Supporting Information

Efficient *O*-phthalaldehyde-amine Coupling Reaction for the Synthesis of Bottlebrush Polymer under Physiological Conditions

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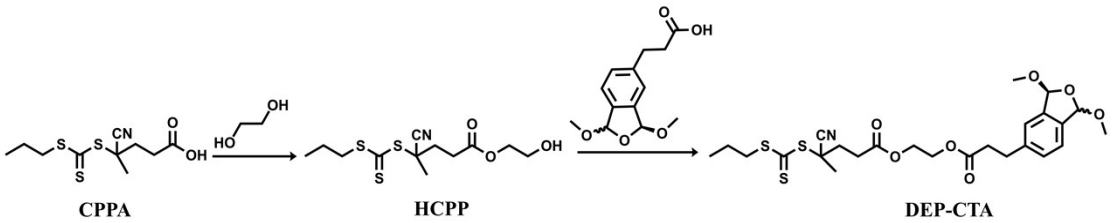
Experimental Section

Materials

N,N-Dimethylacrylamide (DMA; Aldrich, 99%) was passed through a column of basic alumina to remove the stabilizing agents. 2-aminoethyl methacrylate hydrochloride (AMA; J&K, 90%) was purified by washing with tetrahydrofuran (THF) three times to remove the inhibitor. 2′-Azobis(isobutyronitrile) (AIBN; Sinopharm Chemical Reagent, 99%) was purified by recrystallization from ethanol. 4-Cyano-4-(propylthiocarbonothioylthio)pentanoic acid[1] (CPPA) and 3-(1,3-dimethoxy-1,3-dihydroisobenzofuran-5-yl)propanoic acid[2] were synthesized according to

literature procedures. Other reagents were all analytical grade and used as received.

Synthesis of 1,3-diethoxyphthalan (DEP) functionalized RAFT agent (DEP-CTA)



Into a flask ethylene glycol (6.7 g, 108.0 mmol), dicyclohexylcarbodiimide (2.7 g, 13.1 mmol), 4-dimethylaminopyridine (0.3 g, 2.6 mmol) and THF (30 mL) were added. The flask was kept in iced water. CPPA (3.0 g, 10.8 mmol) in THF (15 mL) was then added dropwise into the solution. The mixture was stirred overnight at room temperature. After filtration, the solvent was removed using a rotary evaporator. The crude product was purified by column chromatography on silica gel with petroleum ether/ethyl acetate (V/V = 3/2) to yield HCPP as a yellow oil (2.5 g, 72%). ^{1}H NMR ($CDCl_3$), δ (ppm): 1.05 (t, J = 7.43 Hz, 3H, CH_3CH_2-), 1.77 (q, J = 7.36 Hz, 2H, CH_3CH_2-), 1.91 (s, 3H, -CCH_3), 2.36-2.63 ppm (m, 2H, -CH_2COO-), 2.71 (t, J = 7.69 Hz, 2H, -CH_2CH_2COO-), 3.35 (t, J = 7.13 Hz, 2H, -CH_2S-), 3.88 (t, J = 4.32 Hz, 2H, -CH_2OH), 4.28 (t, J = 3.70 Hz, 2H, -COOCH_2-). ^{13}C NMR ($CDCl_3$), δ (ppm): 13.48, 21.29, 24.84, 29.66, 33.82, 38.85, 46.36, 60.84, 66.63, 119.02, 171.74, 217.00.

HCCP (2.5 g, 7.8 mmol), dicyclohexylcarbodiimide (1.6 g, 7.8 mmol) and 4-dimethylaminopyridine (0.2 g, 1.6 mmol) were dissolved in dichloromethane (15 mL). The solution was kept in an ice bath. To this solution, 3-(1,3-dimethoxy-1,3-dihydroisobenzofuran-5-yl)propanoic acid (2.4 g, 9.4 mmol) dissolved in

