

# Sequence-controlled Polymerization using Dendritic Macromonomers: Precise Chain-Positioning of Bulky Functional Clusters.

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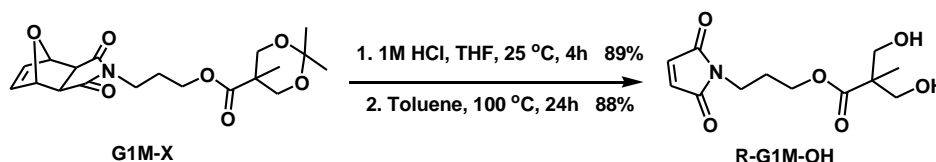
## **A. Experimental procedures:**

**A.1. Chemicals.** The maleimide-containing dendrons 3-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)propyl 2,2,5-trimethyl-1,3-dioxane-5-carboxylate (**D1** R-G1M-X), 2-((3-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)propoxy)carbonyl)-2-methylpropane-1,3-diyl bis(2,2,5-trimethyl-1,3-dioxane-5-carboxylate) (**D2** R-G2M-X), (((2-((3-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)propoxy)carbonyl)-2-methylpropane-1,3-diyl)bis(oxy))bis(carbonyl))bis(2-methylpropane-3,2,1-triyl)tetrakis(2,2,5-trimethyl-1,3-dioxane-5-carboxylate) (**D3** R-G3M-X) were synthesized according to literature procedures.<sup>1-2</sup> 3-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)propyl 3-hydroxy-2-(hydroxymethyl)-2-methylpropanoate (**D4** R-G1M-OH), 2-((3-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)propoxy)carbonyl)-2-methylpropane-1,3-diyl bis(3-hydroxy-2-(hydroxymethyl)-2-methylpropanoate) (**D5** R-G2M-OH), and 2-((3-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)propoxy)carbonyl)-2-methylpropane-1,3-diyl bis(2-methyl-3-(pent-4-enoyloxy)-2-((pent-4-enoyloxy)methyl)propanoate) (**D6** R-G2M-alkene) were synthesized as explained below. The *N*-(2-methylpropyl)-*N*-(1-diethylphosphono-2,2-dimethylpropyl)-*O*-(2-carboxylprop-2-yl)-hydroxylamine initiator (BlocBuilder MA®, Arkema, 99 %), 4-dimethylaminopyridine (DMAP, 99%, Sigma Aldrich), 4-pentenoic anhydride (98%, Sigma Aldrich) and pyridine (99%, Merck) were used as received without further purification. Styrene (Sigma Aldrich, 99 %) was distilled over CaH<sub>2</sub> and stored under argon atmosphere at low temperature prior to use.

## **A.2. Synthesis of dendron-functionalized maleimides.**

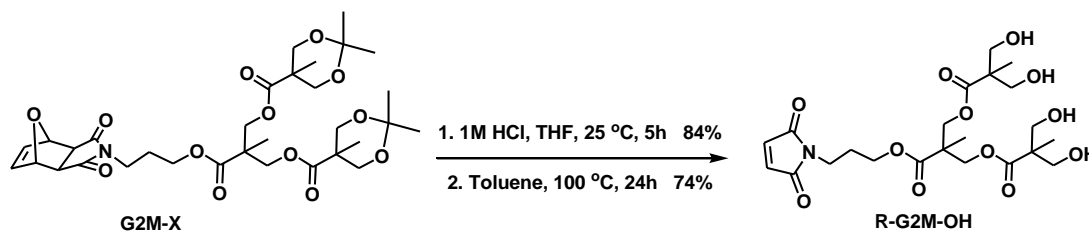
**A.2.1. Synthesis of R-G1M-OH.** Furan protected maleimide containing first generation polyester dendron with acetal units at the periphery (G1M-X) was synthesized according to the literature.<sup>3-4</sup> This compound (1.00 g, 2.64 mmol) was dissolved in THF (10 mL) and to this solution 1M HCl solution (10 mL) was added. The resulting mixture was stirred at 25 °C until the consumption of G1M-X was observed via thin layer chromatography (TLC). Then, THF was evaporated and the resulting aqueous solution was extracted with CH<sub>2</sub>Cl<sub>2</sub>, and the organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. The residue was concentrated *in vacuo*. The crude product was purified by column chromatography to give G1M-OH (0.78 g, 89 %). The obtained product (0.30 g, 0.88 mmol) was then dissolved in toluene (100 mL) and heated up to 100 °C. After the reaction mixture was stirred for 24 hours, toluene was evaporated and the crude product was purified by column chromatography to give R-G1M-OH as a white solid (0.21 g, 88 %). <sup>1</sup>H NMR (CDCl<sub>3</sub>, δ, ppm) 6.69 (s, 2H, CH=CH), 4.11 (t, 2H, *J* = 6.0 Hz,

OCH<sub>2</sub>), 3.88 (d, 2H, *J* = 11.2 Hz, HOCH<sub>2</sub>), 3.74 (d, 2H, *J* = 11.2 Hz, HOCH<sub>2</sub> protons), 3.64 (t, 2H, *J* = 6.8 Hz, NCH<sub>2</sub>), 2.91 (br s, 2H, OH), 2.02-1.94 (m, 2H, NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>O), 1.09 (s, 3H, C(CH<sub>3</sub>)). <sup>13</sup>C NMR (CDCl<sub>3</sub>, δ, ppm) 175.7, 170.8, 134.2, 68.1, 61.3, 49.5, 34.3, 27.5, 17.2. Anal. calcd. for R-G1-OH [C<sub>12</sub>H<sub>17</sub>NO<sub>6</sub>]: C, 53.13; H, 6.32; N, 5.16. Found: C, 53.17; H, 6.42; N, 5.32.



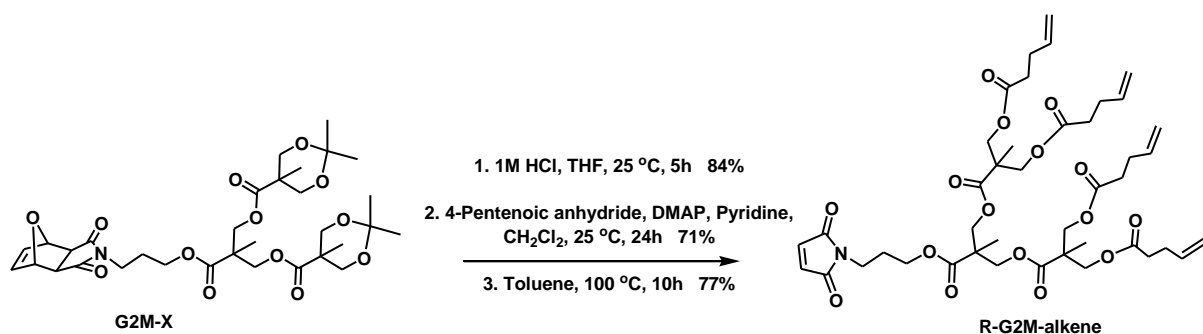
**Figure S1.** Synthesis of R-G1M-OH.

