Electronic Supplementary Material (ESI) for Chemical Communications

Supporting Information

Synthesis of Hybrid Block Copolymers via Integrated Ring-Opening Metathesis Polymerization and Polymerization of NCA

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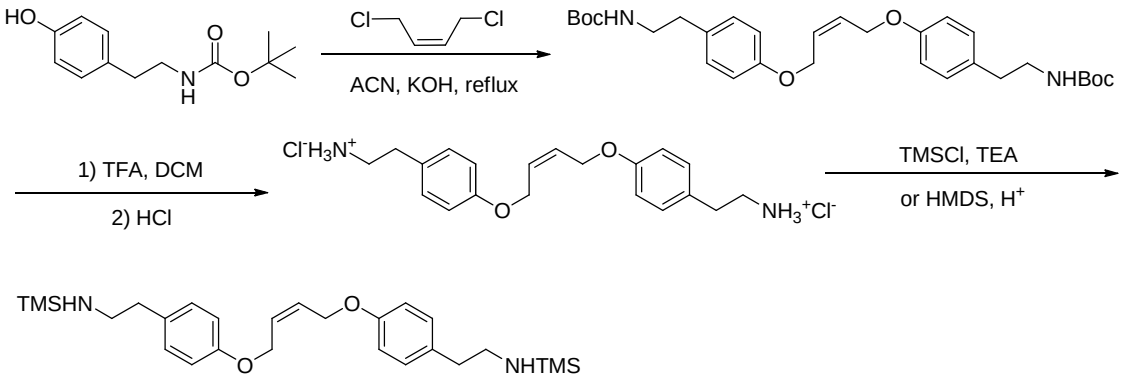
Part I. Experimental Protocols

Materials. All chemicals were purchased from Sigma-Aldrich (St. Louis, MO, USA) and used as received unless otherwise specified. Anhydrous dimethylformamide (DMF) was dried by columns packed with 4Å molecular sieves. Tetrahydrofuran (THF), dichloromethane (DCM) and hexane were dried by alumina columns and stored in a glove-box. Anhydrous toluene and acetonitrile were prepared by treating commercially available, anhydrous toluene and acetonitrile (Sigma, St. Louis, MO, USA) with activated 4Å molecular sieves and then stored in a glove-box. Anhydrous $CDCl_3$ was prepared by treating the regular $CDCl_3$ with $CaSO_4$ overnight, followed by distillation under nitrogen. The purified $CDCl_3$ was stored in the presence of 4Å molecular sieves in a glove box. H-Lys(Z)-OH and H-Glu(OBn)-OH were purchased from Chem-Impex International (Des Plaines, IL, USA) and used as received. Catalyst **1**[1], *N*-benzyl *cis*-5-norbornene-endo-2,3-dicarboximide[2] (**M1**), *N*-glycine *cis*-5-norbornene-endo-2,3-dicarboximide[3], Glu-NCA (**M5**) and Lys-NCA (**M7**)[4] were prepared by following previously reported procedures. Lys(TFA)-NCA (**M6**) and Orn(Z)-NCA (**M8**) were provided by Dr. Ettigounder Ponnusamy from Sigma-Aldrich (St. Louis, MO, USA).

Instrumentation. NMR spectra were recorded on a Varian UI400 MHz, a UI500NB MHz or a VXR-500 MHz spectrometer. Tandem gel permeation chromatography (GPC) experiments were performed on a system equipped with an isocratic pump (Model 1100, Agilent Technology, Santa Clara, CA, USA), a DAWN HELEOS 18-angle laser light scattering detector (also known as multi-angle laser light scattering (MALLS) detector, Wyatt Technology, Santa Barbara, CA, USA) and an Optilab rEX refractive index detector (Wyatt Technology, Santa Barbara, CA, USA). The detection wavelength of HELEOS was set at 658 nm. Separations were performed using serially

connected size exclusion columns (100 Å, 500 Å, 10^3 Å and 10^4 Å Phenogel columns, 5 μm, 300 × 7.8 mm, Phenomenex, Torrance, CA, USA) at 60°C using the DMF containing 0.1 M LiBr as the mobile phase. The MALLS detector was calibrated using pure toluene with no need for external polymer standards and can be used for the determination of the absolute molecular weights. The molecular weights of all polymers were determined based on the *dn*/*dc* value of each sample calculated offline by using the internal calibration system processed by the ASTRA V software (version 5.1.7.3, Wyatt Technology). Infrared spectra were recorded on a Perkin Elmer 100 serial FTIR spectrophotometer calibrated with polystyrene film. High resolution ESI mass spectra were obtained using a Micromass Q-Tof Ultima at UIUC.

