}H NMR characterizations, in which the characteristic UV-VIS adsorption peak (305 nm) of dithioester and ^{1}H NMR signal (10.66 ppm) of orthoquinodimethane end groups were all disappeared completely. This indicated the quantitative ring-closing reaction efficiency for all cases under the used batch reaction conditions. As shown in Figure S3A, the GPC curves were completely overlapped for the cyclic PS obtained with a ring-closing reaction concentration of 1×10^{-5} M and 2×10^{-5} M. When the concentration went above 3×10^{-5} M, however, the more intermolecular coupling byproducts were obtained, indicated by the increased content of high molecular weight peak distribution. As a resultant, the molar concentration of 2×10^{-5} M was selected for ring-closing linear PS and preparing cyclic PS in large scale. With this concentration, preparation of 1g cyclic PS requires to handle 17.3 L solvents.

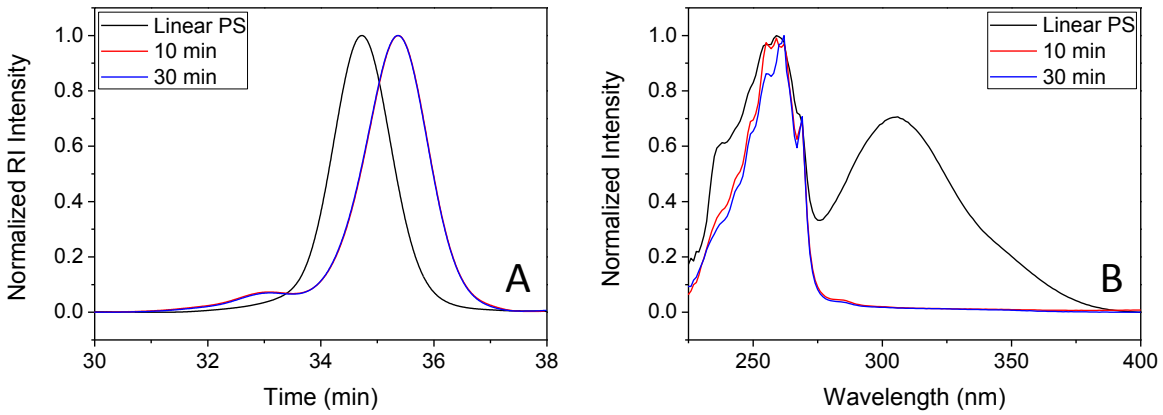


Figure S1. (A) GPC curves of linear PS (black) and cyclic PS prepared at batch reaction condition with 10 min (red) and 30 min (blue) UV irradiation, in which linear PS concentration was used as 1×10^{-5} M for ring-closing reaction; (B) UV-VIS spectra (in THF) of linear PS (black) and cyclic PS prepared at batch reaction condition with 10 min (red) and 30 min (blue) UV irradiation, in which linear PS concentration was used as 1×10^{-5} M for ring-closing reaction.