dichloromethane (10 mL) was added dropwise. After the addition was completed, the reaction mixture was stirred at room temperature overnight. After filtration, the solvent was removed using a rotary evaporator. The crude product was purified by column chromatography on silica gel with petroleum ether/ethyl acetate (V/V = 2/1) to yield DEP-CTA as a yellow oil (3.3 g, 76%). Note: there are four isomers of the DEP groups and their chemical shifts of the proton signals are extensively overlapped. ^{1}H NMR ($CDCl_3$), δ (ppm): 1.03 (t, *J* = 7.38 Hz, 3H, C*H*$_3$CH$_2$-), 1.75 (q, *J* = 7.22 Hz, 2H, CH$_3$C*H*$_2$-), 1.90 (s, 3H, -CC*H*$_3$), 2.31-2.61 ppm (m, 2H, -C*H*$_2$COO-), 2.67 (m, 4H, -C*H*$_2$CH$_2$COO- and ArCH$_2$C*H*$_2$-), 3.03 (m, 2H, ArC*H*$_2$-), 3.33 (t, *J* = 7.16 Hz, 2H, -C*H*$_2$S-), 3.45 (m, 6H, -OC*H*$_3$), 4.30 (s, 4H, -COOC*H*$_2$C*H*$_2$OOC-), 6.05 (d, *J* = 7.14 Hz, 1H, -OC*H*O-), 6.31 (t, *J* = 3.41 Hz, 1H, -OC*H*O-), 7.24-7.52 (m, 3H, Ar). ^{13}C NMR ($CDCl_3$), δ (ppm): 13.48, 21.29, 24.90, 29.64, 30.68, 33.77, 35.57, 38.85, 46.48, 54.19, 54.44, 62.11, 62.73, 105.45, 106.55, 118.95, 122.68, 123.09, 130.04, 130.67, 138.94, 142.33, 171.28, 172.32, 216.90.

Preparation of PAMA polymer backbone

An ampule equipped with a magnetic stir bar was charged with AMA monomer (0.9 g, 5.4 mmol), CPPA chain transfer agent (7.5 mg, 27.0 μmol), 2,2'-azobis(2-methylpropionamidine) dihydrochloride (1.5 mg, 5.4 μmol) and a mixture of methanol and water (1:1 wt./wt., 3.6 g), then degassed by three freeze-pump-thaw cycles, sealed under N_2, and heated at 70 °C for 24 h. The reaction was quenched by cooling in an ice bath, followed by exposure to air. The crude product was purified by

dialysis against water at a pH of 5 and then freeze-dried.

RAFT polymerization kinetics of DMA.

A stock solution in 1,4-dioxane (10 mL) comprising DEP-CTA (36.1 mg, 0.6 mmol) , DMA (6.0 g, 60.6 mmol) and AIBN (9.8 mg, 0.06 mmol) was prepared. Aliquots (2 mL) were transferred to ampules, degassed by three freeze-pump-thaw cycles, sealed, and heated at 65 ^{o}C. After the predetermined intervals, the polymerization was quenched by exposure to air. These samples were then analyzed by ^{1}H NMR and GPC to measure the conversions, number-average molecular weights and dispersities.

RAFT polymerization of DMA with chain transfer agent DEP-CTA

The preparation of $PDMA_{26}$-DEP was given as an example. An ampule equipped with a magnetic stir bar was charged with DMA (3.0 g, 30.3 mmol), DEP-CTA (672.7 mg, 1.1 mmol), AIBN (35.6 mg, 0.24 mmol) and 1,4-dioxane (5 mL), then degassed by three freeze-pump-thaw cycles, sealed under N_2, and heated at 65 °C for 3 h. The reaction was quenched by cooling in an ice bath, followed by exposure to air. The crude product was precipitated in ethyl ether three times and dried under vacuum.

Synthesis of OPA-terminated PDMA side chains

The preparation of $PDMA_{26}$-OPA was given as an example. $PDMA_{26}$-DEP (1.0 g, 0.3 mmol) was dissolved in TFA/dichloromethane mixture (V/V=1:4, 10 mL) and stirred at room temperature for 2 h. The reaction mixture was then evaporated under vacuum

to remove the solvent, redissolved in dichloromethane, precipitated in diethyl ether/petroleum ether (V/V = 1: 1) and dried in vacuo.