**A.2.2. Synthesis of R-G2M-OH.** Furan protected maleimide containing second generation polyester dendron with acetal units at the periphery (G2M-X) was synthesized according to the literature.<sup>3-4</sup> This compound (3.70 g, 5.68 mmol) was dissolved in THF (30 mL) and to this solution 1M HCl solution (30 mL) was added. The resulting mixture was stirred at 25 °C until the consumption of G2M-X was observed via TLC. Then, THF was evaporated and the resulting aqueous solution was extracted with CH<sub>2</sub>Cl<sub>2</sub>, and the organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. The residue was concentrated in *vacuo*. The crude product was purified by column chromatography to give G2M-OH (2.70 g, 84 %). The obtained product (0.60 g, 1.05 mmol) was then dissolved in toluene (200 mL) and heated up to 100 °C. After the reaction mixture was stirred for 24 hours, toluene was evaporated and the crude product was purified by column chromatography to give R-G2M-OH as a white solid (0.39 g, 74 %). <sup>1</sup>H NMR (CDCl<sub>3</sub>, δ, ppm) 6.70 (s, 2H, CH=CH), 4.43 (d, 2H, *J* = 11.2 Hz, CH<sub>2</sub> ester protons), 4.28 (d, 2H, *J* = 11.2 Hz, CH<sub>2</sub> ester protons), 4.10 (t, 2H, *J* = 5.8 Hz, OCH<sub>2</sub>), 3.81 (dd, 4H, *J* = 11.4, 2.4 Hz, HOCH<sub>2</sub>), 3.69 (dd, 4H, *J* = 11.4, 2.4 Hz, HOCH<sub>2</sub>), 3.61 (t, 2H, *J* = 6.4 Hz, NCH<sub>2</sub>), 2.50 (br s, 4H, OH), 1.98-1.92 (m, 2H, NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>O), 1.31 (s, 3H, C(CH<sub>3</sub>)), 1.04 (s, 6H, C(CH<sub>3</sub>)). <sup>13</sup>C NMR (CDCl<sub>3</sub>, δ, ppm) 175.1, 172.8, 170.7, 134.2, 60.8, 64.9, 62.4, 49.8, 46.5, 34.5, 27.6, 18.0, 17.1. Anal. calcd. for R-G2-OH [C<sub>22</sub>H<sub>33</sub>NO<sub>12</sub>]: C, 50.91; H, 6.74; N, 2.70. Found: C, 50.74; H, 6.68; N, 2.69.



**Figure S2.** Synthesis of R-G2M-OH.

**A.2.3. Synthesis of R-G2M-alkene.** Furan protected maleimide containing second generation polyester dendron with hydroxy units at the periphery (G2M-OH) was synthesized as described before.<sup>3-4</sup> To a solution of G2M-OH (0.40 g, 0.7 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (25 mL), 4-pentenoic anhydride (1.02 g, 5.60 mmol), DMAP (0.14 g, 1.15 mmol) and pyridine (0.51 mL) were added. The mixture was stirred at 25 °C for 24 hours followed by quenching of excess anhydride with (1:1 v/v) mixture of pyridine and water (1.00 mL) for 2 h. Then, the reaction mixture was extracted with 1 M NaHSO<sub>4</sub> (3 x 20 mL), 10 % Na<sub>2</sub>CO<sub>3</sub> (3 x 20 mL) and then with brine (1 x 20 mL), and combined organic layers were dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. The residue was concentrated *in vacuo*. The product (G2M-alkene) was obtained as a light yellow solid (0.45 g, 71 %). The obtained product (0.20 g, 0.22 mmol) was then dissolved in toluene (200 mL) and heated up to 100 °C. After the reaction mixture was stirred for 10 hours, toluene was evaporated and the crude product was purified by column chromatography to give R-G2M-alkene as a light yellow solid (0.14 g, 77 %). <sup>1</sup>H NMR (CDCl<sub>3</sub>, δ, ppm) 6.69 (s, 2H, CH=CH), 5.82-5.72 (m, 4H, CH=CH<sub>2</sub>), 5.05-4.96 (m, 8H, CH=CH<sub>2</sub>), 4.26 (s, 4H, CH<sub>2</sub> ester protons), 4.28 (dd, 8H, *J* = 11.2, 2.4 Hz, CH<sub>2</sub> ester protons), 4.07 (t, 2H, *J* = 6.2 Hz, OCH<sub>2</sub>), 3.60 (t, 2H, *J* = 6.6 Hz, NCH<sub>2</sub>), 2.41-2.30 (m, 16H, OCCH<sub>2</sub>CH<sub>2</sub>), 1.98-1.92 (m, 2H, NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>O), 1.26 (s, 3H, C(CH<sub>3</sub>)), 1.21 (s, 6H, C(CH<sub>3</sub>)). <sup>13</sup>C NMR (CDCl<sub>3</sub>, δ, ppm) 172.4, 172.0, 171.9, 170.6, 136.4, 134.2, 115.6, 65.7, 65.1, 62.2, 46.6, 46.4, 34.4, 33.2, 28.7, 27.5, 17.8, 17.5. Calculated: [M]<sup>+</sup> *m/z* = 831.9. Found: MALDI-TOF MS: [M]<sup>+</sup> *m/z* = 833.5, [M+Na]<sup>+</sup> *m/z* = 854.8.



**Figure S3.** Synthesis of R-G2M-alkene.

**A.3. General procedure for the direct NMP copolymerization of styrene with macromonomers D1-D5.** BlocBuilder MA® (1 equiv.) and a dendron-functionalized maleimide (1 equiv.) were added into a flask, sealed with a septum and purged with dry argon for 30 minutes. Then degassed styrene (50 equiv.) was added with a degassed syringe. The mixture was immersed in a preheated oil bath at 120 °C. During the polymerization, aliquots were taken from the reaction mixture with a degassed syringe in order to monitor the incorporation of maleimide in the growing copolymer chains by <sup>1</sup>H NMR spectroscopy. After approximately 240 minutes of polymerization, the reaction mixture was cooled down to room temperature (RT), diluted in a small amount of THF and poured in a large amount of cold methanol. The precipitated copolymer was filtered and dried *in vacuo* at RT.

**A.4. General procedure for the time-controlled addition of macromonomers D1-D5 during the NMP of styrene.** BlocBuilder MA® (1 equiv.) was added into a flask, sealed with a septum and purged with dry argon for 30 minutes. Then degassed styrene (50 equiv.) was added with a degassed syringe. The mixture was then immersed in a preheated oil bath at 120 °C. After 45 minutes of polymerization, a degassed solution of dendron-functionalized maleimide (1 equiv.) in degassed anisole was added with a degassed syringe. During the copolymerization, aliquots were taken from the mixture with a degassed syringe in order to monitor the incorporation of maleimide in the growing copolymer chains. After 240 minutes of polymerization, the reaction mixture was cooled down to RT, diluted in a small amount of THF and poured in a large amount of cold methanol. The precipitated copolymer was filtered and dried *in vacuo* at RT.