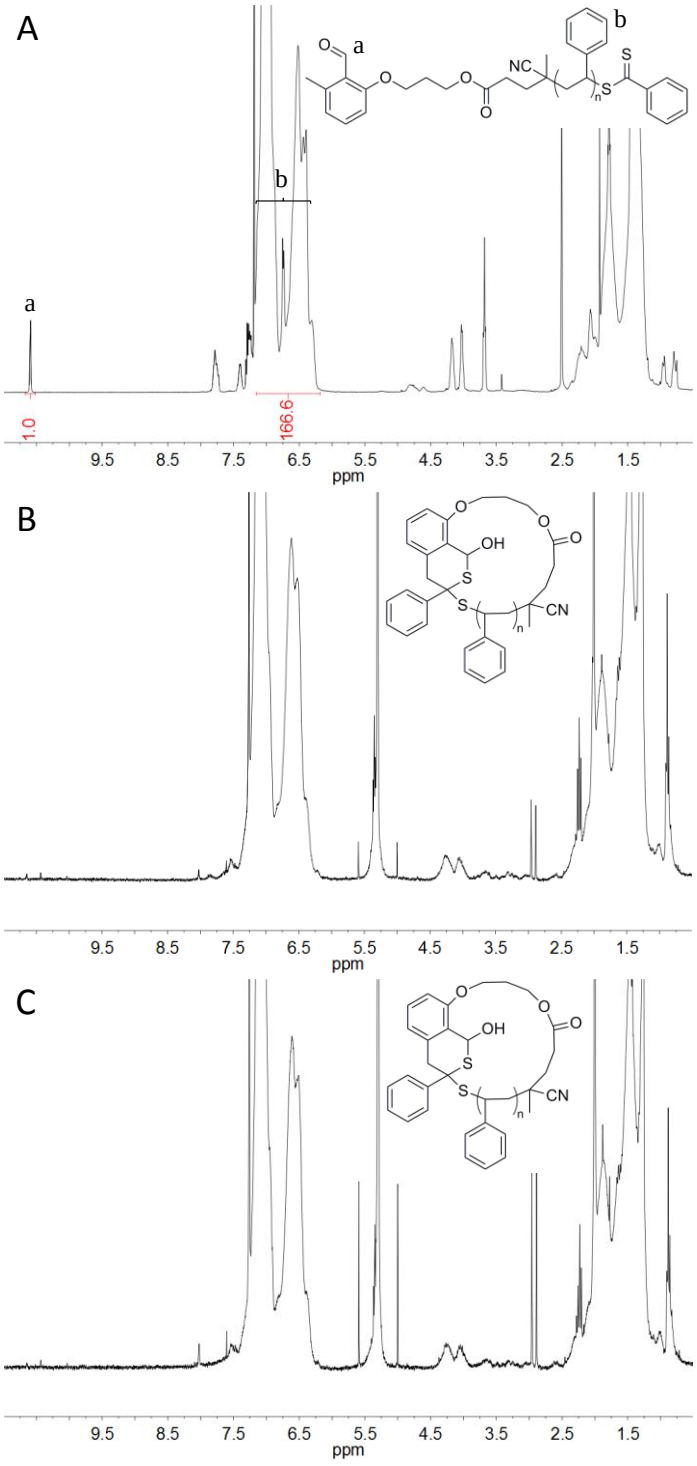


Figure S2. ^{1}H NMR spectrum (in $CDCl_3$) of linear PS (A) and cyclic PS prepared at batch reaction condition with 10 min (B) and 30 min (C) UV irradiation, in which linear PS concentration was used as 1×10^{-5} M for ring-closing reaction.