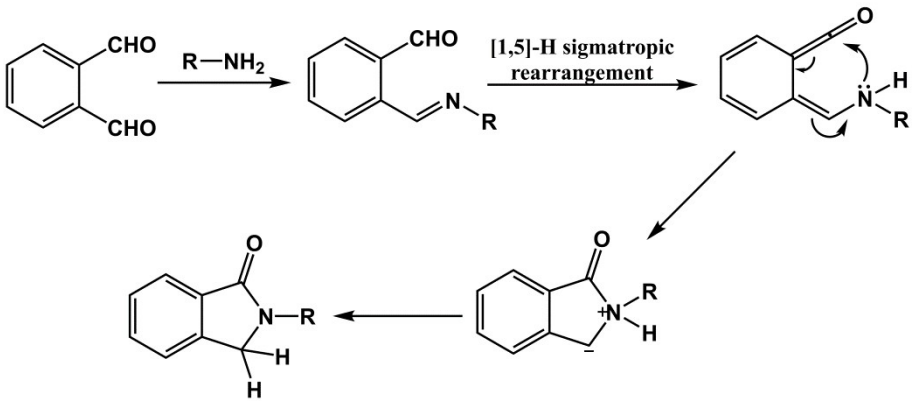
Preparation of brush polymers via OPA-amine reaction

The preparation of $PAMA_{147}$-*g*-$PDMA_{26}$ was given as an example. $PDMA_{26}$-OPA (123.3 mg, 40.0 μmol) was dissolved in 3.0 mL of PBS buffer (pH=7.4). $PAMA_{147}$ (5.6 mg, 33.3 μmol of $-NH_2$) in 1.0 mL of PBS buffer (pH=7.4) was added into the above side chain solution. The reaction mixture was stirred at room temperature. Samples were taken out at different reaction time periods and then quenched by glycine for tracing the reaction. After the reaction, the final crude product was purified by preparative GPC.

Characterization

^1H NMR and ^{13}C NMR spectra were recorded using a Bruker Avance III 400 spectrometer (400 MHz). The number-average molecular weight (M_n) and molecular weight distribution (M_w/M_n) were measured by gel permeation chromatography (GPC) against PMMA standard in DMF at a flow rate of 1.0 mL min^{-1} at 35 °C on three Waters Styragel columns (measurable molecular weight range: 100-5000, 500-30 000, and 5000-600 000) connected to a Waters 1515 pump and a Waters 2414 refractive index detector. Prior to GPC studies, to improve the solubility of PAMA, the primary amine groups were derivatised with excess di-tert-butyldicarbonate in DMF containing triethylamine. UV-Vis adsorption spectra were recorded on PGENERAL

TU-1901 UV-Vis spectrophotometer. Atomic force microscopy (AFM) experiments were performed in the ScanAyst mode in air at room temperature with a Bruker Multimode 8 AFM (Bruker Nano Inc.). Measurements were performed using non-conductive silicon nitride AFM probes (Bruker Nano Inc.). For sample preparation, a polymer aqueous solution (0.005 mg mL^{-1}) was dropped on a mica wafer and then dried at room temperature.



Scheme S1. Mechanism of the OPA-amine reaction

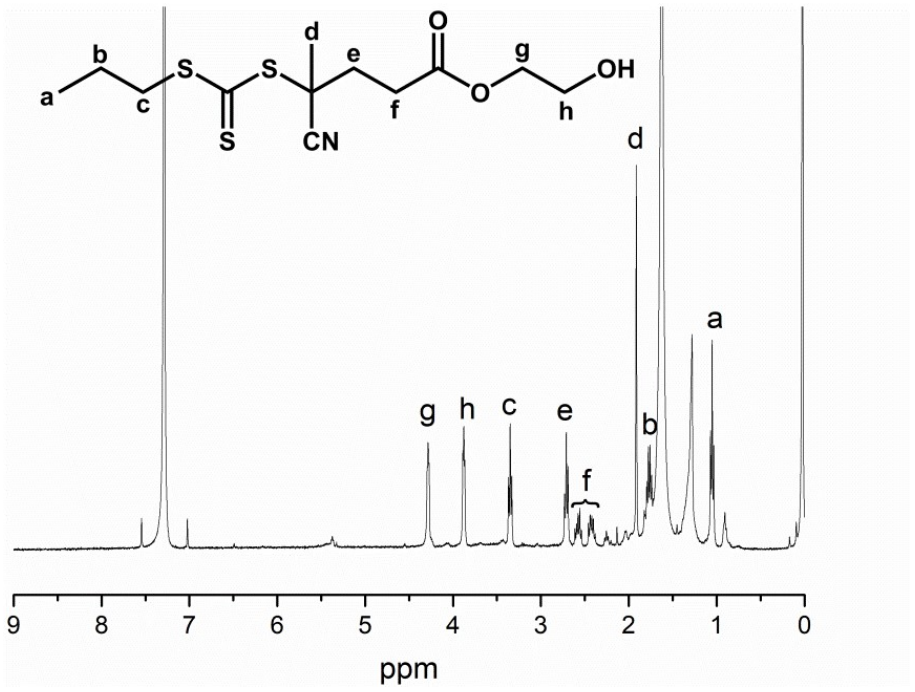


Figure S1. ^{1}H NMR spectrum of HCPP in $CDCl_3$.