Abbreviations of Polymers: PNBBn = Poly-**M1**; PNBEt = Poly-**M2**; PNBGlyMe = Poly-**M3**; PoNB = Poly-**M4**; PBLG = Poly-**M5**, poly(γ-benzyl-$_L$-glutamate); PTLL = Poly-**M6**, poly(N^{ε}-trifluoroacetyl-$_L$-lysine); PZLL = Poly-**M7**, poly(N^{ε}-Cbz-$_L$-lysine); PZLO = Poly-**M8**, poly(N^{δ}-Cbz-$_L$-ornithine).



Scheme S1 Synthesis of the *N*-TMS amine bearing chain-transfer agent

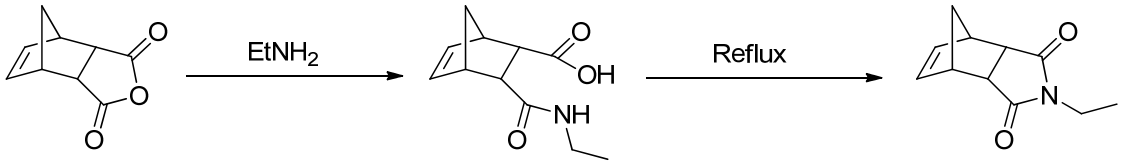
Synthesis of *cis*-1,4-di(4-aminoethylphenoxyl)-2-butene dihydrochloride: *cis*-1,4-Dichloro-2-

butene (0.57 mL, 0.63 g, 5 mmol) was dissolved in anhydrous acetonitrile (30 mL). *N*-Boc-tyramine (3.56 g, 15 mmol) and KOH (3 g, 53 mmol) were added to the solution sequentially. The suspension was refluxed for 24 h. The volatiles were removed under reduced pressure. The residual was treated with NaOH (1 M, 20 mL) and ethyl acetate (30 mL). The organic layer was separated from the aqueous phase, washed by water (20 mL) and brine (20 mL), and dried over sodium sulfate. The solvent was removed under reduced pressure and the residue was dissolved in TFA (40% in dichloromethane, 20 mL) for 3 hours with stirring. The volatiles were then removed under reduced pressure. The pure hydrochloride acid salt can be obtained by two different methods. Method A: HCl in aqueous solution (3 M, 30 mL) was added with stirring to the viscous residue to precipitate the product. The suspension was heated until a clear solution was obtained, and then cooled down to 5°C to give white precipitates. The precipitates were collected by filtration and dried at 40°C under vacuum to give a white solid (1.1 g, 65% yield). Method B: HCl in dioxane (4 M, 5 mL) was diluted by diethyl ether (30 mL). The HCl solution was poured into the viscous residue to yield the product as white powders. The product was filtered, washed by ether and dried under vacuum to give product as a white solid (1.9 g, 95% yield). ^{1}H-NMR (DMSO-d_6, 500 MHz): δ 8.19 (broad, 6H, $CH_2N\underline{H}_3^+$), 7.17 (d, 4H, ArH, J = 8.6 Hz), 6.88 (d, 4H, ArH, J = 8.6 Hz), 5.80 (t, 2H, $OCH_2C\underline{H}$=C$\underline{H}$, J = 3.5 Hz), 4.66 (d, 4H, $OC\underline{H}_2CH$=CH, J = 3.9 Hz), 2.86-2.96 (m, 4H, $C\underline{H}_2NH_3^+$), 2.76-2.83 (m, 4H, $ArC\underline{H}_2$). ^{13}C-NMR (DMSO-d_6, 500 MHz): δ 157.6, 130.3, 130.2, 129.1, 115.5, 64.5, 32.7. The aminomethyl carbon peak overlaps with DMSO's carbon peaks and cannot be identified in the ^{13}C-NMR spectrum.