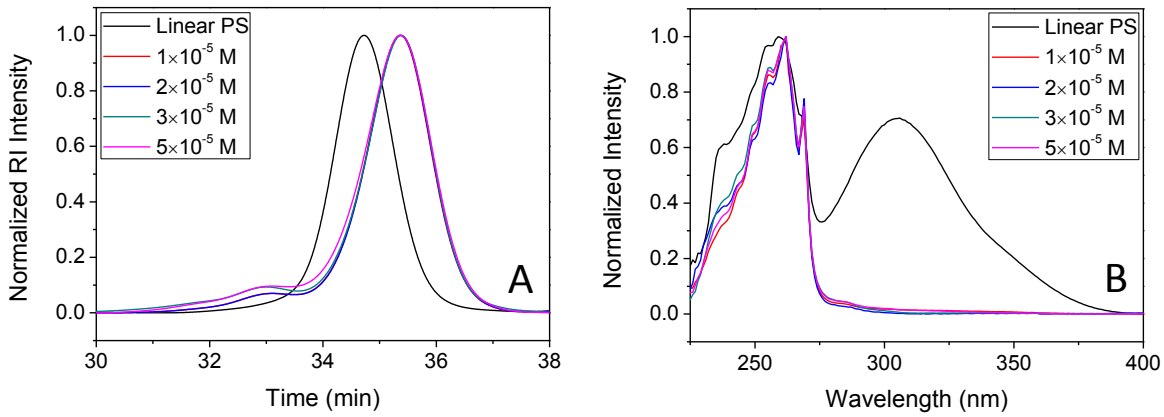


Figure S3. (A) GPC curves of linear PS (black) and cyclic PS prepared at batch reaction condition with different ring-closing reaction concentration of 1×10^{-5} M (red), 2×10^{-5} M (blue), 3×10^{-5} M (dark cyan), and 5×10^{-5} M (magenta), where UV irradiation time was used as 30 min; (B) UV-VIS spectra (in THF) of linear PS (black) and cyclic PS prepared at batch reaction condition with different ring-closing reaction concentration of 1×10^{-5} M (red), 2×10^{-5} M (blue), 3×10^{-5} M (dark cyan), and 5×10^{-5} M (magenta), where UV irradiation time was used as 30 min.