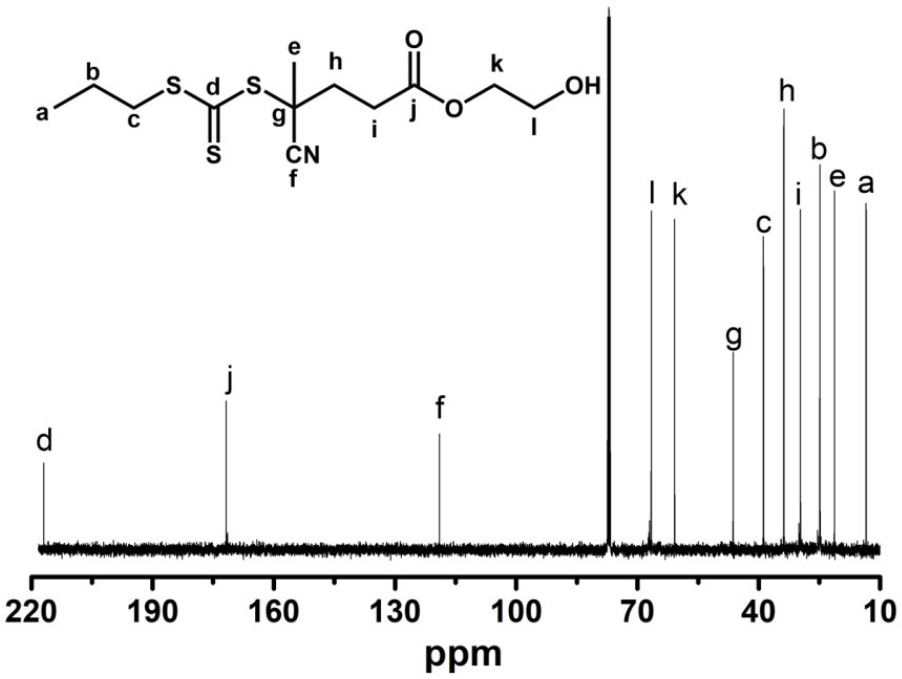


Figure S2. ^{13}C NMR spectrum of HCPP in $CDCl_3$.

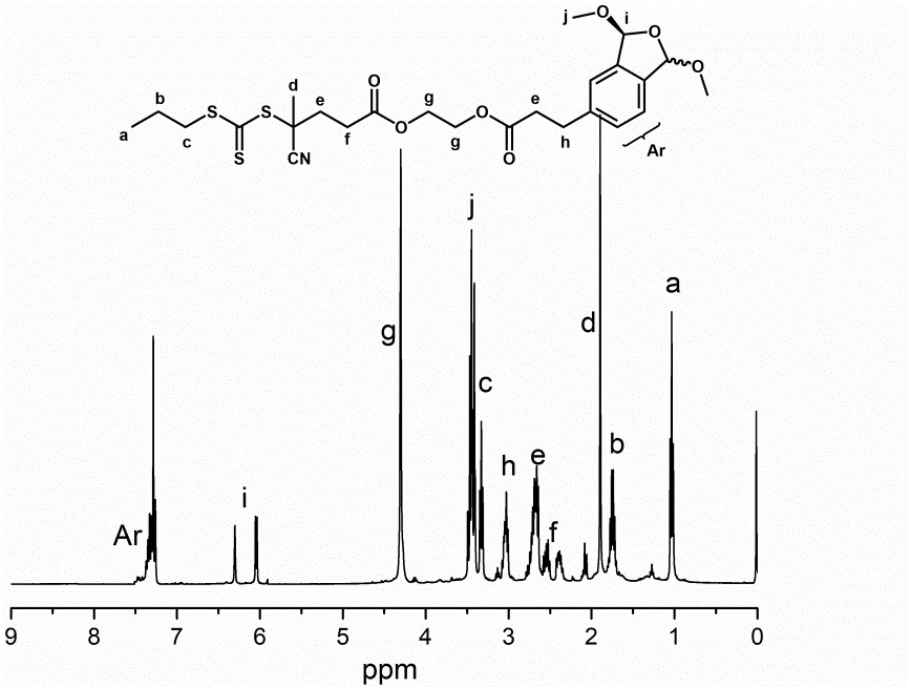


Figure S3. ^{1}H NMR spectrum of DEP-CTA in $CDCl_3$.