**A.5. General procedure for the time-controlled addition of D6 in styrene NMP.** BlocBuilder MA® (1 equiv.) was added into a flask, sealed with a septum and purged with dry argon for 30 minutes. Then degassed styrene (50 equiv.) was added with a degassed syringe. The mixture was immersed in a preheated oil bath at 120 °C. After 55 minutes of polymerization, a degassed solution of D6 (1 equiv.) in degassed anisole was added with a degassed syringe. During the polymerization, aliquots were taken from the mixture with a degassed syringe in order to monitor the incorporation of maleimide in the growing copolymer chains by <sup>1</sup>H NMR spectroscopy. After 240 minutes of polymerization, the reaction mixture was cooled down to RT, diluted in a small amount of THF and poured in a large amount of cold methanol. The precipitate copolymer was filtered and dried *in vacuo* at RT.

**A.6. Procedure for the thiol-ene modification of the copolymer P(S-co-D6) with thio-glycerol.** Alkene functionalized copolymer P(S-co-D6) (20.0 mg,  $3 \times 10^{-3}$  mmol) and 2,2'-dimethoxy-2-phenylacetophenone (DMPA) were added into a vial, sealed with a teflon cap and purged with nitrogen for 10 minutes. Then they were dissolved in degassed DMF (0.1 mL) and finally thio-glycerol (2.08  $\mu$ L,  $24 \times 10^{-3}$  mmol) was added into the vial. Then, the vial content was purged with nitrogen for an additional 10 min and irradiated for 3 hours with 365 nm light at room temperature. Subsequently, the crude mixture was precipitated in cold methanol. The precipitated copolymer was filtered and dried *in vacuo* to give thio-glycerol conjugated copolymer (18.2 mg, 78 % yield).  $M_{n,theo} = 7515 \text{ gmol}^{-1}$ ,  $M_{n,SEC} = 7440 \text{ gmol}^{-1}$ ,  $M_w/M_n = 1.21$ .

## **B. Measurements and analysis:**

**B.1. Nuclear Magnetic Resonance Spectroscopy (NMR).** The NMR spectra were recorded using a 400 MHz Bruker Avance or a 400 MHz Varian spectrometer at 25 °C.  $^1\text{H}$  NMR measurements were made at frequency of 400.13 MHz, and calibrated with respect to the solvent signal. Styrene conversion ( $\text{conv}_s$ ) and the consumption of the dendronic maleimides ( $\text{conv}_{MI}$ ) were calculated from  $^1\text{H}$  NMR spectra of the crude reaction samples by comparing the integration of unreacted monomers peaks to the integration of proton signals of the formed copolymer. The measurements were performed in deuterated chloroform ( $\text{CDCl}_3$ ).

**B.2. Size Exclusion Chromatography (SEC).** Characterizations of copolymers were performed at 30 °C in THF at a flow rate of 1 mL/min. The number-average molar mass ( $M_n$ ) and the polydispersity index ( $M_w/M_n = \text{PDI}$ ) were estimated using a calibration based on linear polystyrene standards (PSS, Germany). The SEC set-up was equipped with four 5  $\mu$ -SDV columns (PLgel mixed C, one guard column and three columns of  $4 \cdot 10^3$ ,  $3 \cdot 10^5$ ,  $2 \cdot 10^6$  Å). The detection was performed with a refractometer (DN-1000, WGE Dr. Bures) and a UV/Vis detector (UV 2000, 260 nm).

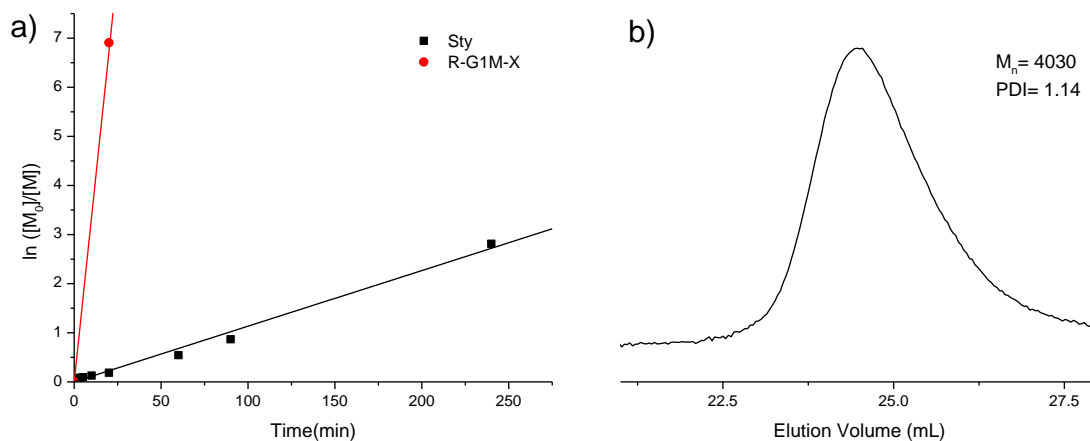
**B.3. MALDI-TOF Mass Spectroscopy (MS).** The MALDI-TOF MS spectrum acquisition for R-G2M-alkene was obtained on a Shimadzu Biotech Axima Performance System using 2,5-dihydroxybenzoic acid as a matrix.

**B.4. Elemental analysis.** The elemental analysis of the dendrons was done on a FlashEA 1112 Series Elemental Analyzer (CHNS Separation Column, PTFE; 2 m; 6 x 5 mm).

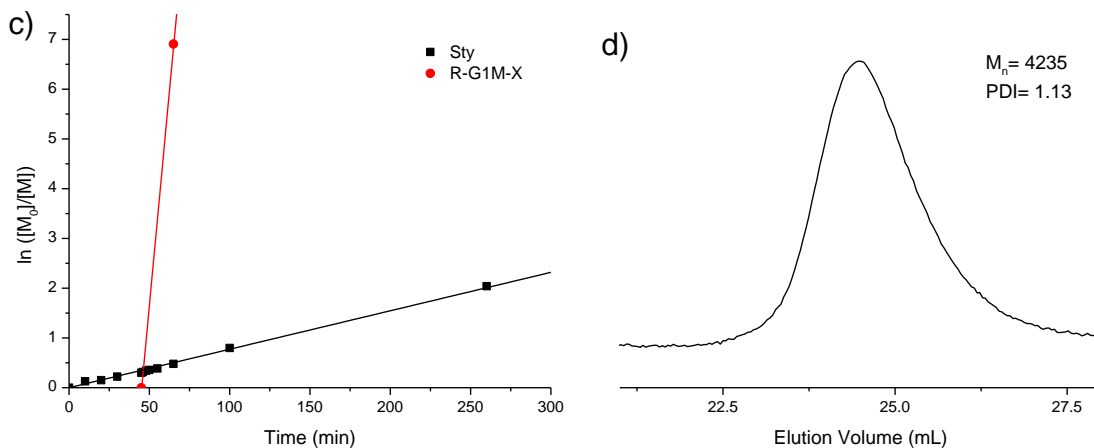
## C. Additional data and Figures:

### C.1. Copolymerization of Styrene and D1.

- R-G1M-X added at beginning of reaction



- R-G1M-X added after 45 min of reaction

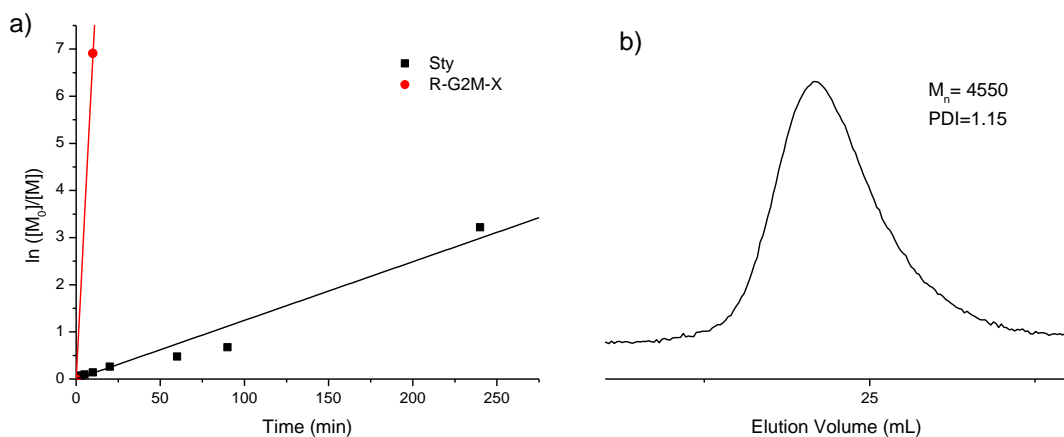


**Figure S4.** (a) and (c) Semi-logarithmic plots of monomers conversion versus time for nitroxide-mediated copolymerization of styrene (Sty, 50 equiv.) (black squares) with **D1** (R-G1M-X, 1 equiv.) (red dots) added at beginning or after 45 minutes of reaction. Experimental conditions: bulk, 120 °C, Sty/MI/BlocBuilder=50/1/1. (b) and (d) Size exclusion chromatograms of the isolated copolymers.

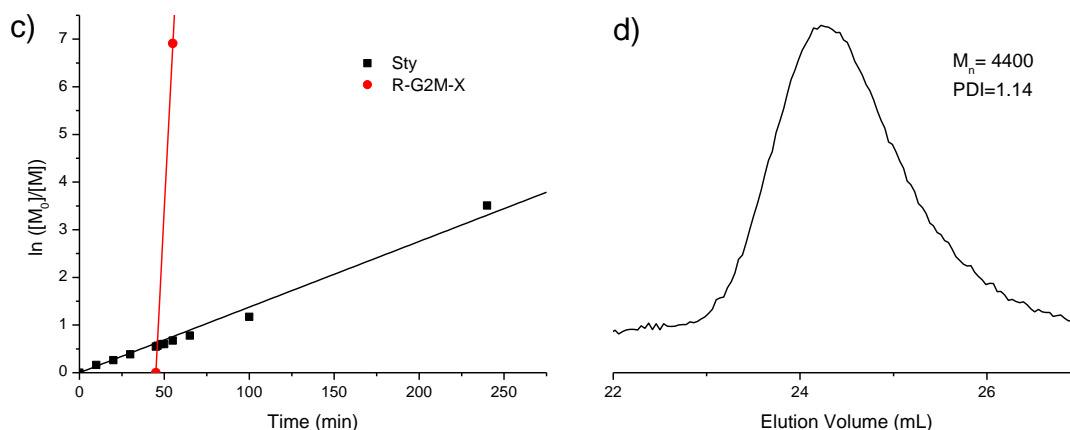


## C.2. Copolymerization of Styrene and D2.

- R-G2M-X added at the beginning of the reaction



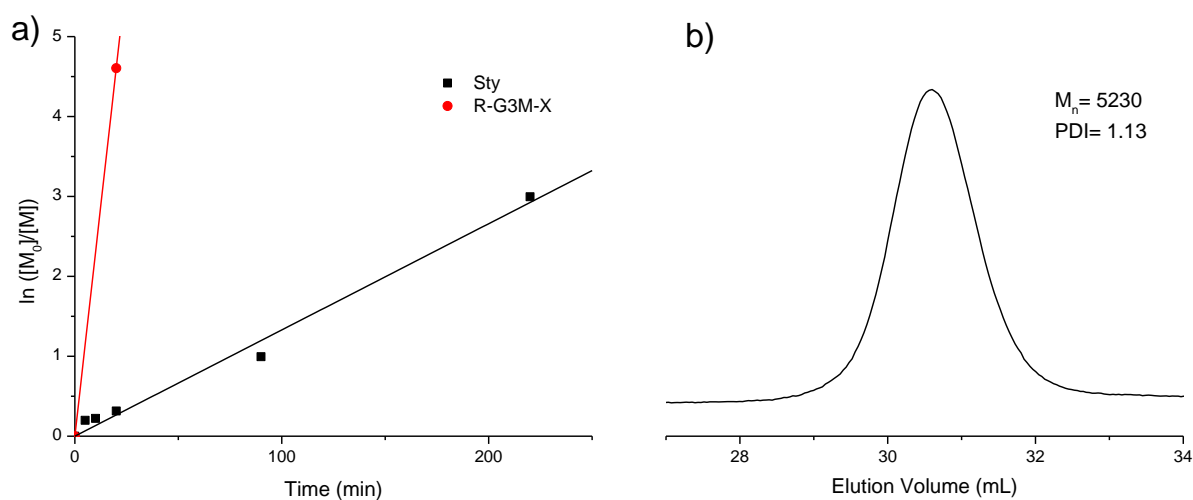
- R-G2M-X added after 45 minutes of the reaction



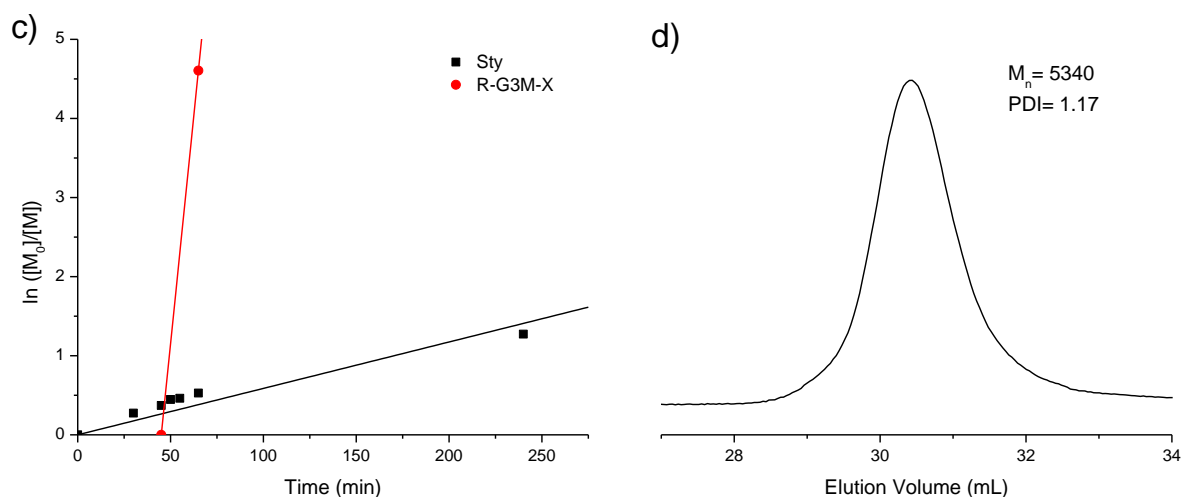
**Figure S5.** (a) and (c) Semi-logarithmic plots of monomers conversion versus time for nitroxide-mediated copolymerization of styrene (Sty, 50 equiv.) (black squares) with **D2** (R-G2M-X, 1 equiv.) (red dots) added at beginning or after 45 minutes of reaction. Experimental conditions: bulk, 120 °C, Sty/MI/BlocBuilder=50/1/1. (b) and (d) Size exclusion chromatograms of the isolated copolymers.