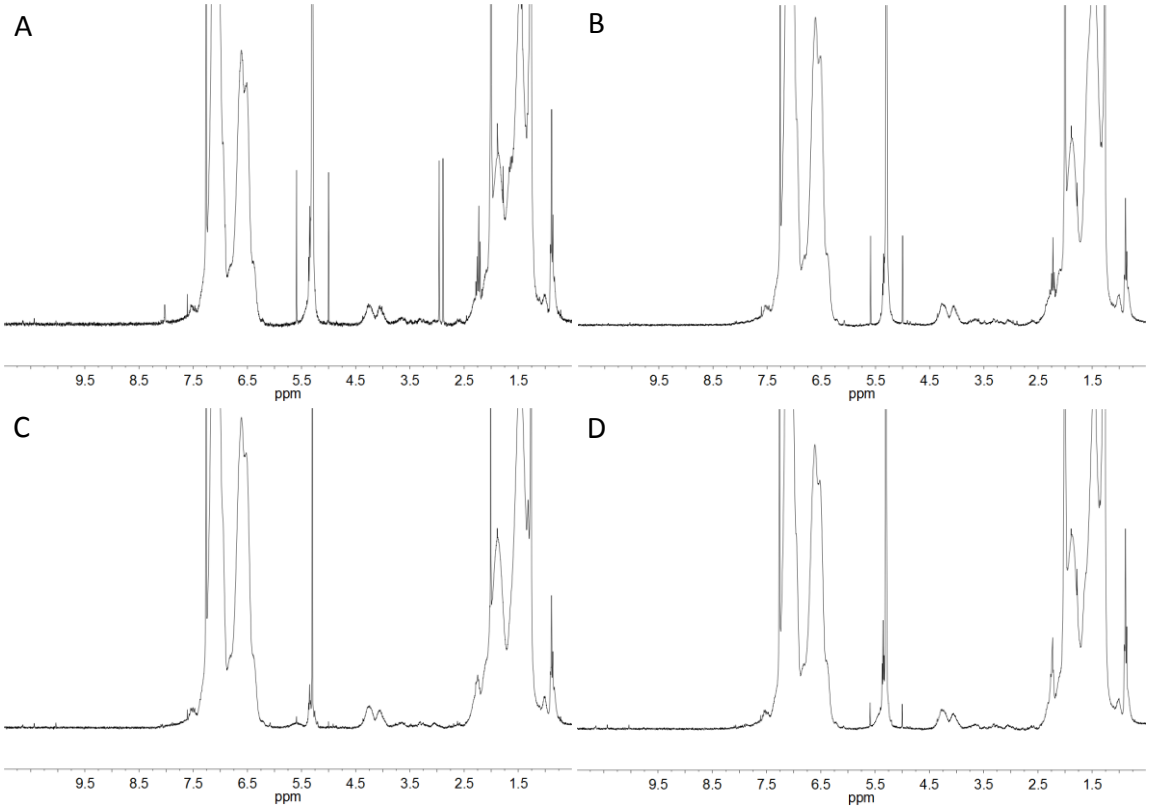


Figure S4. ^{1}H NMR spectrum (in $CDCl_3$) of cyclic PS prepared at batch reaction condition with different ring-closing reaction concentration of 1×10^{-5} M (A), 2×10^{-5} M (B), 3×10^{-5} M (C), and 5×10^{-5} M (D), where UV irradiation time was used as 30 min.

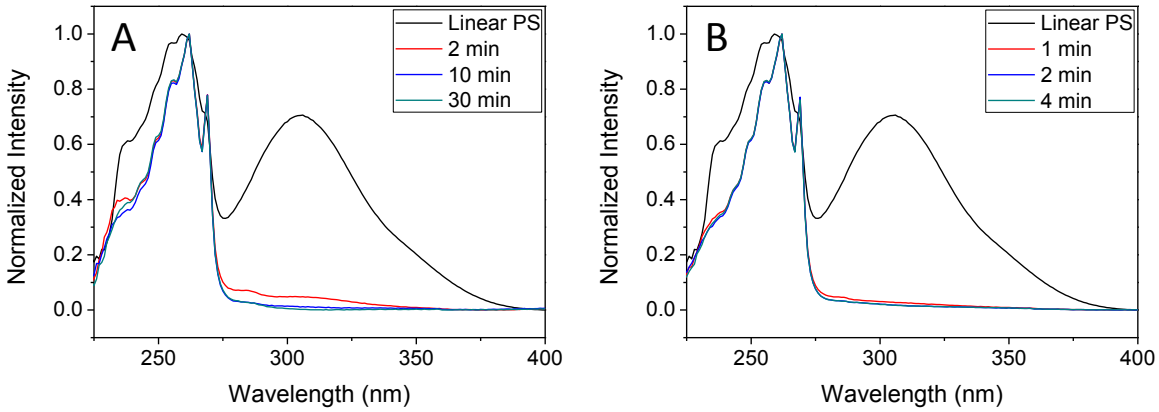


Figure S5. (A) UV-VIS spectra (in THF) of linear PS (black) and cyclic PS prepared under batch condition with different UV irradiation time of 2 min (red), 10 min (blue), and 30 min (dark cyan), where the ring-closing reaction concentration of linear PS precursor was used as 2×10^{-5} M; (B) UV-VIS spectra (in THF) of linear PS (black) and cyclic PS prepared under continuous-flow condition with different UV irradiation time of 1 min (red), 2 min (blue), and 4 min (dark cyan), where the ring-closing reaction concentration of linear PS precursor was used as 2×10^{-5} M.