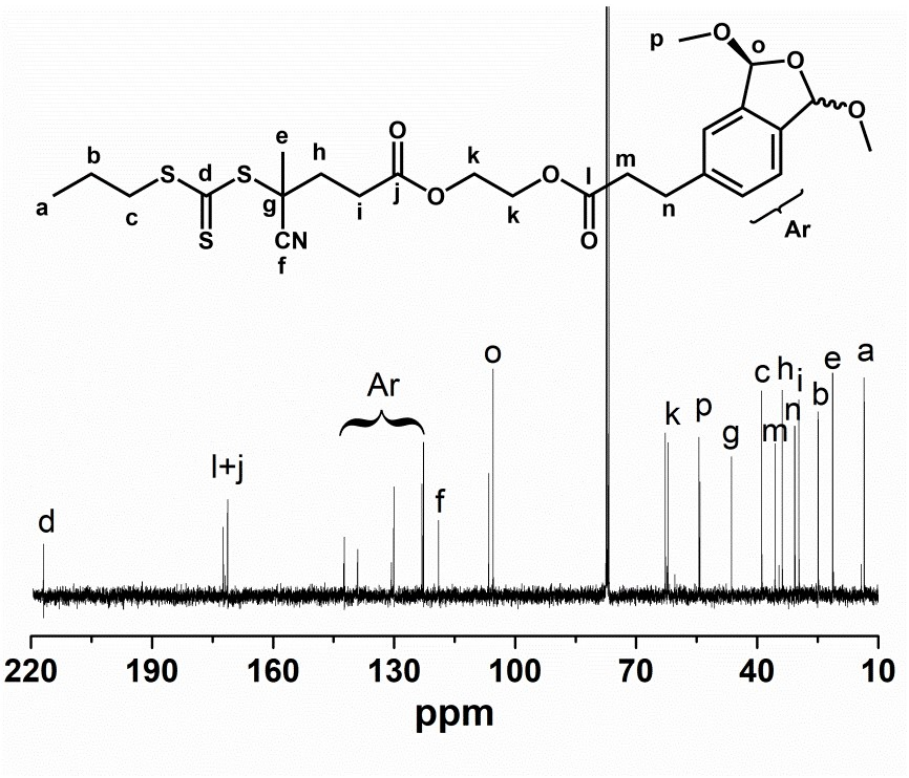


Figure S4. ^{13}C NMR spectrum of DEP-CTA in $CDCl_3$.

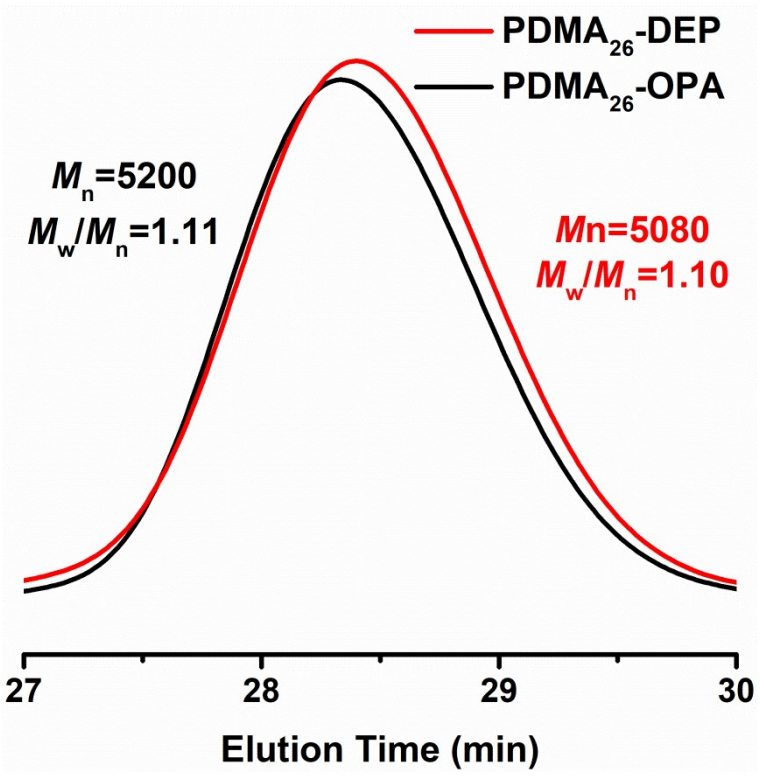


Figure S5. GPC traces of $PDMA_{26}$-DEP (red) and $PDMA_{26}$-OPA (black).