### C.3. Copolymerization of Styrene D3.

- R-G3M-X added at the beginning of the reaction



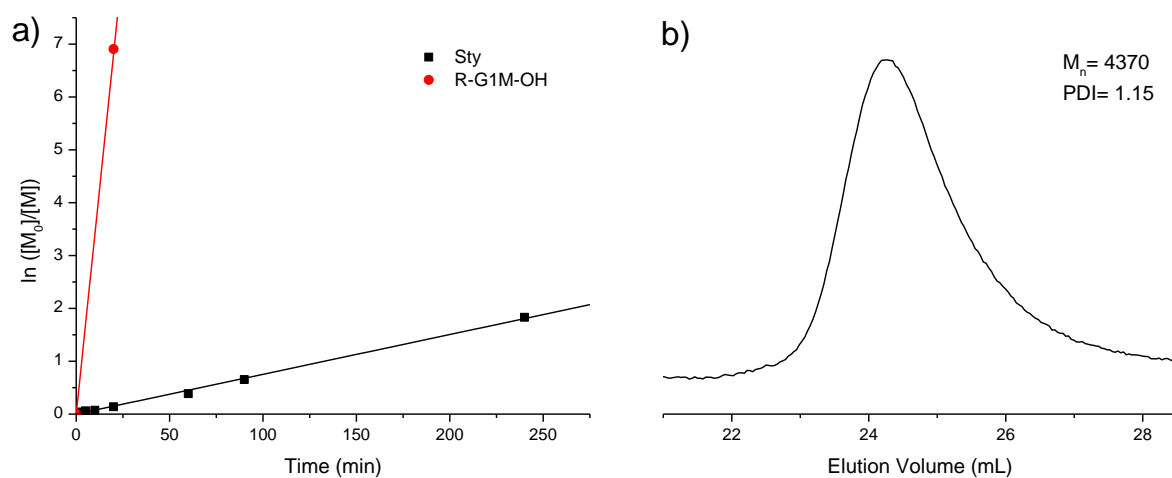
- R-G3M-X added after 45 minutes of the reaction



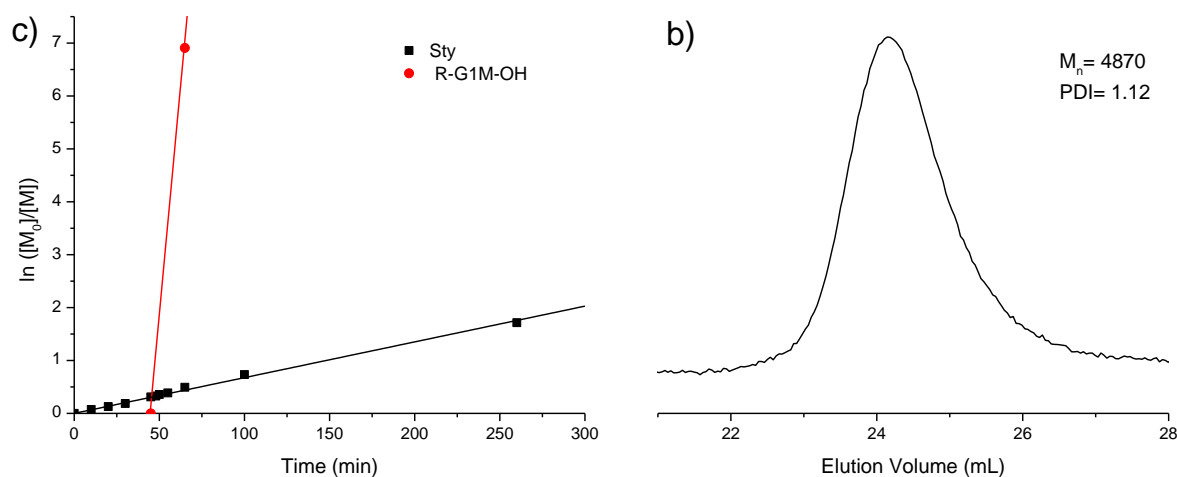
**Figure S6.** (a) and (c) Semi-logarithmic plots of monomers conversion versus time for nitroxide-mediated copolymerization of styrene (Sty, 50 equiv.) (black squares) with **D3** (R-G3M-X, 1 equiv.) (red dots) added at beginning or after 45 minutes of reaction. Experimental conditions: bulk, 120 °C, Sty/MI/BlocBuilder=50/1/1. (b) and (d) Size exclusion chromatograms of the isolated copolymers.

### C.4. Copolymerization of Styrene and D4.

- R-G1M-OH added at beginning of reaction



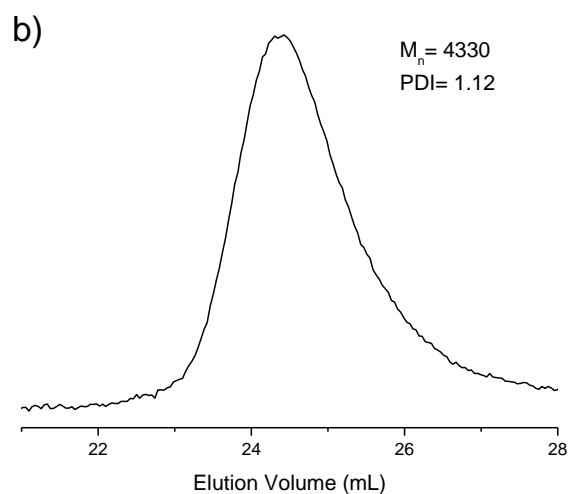
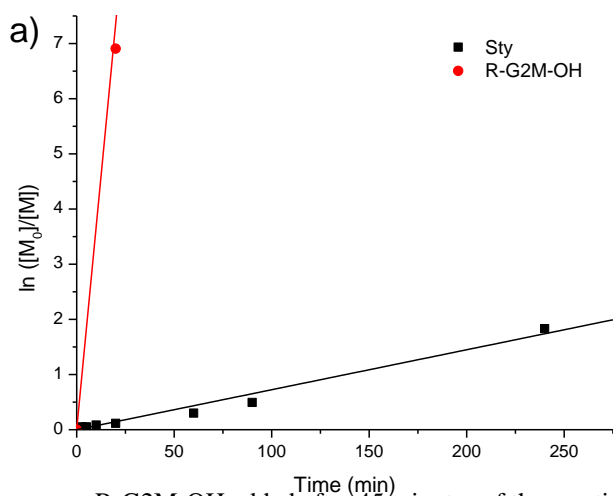
- R-G1M-OH added after 45 minutes of reaction