Synthesis of the TA, *cis*-1,4-di(4-trimethylsilylaminoethylphenoxyl)-2-butene (2)

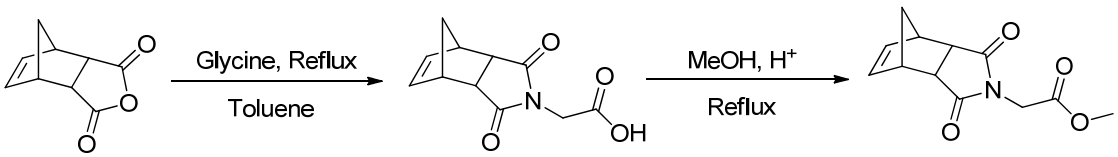
Method A: *cis*-1,4-Di(4-aminoethylphenoxyl)-2-butene dihydrochloride (1.0 g, 2.5 mmol) was

suspended in anhydrous acetonitrile (30 mL). Chlorotrimethylsilane (0.64 mL, 5 mmol) and triethylamine (0.83 mL, 6 mmol) were added sequentially. The mixture was refluxed for 36 h. The volatiles were removed under vacuum. The solid residue was transferred to a glove-box. Anhydrous hexane (20 mL) was added. The suspension was stirred vigorously for 10 min and then centrifuged. The clear solution was collected and the solid was washed again by hexanes and centrifuged (15 mL × 2). The clear solutions were combined and evaporated. The residue (an oil) was purified by dissolving it in diisopropyl ether/pentanes (3:1 v/v) and then passing the solution through pre-activated (oven-dried at 473 K for 4 h) neutral aluminum oxide under argon. The pure product was recovered by evaporation of the solvent (0.35 g, 30%). Method B: *cis*-1,4-Di-(4-aminoethylphenoxyl)-2-butene hydrochloride (1.0 g, 2.5 mmol) was suspended in hexamethyldisilazane (15 mL). Concentrated H_2SO_4 (commercial AR product, 98%, 50 μL) was added at room temperature. The suspension was refluxed until a clear solution was obtained, and refluxed for an additional 1.5 h before the solution was cooled to room temperature. The volatiles were removed under vacuum and the residue was transferred to a glove-box. Anhydrous hexane (30 mL) was added. The suspension was vigorously stirred for 5-10 min before centrifugation. The clear solution collected from the centrifugation tubes was evaporated under reduced pressure. The residue was purified by dissolving it in diisopropyl ether/pentane (3:1 v/v) and then repeatedly passing the solution through pre-activated (oven-dried at 473 K for 4 h) neutral aluminum oxide under argon. The product was recovered after evaporation of the solvent (0.8 g, 68 %). ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 7.06 (d, 4H, ArH, J = 8.4 Hz), 6.85 (m, 4H, ArH, J = 8.4 Hz), 5.93 (t, 2H, $OCH_2CH{=}CH$, J = 3.3 Hz), 4.65 (d, 4H, $OCH_2CH{=}CH$, J = 3.6 Hz), 2.90-2.96 (m, 4H, $TMSHNCH_2$), 2.54-2.60 (m, 4H, $ArCH_2$). 0.15 (s, 18H, $Si(CH_3)_3$). ^{13}C-NMR ($CDCl_3$, 500 MHz): δ 157.0, 133.1, 129.7, 128.9, 114.9, 64.5, 48.3, 41.4, 2.3.



Scheme S2 Synthesis of *N*-ethyl *cis*-5-norbornene-*endo*-2,3-dicarboximide (**M2**)