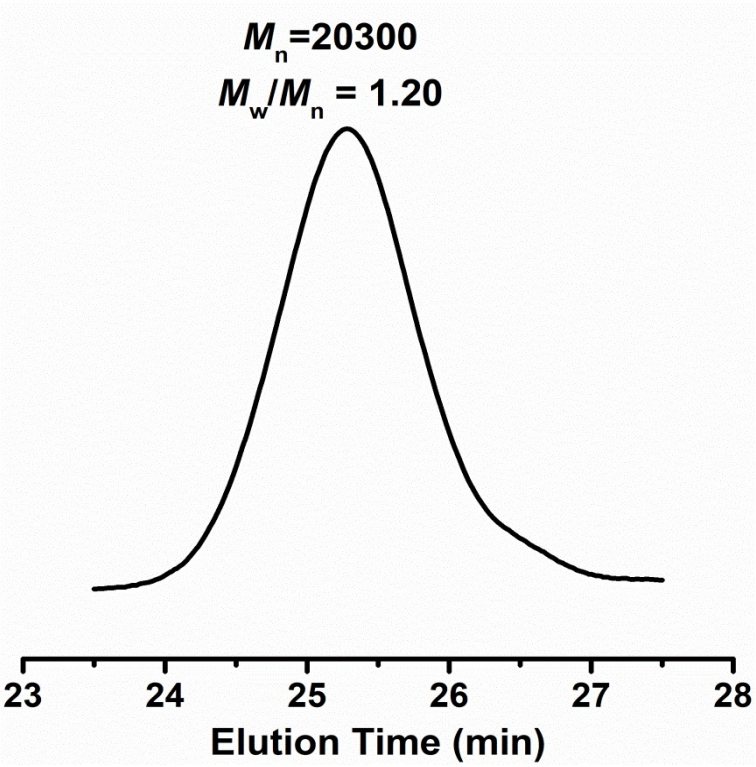


Figure S6. GPC trace of $PAMA_{147}$.

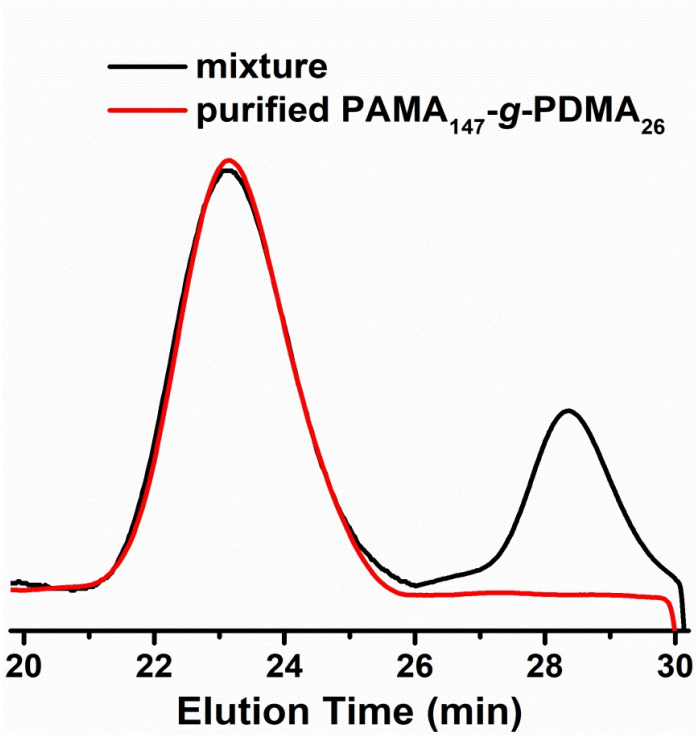


Figure S7. GPC traces of the bottlebrush polymer $PAMA_{147}$-*g*-$PDMA_{26}$ with 15min reaction time before and after purification.