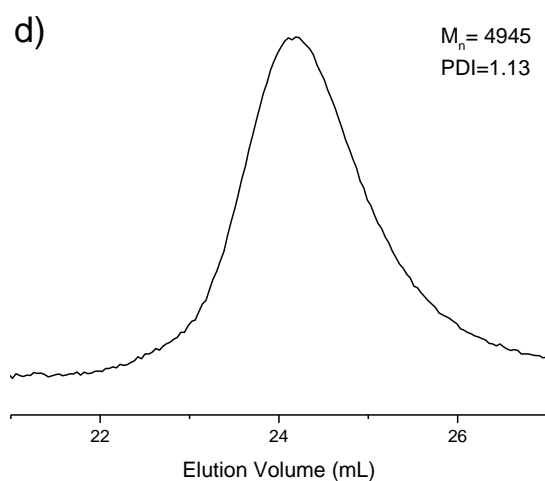
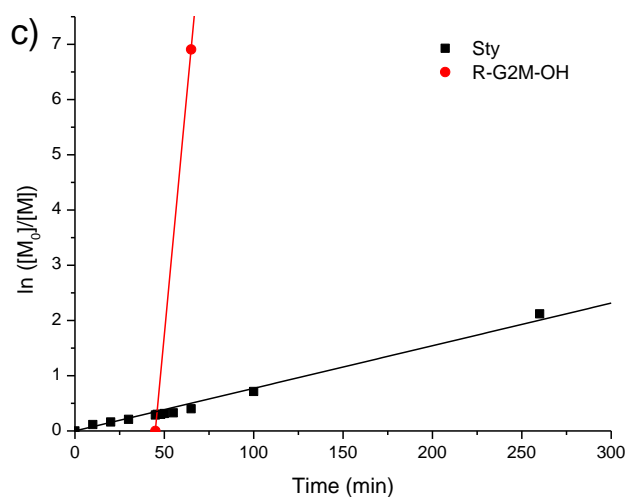
**Figure S7.** (a) and (c) Semi-logarithmic plots of monomers conversion versus time for nitroxide-mediated copolymerization of styrene (Sty, 50 equiv.) (black squares) with **D4** (R-G1M-OH, 1 equiv.) (red dots) added at beginning or after 45 minutes of reaction. Experimental conditions: bulk, 120 °C, Sty/MI/BlocBuilder=50/1/1. (b) and (d) Size exclusion chromatograms of the isolated copolymers.

### C.5. Copolymerization of Styrene and D5.

- R-G2M-OH added at the beginning of the reaction



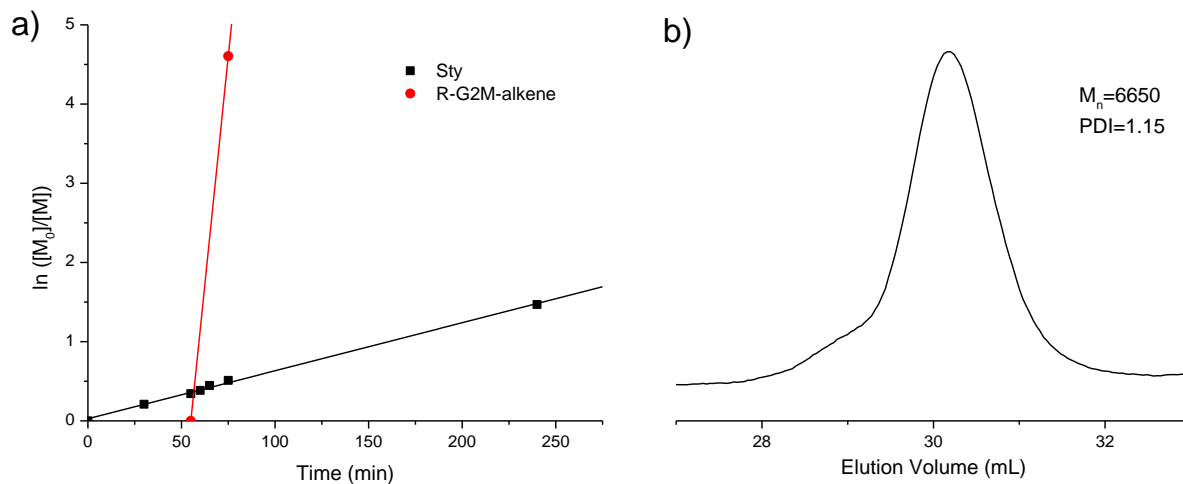
- R-G2M-OH added after 45 minutes of the reaction



**Figure S8.** (a) and (c) Semi-logarithmic plots of monomers conversion versus time for nitroxide-mediated copolymerization of styrene (Sty, 50 equiv.) (black squares) with **D5** (R-G2M-OH, 1 equiv.) (red dots) added at beginning or after 45 minutes of reaction. Experimental conditions: bulk, 120 °C, Sty/MI/BlocBuilder=50/1/1. (b) and (d) Size exclusion chromatograms of the isolated copolymer.

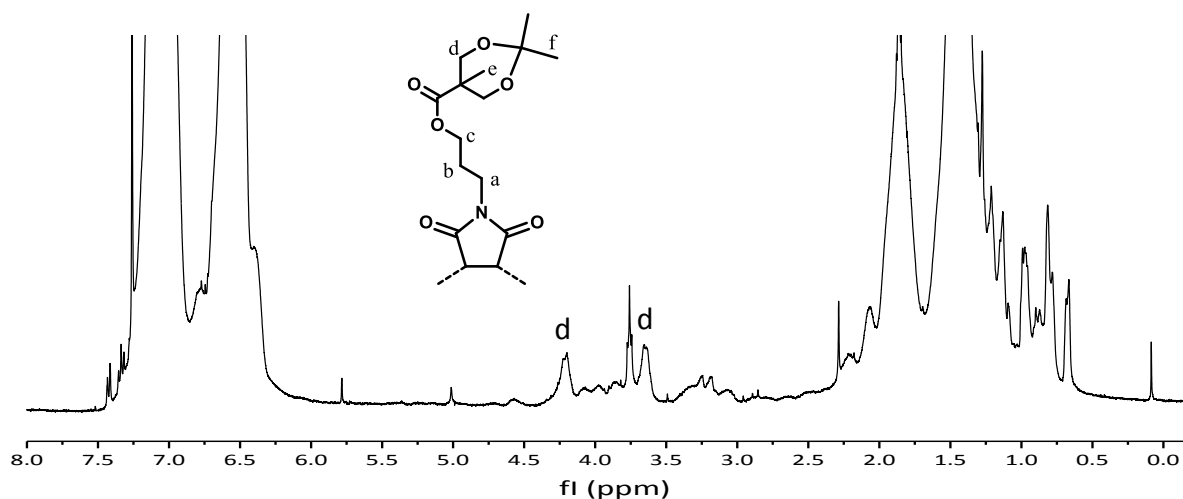
## C.6. Copolymerization of Styrene and D6.