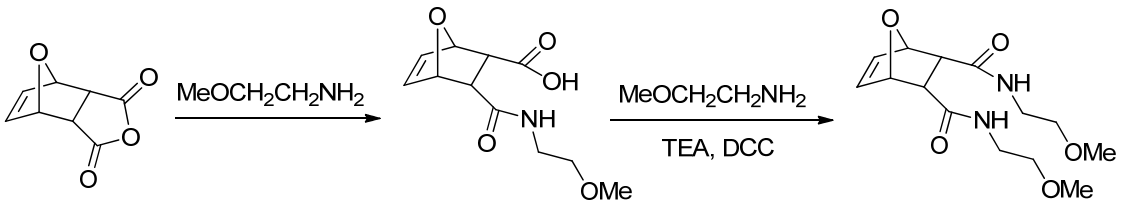
Synthesis of *N*-ethyl *cis*-5-norbornene-*endo*-2,3-dicarboximide (M2): *cis*-5-Norbornene-endo-2,3-dicarboxylic anhydride (1.64 g, 10 mmol) was partially dissolved in dry toluene (30 mL). Ethylamine (2.0 M in THF, 5.1 mL, 10.2 mmol) was added dropwise and precipitates were observed instantly. After the completion of addition, the suspension was heated overnight at 105-110°C to give a light-yellow clear solution. The solution was cooled to room temperature and the solvent was removed under vacuum to give the product as a light yellow solid in qualitative yield. The pure product in crystalline form was obtained by recrystallization in ethyl acetate/hexanes at -20 °C (1.1 g, 58 %). ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 6.08 (s, 2H, C<u>H</u>=C<u>H</u>), 3.39 (m, 4H, bridgehead CH and NC<u>H</u>$_2$CH$_3$), 3.23 (s, 2H, CH next to carbonyl), 1.71 (d, 1H, bridge CH_2, J = 8.7 Hz), 1.52 (d, 1H, bridge CH_2, J = 8.7 Hz), 1.03 (t, 3H, NCH$_2$C<u>H</u>$_3$, J = 7.2 Hz). ^{13}C-NMR ($CDCl_3$, 500 MHz): δ 177.8, 134.5, 52.4, 45.9, 45.1, 33.5, 13.3. ESI-MS (m/z): calcd for $C_{11}H_{13}NO_2$, 191.1; found, 192.1 $(M+H)^+$.



Scheme S3 Synthesis of *N*-methoxycarbonylmethyl *cis*-5-norbornene-*endo*-2,3-dicarboximide (**M3**)

Synthesis of *N*-methoxycarbonylmethyl *cis*-5-norbornene-*endo*-2,3-dicarboximide (M3): *N*-

Glycine *cis*-5-norbornene-endo-2,3-dicarboximide was synthesized by following the reported procedure[3]. *p*-Toluenesulfonic acid monohydrate (100 mg, 0.5 mmol) was added to a solution of *N*-glycine *cis*-5-norbornene-endo-2,3-dicarboximide (1.66 g, 7.5 mmol) in methanol (30 mL). The solution was refluxed overnight. The solution was cooled to room temperature and the solvent was removed under vacuum. The residue was partitioned between ethyl acetate (20 mL) and saturated aqueous $NaHCO_3$ (20 mL). The organic phase was collected, washed with water (20 mL) and then with brine (20 mL). The solution was dried over Na_2SO_4, concentrated, and recrystallized in ethyl acetate/hexanes to give the product as a white solid (1.45 g, 82 %). ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 6.15 (s, 2H, C<u>H</u>=C<u>H</u>), 4.10 (s, 2H, NC<u>H</u>$_2$COOMe), 3.73 (s, 3H, COOC<u>H</u>$_3$), 3,42 (s, 2H, CH next to carbonyl), 3.36 (s, 2H, bridgehead CH), 1.76 (d, 1H, bridge CH_2, J = 8.8 Hz), 1.57 (d, 1H, bridge CH_2, J = 8.8 Hz). ^{13}C-NMR ($CDCl_3$, 500 MHz): δ 176.9, 167.2, 134.7, 52.7, 52.5, 46.4, 45.2, 39.2. ESI-MS (m/z): calcd for $C_{12}H_{13}NO_4$, 235.1; found, 236.1 $(M+H)^+$.