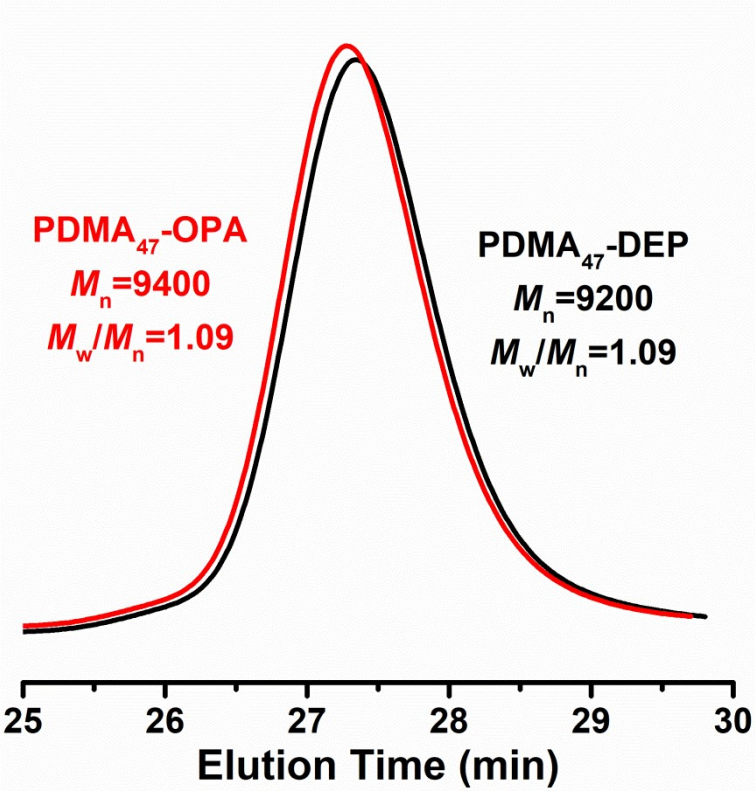


Figure S8. GPC traces of $PDMA_{47}$-DEP (black) and $PDMA_{47}$-OPA (red).

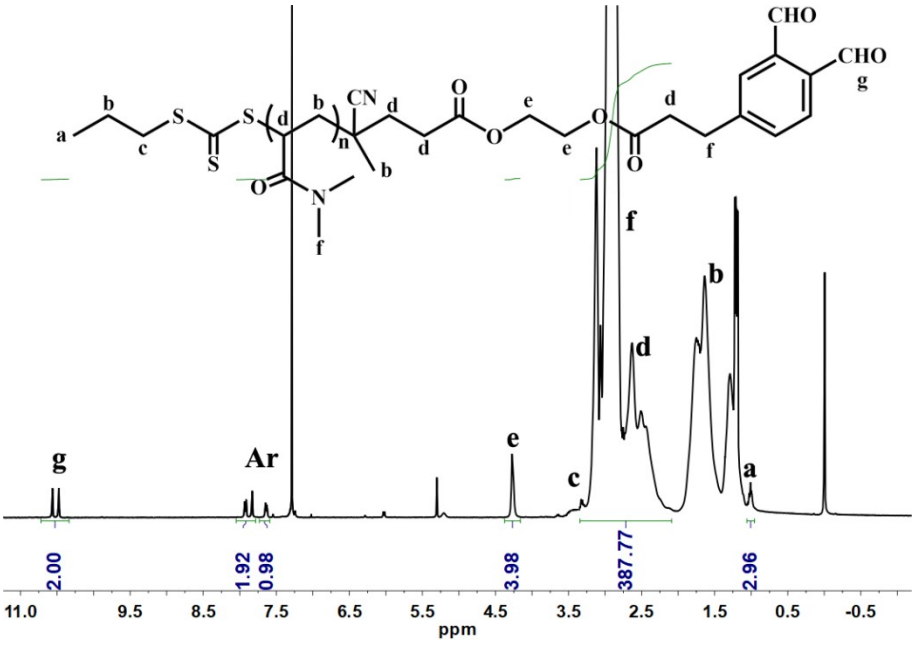


Figure S9. ^{1}H NMR spectrum of $PDMA_{47}$-OPA in $CDCl_3$.