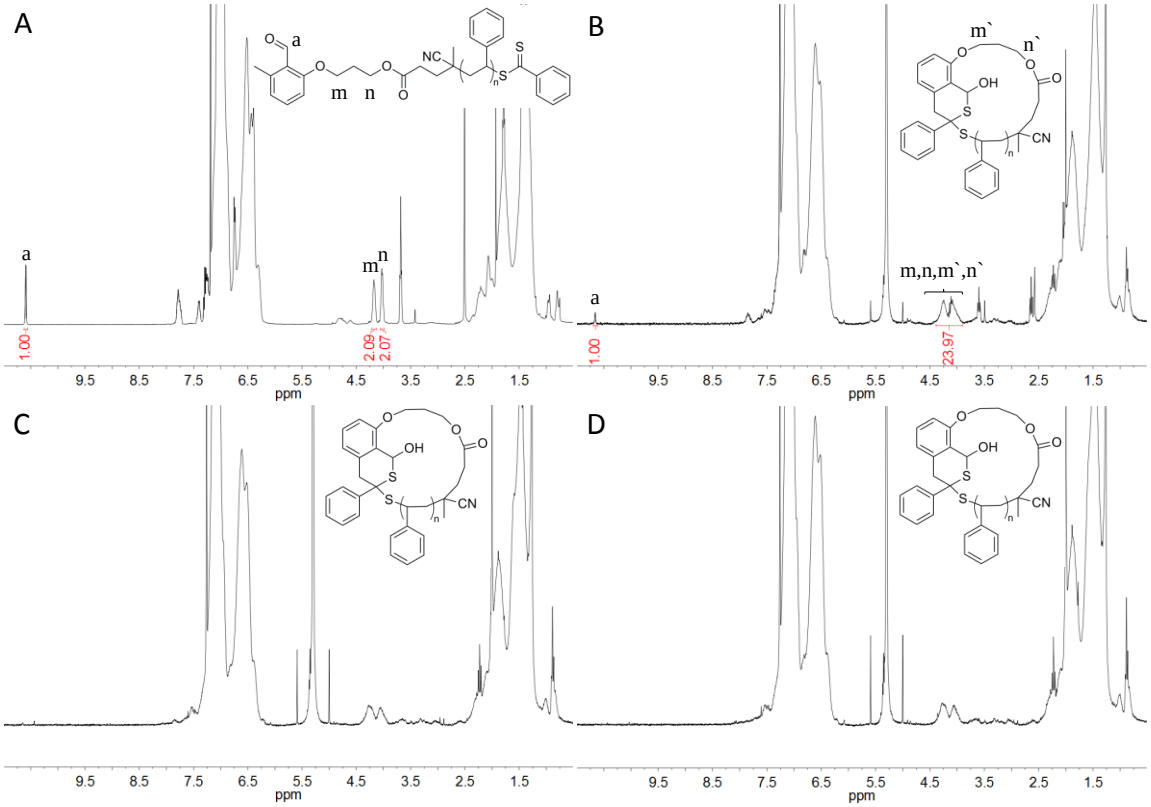


Figure S6. ^{1}H NMR spectrum (in $CDCl_3$) of linear PS (A) and cyclic PS prepared at batch reaction condition with different UV irradiation time of 2 min (B), 10 min (C), and 30 min (D), where the ring-closing reaction concentration of linear PS precursor was used as 2×10^{-5} M. The unreacted orthoquinodimethane end group from UV-induced Diels-Alder reaction could be quantified by the equation of $4*Area_a/(Area_m+Area_n+Area_{m'}+Area_{n'})$.