- R-G2M-Alkene added after 55 minutes of the reaction

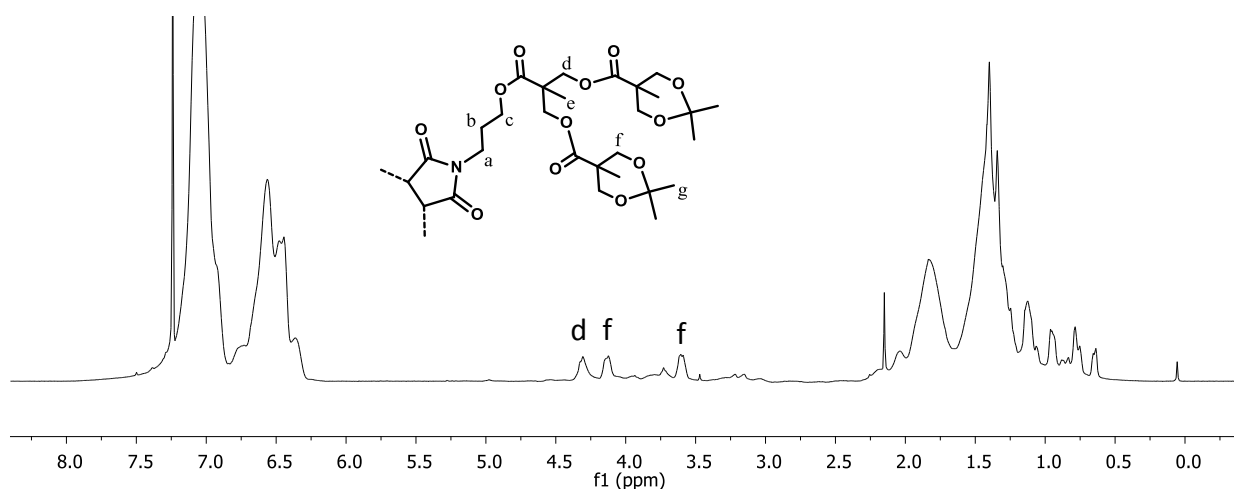


**Figure S9.** (a) Semi-logarithmic plot of monomers conversion versus time for nitroxide-mediated copolymerization of styrene (Sty, 50 equiv.) (black squares) with **D6** (R-G2M-alkene, 1 equiv.) (red dots) added after 55 minutes of reaction. Experimental conditions: bulk, 120 °C, Sty/MI/BlocBuilder=50/1/1. (b) Size exclusion chromatogram of the isolated copolymer.

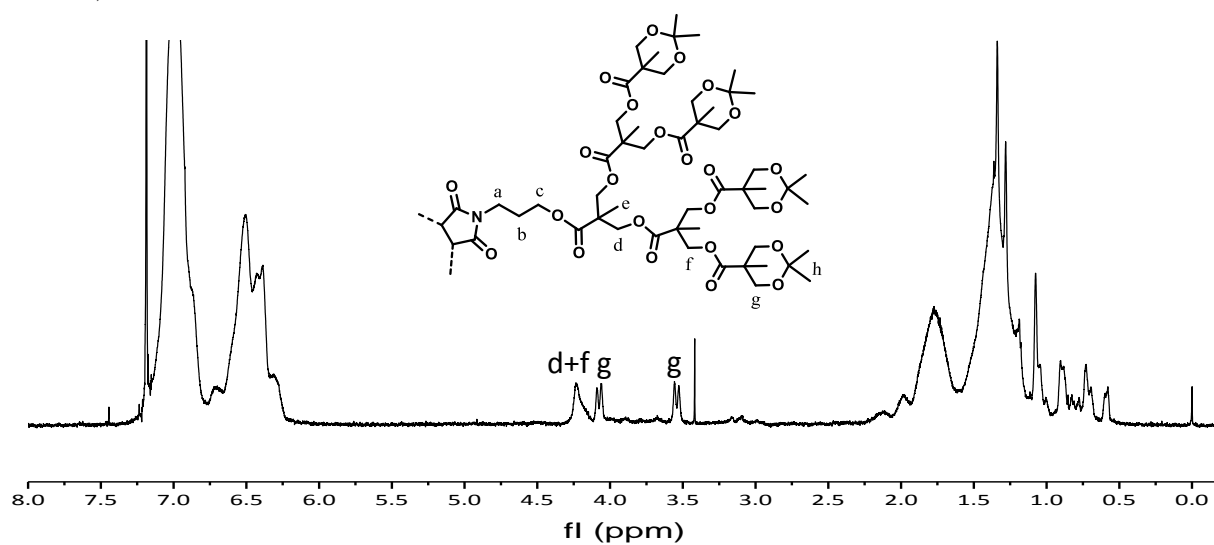
## C.7. NMR spectra of the purified copolymers.



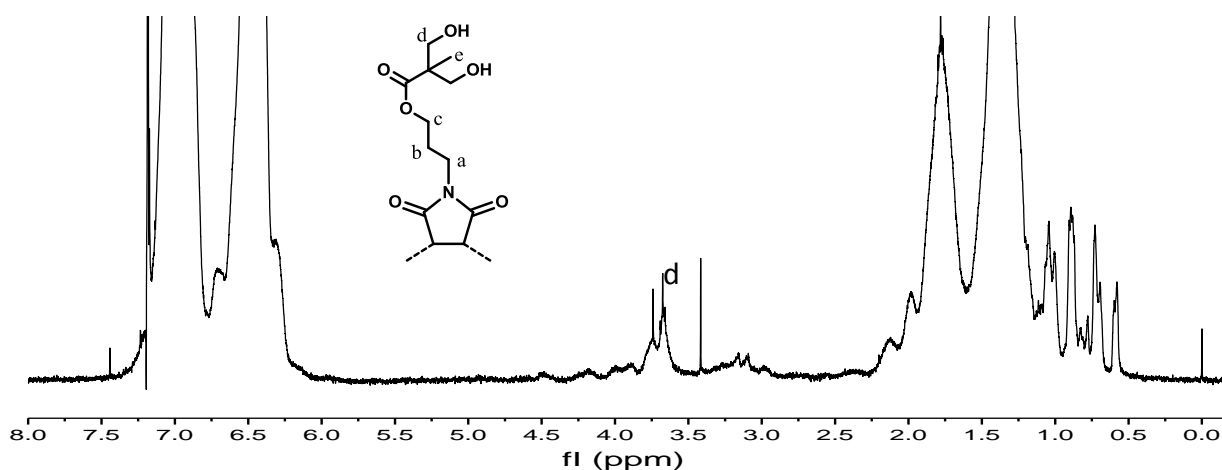
**Figure S10.** <sup>1</sup>H NMR spectrum of a copolymer P(S-co-D1) recorded at RT in CDCl<sub>3</sub> (Entry 2 in Table 1).