Scheme S4 Synthesis of *N,N'*-dimethoxyethyl *cis*-5-oxanorbornene-*endo*-2,3-dicarboxamide (**M4**)

Synthesis of *N,N'*-dimethoxyethyl *cis*-5-oxanorbornene-*endo*-2,3-dicarboxamide (M4): *cis*-5-Oxanorbornene-*endo*-2,3-dicarboxylic anhydride (2.0 g, 12 mmol) was dissolved in dry DCM (80 mL). Methoxyethylamine (2.05 mL, 24 mmol) was added to the solution slowly. The mixture

was then stirred at room temperature for 30 min before the addition of *N*, *N*'-dicyclohexylcarbodiimide (DCC, 2.48 g, 12 mmol). The solution was stirred for another 10 min and TEA (3 mL) was added. After stirred overnight, the reaction mixture was quenched with methanol (20 mL). The suspension was then cooled to -78 °C and filtered to remove dicyclohexylurea (DCU). The solvent was removed under reduced pressure. The crude product was purified by column chromatography (DCM/methanol, 20:1). The product was collected by evaporation of the solvent. The obtained solid was dissolved in minimum amount of DCM/methanol mixture (v/v = 4:1), cooled to -78 °C and remove residual DCU by filtration. The final product was obtained by removing the solvent under vacuum (2.1 g, 59 %). ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 6.43 (s, 2H, C<u>H</u>=C<u>H</u>), 6.38 (broad, 2H, CON<u>H</u>), 5.24 (s, 2H, bridgehead CH), 3.33-3.43 (m, 8H, CONHC<u>H</u>$_2$C<u>H</u>$_2$OCH$_3$), 3.34 (s, 6H, OC<u>H</u>$_3$), 2.72 (s, 2H, CH next to carbonyl). ^{13}C-NMR ($CDCl_3$, 500 MHz): δ 171.5, 136.6, 80.3, 71.1, 59.0, 48.7, 39.5. ESI-MS (m/z): calcd for $C_{14}H_{22}N_2O_5$, 298.2; found, 299.2 $(M+H)^+$.

General procedure of the ROMP in the presence of CTA for the synthesis of bis-telechelic poly(*N*-benzyl-*cis*-5-norbornene-*endo*-2,3-dicarboximide). To a 7-mL vial was charged with **1** in DCM (0.01 M, 1 mL) and **3** in DCM (0.05 M, 1 mL) under argon. The mixture was stirred at room temperature for 1 h and the color of the solution changed from green to brown gradually. Monomer **M1** (76.0 mg, 0.3 mmol) in DCM (1 mL) was then added quickly to the vigorously stirred solution under argon. The reaction mixture was stirred for another 4 h followed by addition of diethyl ether/hexanes (20 mL, 1:1 v/v) which partially precipitated the polymer. The solvent was removed under vacuum to give the polymer as a fine powder. The resulting powder was repeatedly triturated by THF/ether (10 mL × 4, 1:5 v/v) and centrifuged before it was dried under vacuum to give **P1** as a light-yellow powder (69 mg, 91% yield). ^{1}H-NMR ($CDCl_3$, 500

MHz): δ 7.10-7.50 (b, 5n H), 7.06 (m, 4H), 6.84 (m, 4H), 5.41-5.73 (b, 2n H + 2H), 4.43-4.69 (b, 2n H + 4H), 3.30-2.71 (m, 4n H + 8H), 1.60-1.92 (m, n H), 0.89-1.27 (m, n H), 0.09 (s, 18H). The integration ratio of the TMS proton (0.09 ppm) versus the double bond proton (5.41-5.73 ppm) is 0.65/2.07 (19/62), which is very close to the expected ratio of 18/62, indicating that each polymer chain has two *N*-TMS amine groups successfully tethered to the termini of the ROMP polymer **P1**.