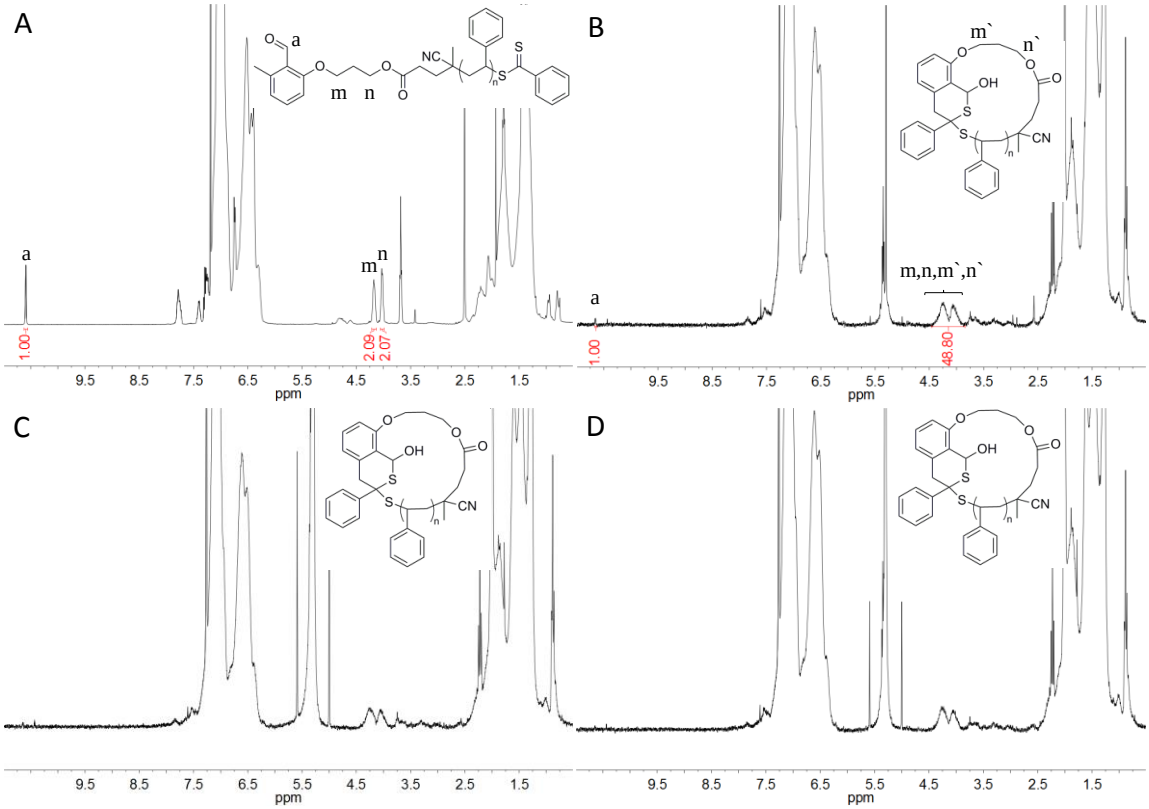


Figure S7. ^{1}H NMR spectrum (in $CDCl_3$) of linear PS (A) and cyclic PS prepared at continuous-flow condition with different UV irradiation time of 1 min (B), 2 min (C), and 4 min (D), where the ring-closing reaction concentration of linear PS precursor was used as 2×10^{-5} M. The unreacted orthoquinodimethane end group from UV-induced Diels-Alder reaction could be quantified by the equation of $4*Area_a/(Area_m+Area_n+Area_{m'}+Area_{n'})$.

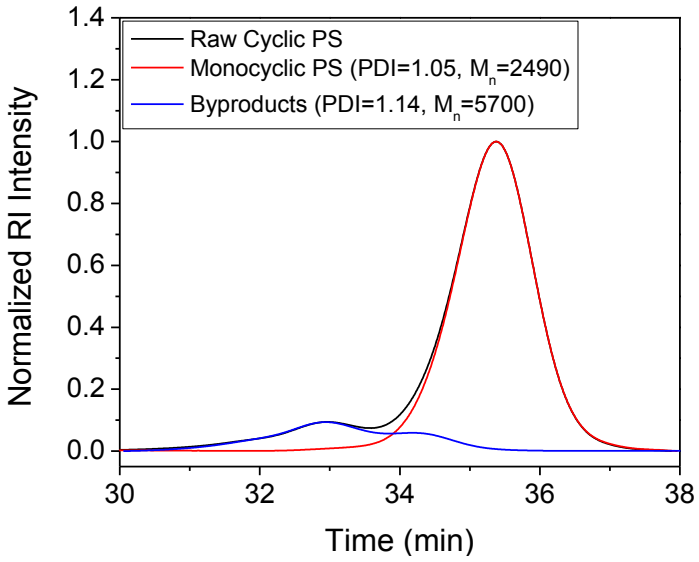


Figure S8. GPC curves of raw cyclic PS (black) and fractionated monocyclic PS (red) and inter-molecular coupling byproducts (blue).

References

(1) Tang, Q. Q.; Wu, Y.; Sun, P.; Chen, Y. M.; Zhang, K. *Macromolecules* **2014**, *47*, 3775.