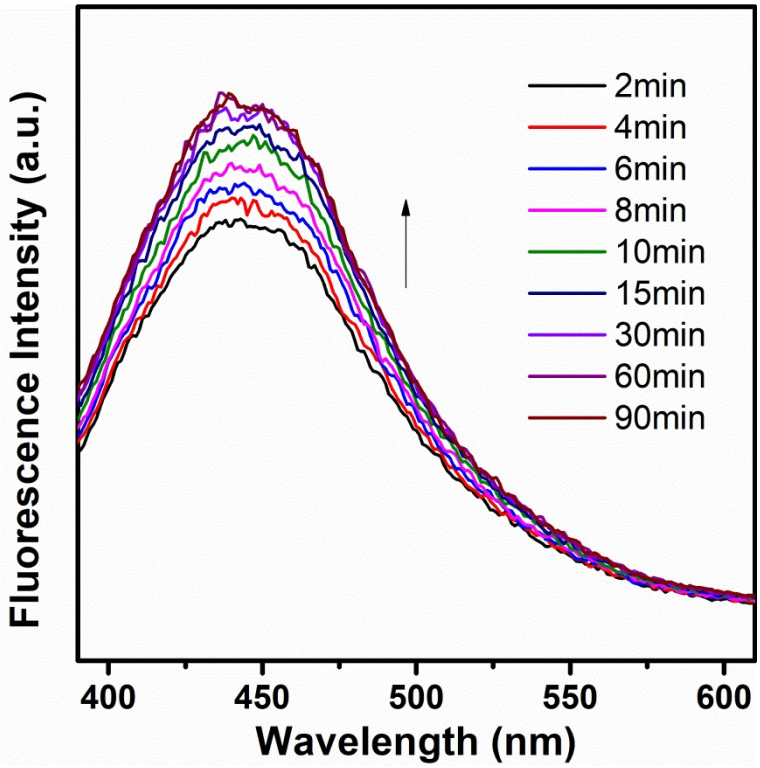


Figure S10. Fluorescence spectra as a function of time recorded for the coupling reaction of $PAMA_{147}$ with $PDMA_{47}$-OPA.

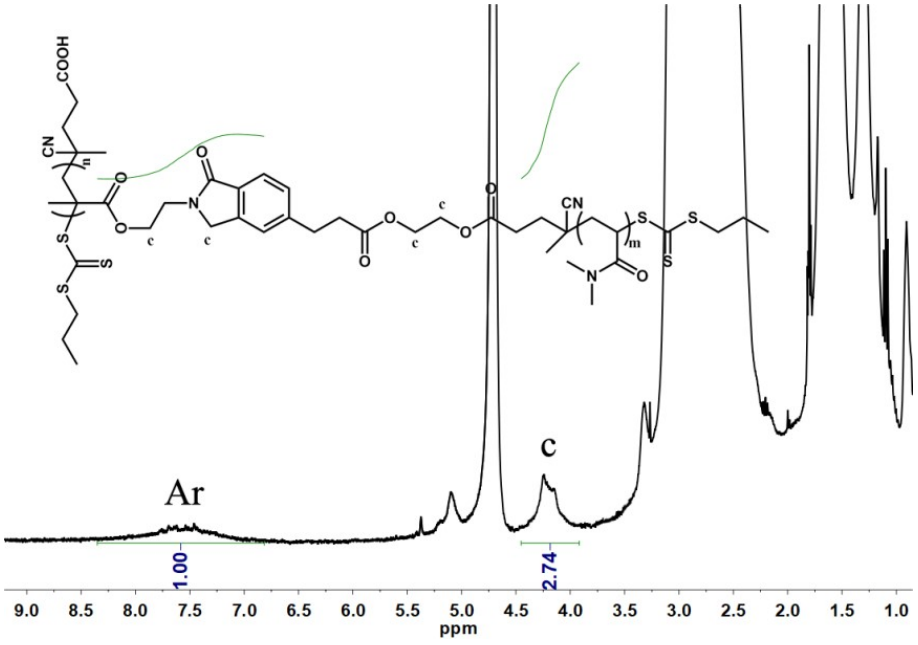


Figure S11. ^{1}H NMR spectrum of bottlebrush polymer $PAMA_{147}$-*g*-$PDMA_{47}$ in D_2O.

References

1. X. Xu, A. E. Smith, S. E. Kirkland, C. L. McCormick, *Macromolecules* **2008**, 41, 8429-8435.

2. C. L. Tung, C. T. T. Wong, E. Y. M. Fung, X. Li, *Org. Lett.* **2016**, 18, 2600-2603.