General procedure of the ROMP for the synthesis of mono-telechelic poly-(*N*-benzyl-*cis*-5-norbornene-*endo*-2,3-dicarboximide). A 7-mL vial was charged with **1** in DCM (0.01 M, 1 mL). **M1** (76.0 mg, 0.3 mmol) in DCM (1 mL) was added to the vigorously stirred solution of **1**. The colour of the solution gradually changed from green to brown. The reaction mixture was stirred for 1.5 h before **2** in DCM (0.05 M, 1 mL) was added. The polymer was precipitated by diethyl ether/hexanes (20 mL, 1:1 v/v) 2 hours after the addition of **2**. The solvent was removed under vacuum to give the polymer as a fine powder, which was triturated by THF/ether (10 mL × 4, 1:5 v/v) and dried under vacuum. The resulting polymer **P15** is a fine, light-yellow powder (54 mg, 85% yield). ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 7.08-7.46 (b, 5n H + 5H), 7.06 (m, 2H), 6.85 (m, 2H), 6.40 (m, 1H), 5.95 (m, 1H), 5.41-5.70 (b, 2n H), 4.41-4.68 (b, 2n H + 2H), 3.32-2.76 (m, 4n H + 4H), 1.60-1.90 (m, n H), 0.85-1.24 (n H), 0.09 (s, 9H). The integration ratio of the TMS proton (0.09 ppm) versus the double bond proton (5.41-5.70 ppm) is 0.35/2.0 (10/60), which is very close to the expected ratio of 9/60, indicating the successful mono-functionalization of **P15** with *N*-TMS amine. Peaks at 5.95 and 6.40 ppm also indicate that a phenyl group is attached at the other end of the polymer.

Transformation of the terminal *N*-TMS group to *N*-Boc group. The *N*-TMS amine bearing

polymer **P1** (30 mg, 0.004 mmol) was dissolved in DCM (3 mL). Di-*tert*-butyl dicarbonate (100 mg, 0.46 mmol) and one drop of methanol were added and the solution was stirred at room temperature for 1.5 h. Diethyl ether/hexanes (35 mL, 1:1 v/v) was added to precipitate the polymer. The suspension was sonicated for 10 min and the polymer was collected by centrifugation. The crude product was triturated with ether (10 mL × 3) and then dried under vacuum to give the polymer bearing bis(*N*-Boc) terminal groups (27 mg, 90% yield). ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 7.13-7.49 (b, 5n H), 7.05 (m, 4H), 6.84 (m, 4H), 5.41-5.68 (b, 2n H + 2H), 4.45-4.70 (b, 2n H + 4H), 3.25-2.71 (m, 4n H + 8H), 1.58-1.94 (m, n H), 1.42 (s, 18H), 0.93-1.30 (m, n H). TMS proton peak at 0.1 ppm completely disappeared and a Boc proton peak at 1.4 ppm appeared on the spectrum. The integration ratio of the Boc proton peak (1.4 ppm) to the double bond proton peak (5.41-5.68) was 0.57/2.00 (18/62), very close to the expected value of 18/62.

General procedure of the polymerization of NCA for the synthesis of polypeptide-containing hybrid block copolymers. In a glove box, a 7-mL vial was charged with **M5** (26.3 mg, 0.1 mmol) in anhydrous DMF (1 mL). The macroinitiator **P1** (25.3 mg, 0.001 mmol) in anhydrous DMF (1 mL) was quickly added to the NCA solution. The polymerization was monitored using FT-IR by observing the NCA anhydride band at 1792 cm^{-1}. When the polymerization was complete, one drop of methanol was added to quench the reaction. The polymer was precipitated by diethyl ether (30 mL), collected by centrifugation, and triturated with ether (15 mL × 3) before it was dried under vacuum (41 mg, 80% isolated yield). The polymer MWs were analyzed by GPC.