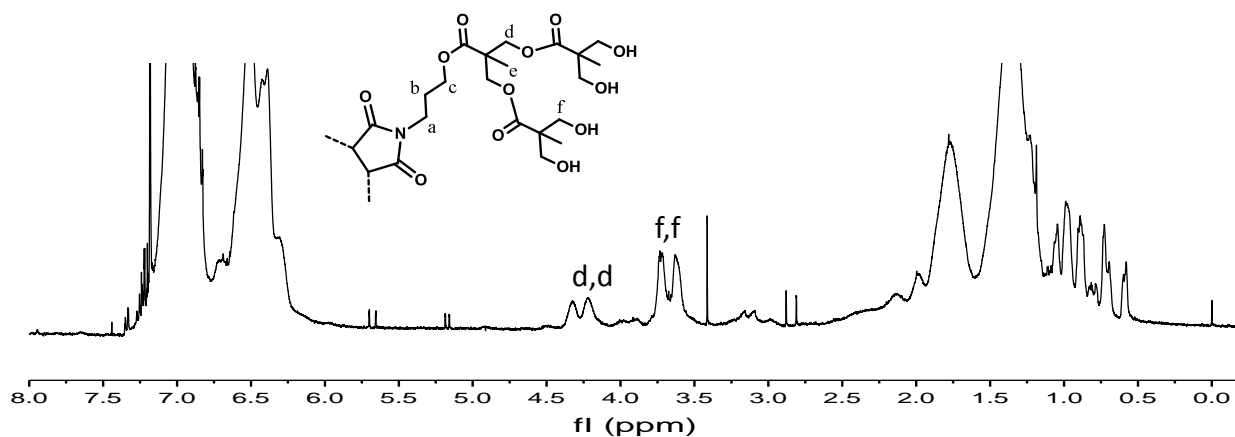
**Figure S11.** <sup>1</sup>H NMR spectrum of a purified copolymer P(S-co-D2) recorded at RT in CDCl<sub>3</sub> (Entry 3 in Table 1).



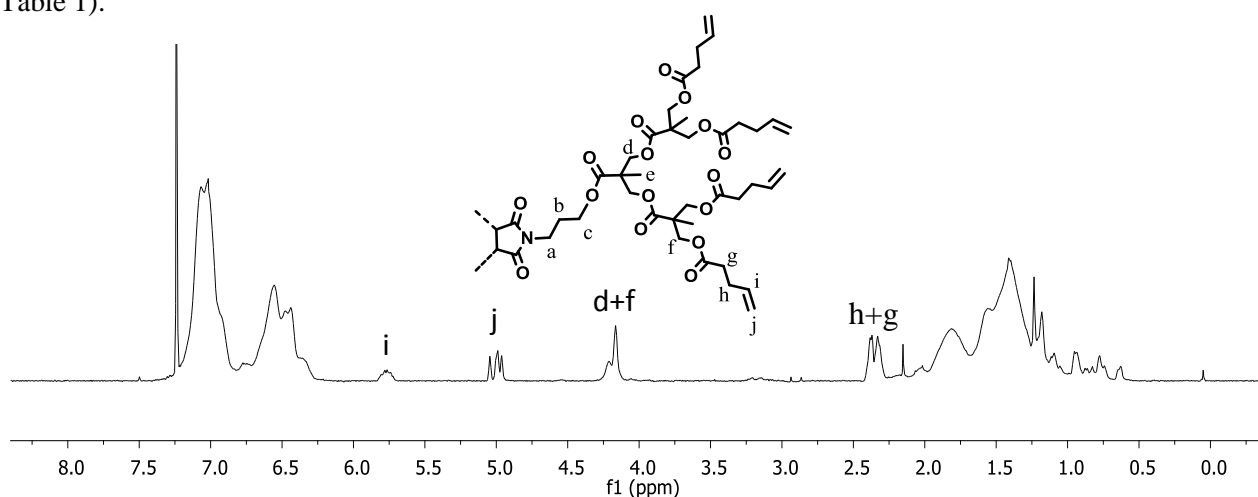
**Figure S12.** <sup>1</sup>H NMR spectrum of a copolymer P(S-co-D3) recorded at RT in CDCl<sub>3</sub> (Entry 5 in Table 1).



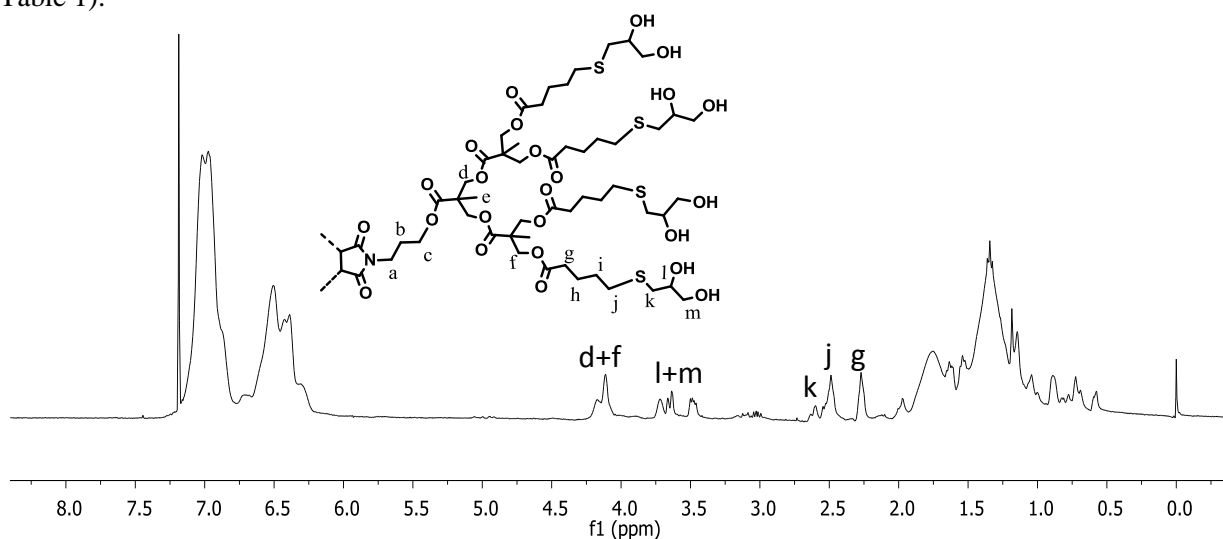
**Figure S13.** <sup>1</sup>H NMR spectrum of a copolymer P(S-co-D4) recorded at RT in CDCl<sub>3</sub> (Entry 8 in Table 1).



**Figure S14.** <sup>1</sup>H NMR spectrum of a copolymer P(S-co-D5) recorded at RT in CDCl<sub>3</sub> (Entry 10 in Table 1).



**Figure S15.** <sup>1</sup>H NMR spectrum of a copolymer P(S-co-D6) recorded at RT in CDCl<sub>3</sub> (Entry 11 in Table 1).



**Figure S16.** <sup>1</sup>H NMR spectrum of the copolymer P(S-co-D6') recorded at RT in CDCl<sub>3</sub> after thiol-ene modification with thio-glycerol.

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