Part II. Supplementary Table and Figure

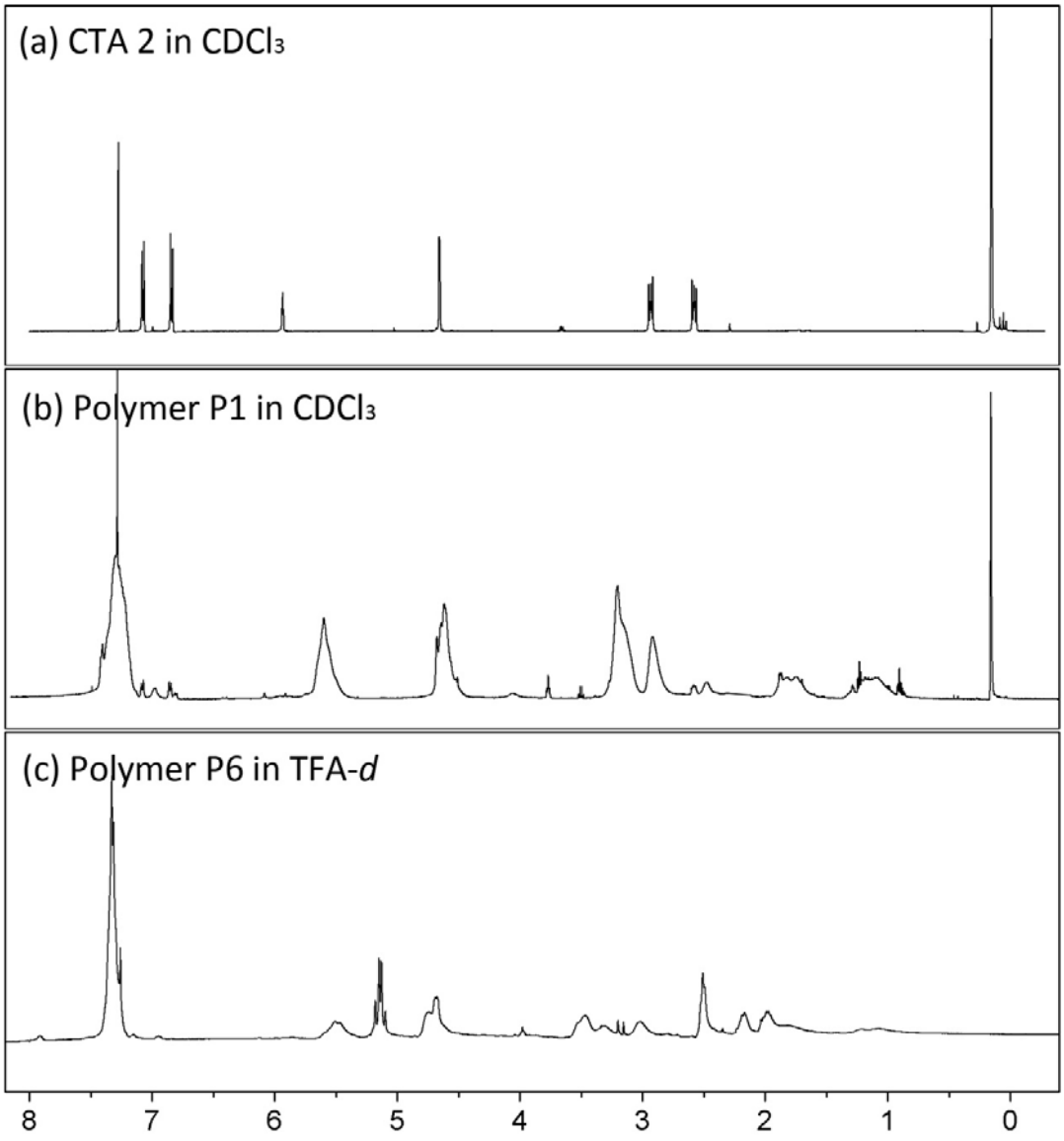


Figure S1. Example of ^{1}H-NMR characterization of the CTA, bis-telechelic ROMP polymer and block copolymer.

Some residual solvent peaks (THF, hexanes and diethyl ether for **P1**, DMF for Polymer **P6,** and chloroform for **P1** and **P6**) were observed.[5] Polynorbornene peaks are known to shift to higher frequencies when the solvent is changed from $CDCl_3$ to TFA-*d*.[6]

Table S1. Characterization of **P13**-**P18** by GPC

Polymer	Monomer	Initiator	M/I[a]	M_n (M_n*)[b] ($\times 10^3$ g/mol)	PDI[c]
P13	**M8**	**P2**	100:1	50.6 (50.6)	1.02
P14	**M7**	**P3**	100:1	51.7 (46.5)	1.04
P15	**M1**	**1**	30:1	7.7 (7.9)	1.01
P16	**M1**	**1**	100:1	25.8 (25.6)	1.02
P17	**M5**	**P16**	200:1	62.4 (69.6)	1.05
P18	**M8**	**P16**	200:1	79.3 (75.0)	1.02

[a] M/I = monomer/initiator ratio.
[b] M_n = the molecular weight measured by GPC; M_n* = the expected molecular weight.
[c] polydispersity index (M_w/M_n).

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