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Degradable precision polynorbornenes *via* ring-opening metathesis polymerization

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Supporting information

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Materials and Methods

Benzaldehyde (>99.5%), *cis*-2-butene-1,4-diol (97%), *p*-toluenesulfonic acid monohydrate (99%), acetaldehyde (99%), 1-pyrenecarboxaldehyde (99%), and 4-(2-aminoethyl)morpholine (99%) were purchased from Sigma-Aldrich and used without further purification. Solvents were purchased from Fisher Scientific and used as received.

Nuclear magnetic resonance (^{1}H and ^{13}C NMR) spectra were recorded in $CDCl_3$ or CD_2Cl_2 solutions on a Bruker AC-250, a Bruker DPX-300, a Bruker AV-400 or a Bruker DPX- 400, a DRX-500, and a Bruker AV II-700 spectrometer. Chemical shifts are reported as δ in parts per million (ppm) and referenced to the chemical shift of the residual solvent resonances ($CDCl_3$ ^{1}H: δ = 7.26 ppm; ^{13}C: δ = 77.16 ppm) and/or internal standards (TMS ^{1}H: δ = 0.00 ppm; ^{13}C: δ = 0.00 ppm). High resolution mass spectra (HRMS) were collected using a Bruker MaXis UHR-ESI TOF. MALDI ToF mass spectra were acquired on a Bruker Daltonics Ultraflex and an Autoflex MALDI-ToF mass spectrometer in positive ion ToF detection performed using an accelerating voltage of 25 kV. Solutions in THF of dithranol as matrix (30 mg/mL), sodium or potassium trifluoroacetate as ionization agent (2 mg/mL) and analyte (1 mg/mL) were mixed prior to being spotted on the MALDI plate and air-dried. The samples were measured in reflector ion mode and calibrated by comparison to SpheriCal (Polymer Factory) single molecular weight standards (1,200-8,000 Da). Simulated masses were obtained using the software "Molecular weight calculator" Version 6.49 developed by Matthew Monroe. All reported masses are based

on the isotopic abundances of the reported chemical formulae. SEC measurements were performed on an Agilent 390-MDS equipped with differential refractive index and UV detectors. The separation was achieved by a guard column (Varian PLGel 5 µm) and two mixed-D columns (Varian PLGel 5 µm) using THF (2% Et_3N mixture) or chloroform (2% Et_3N mixture) as the eluent at a flow rate of 1 mL/min. Data analysis was performed using Cirrus v3.3 with calibration curves produced using Varian Polymer laboratories Easi-Vials linear poly(styrene) standards with molecular weights ranging from 162 to 2.4×10^5 g/mol.

Addition of DxpPyr in the ROMP of *endo*NbHex

TABLE S1 Molecular weights and molecular weight distributions of the polymers obtained from the polymerization of *endo*NbHex before and after addition of DxpPyr.

	Reaction Time (min)	M_n (g/mol)	M_w (g/mol)	$Đ_M$
poly(NbHex)	0	3.6	4.0	1.11
+ DxpPyr (30 min)	30	3.5	4.0	1.14
+DxpPyr (60 min)	60	3.7	4.2	1.13
+DxpPyr (120 min)	120	3.5	4.0	1.14
+DxpPyr (300 min)	300	3.5	4.1	1.17

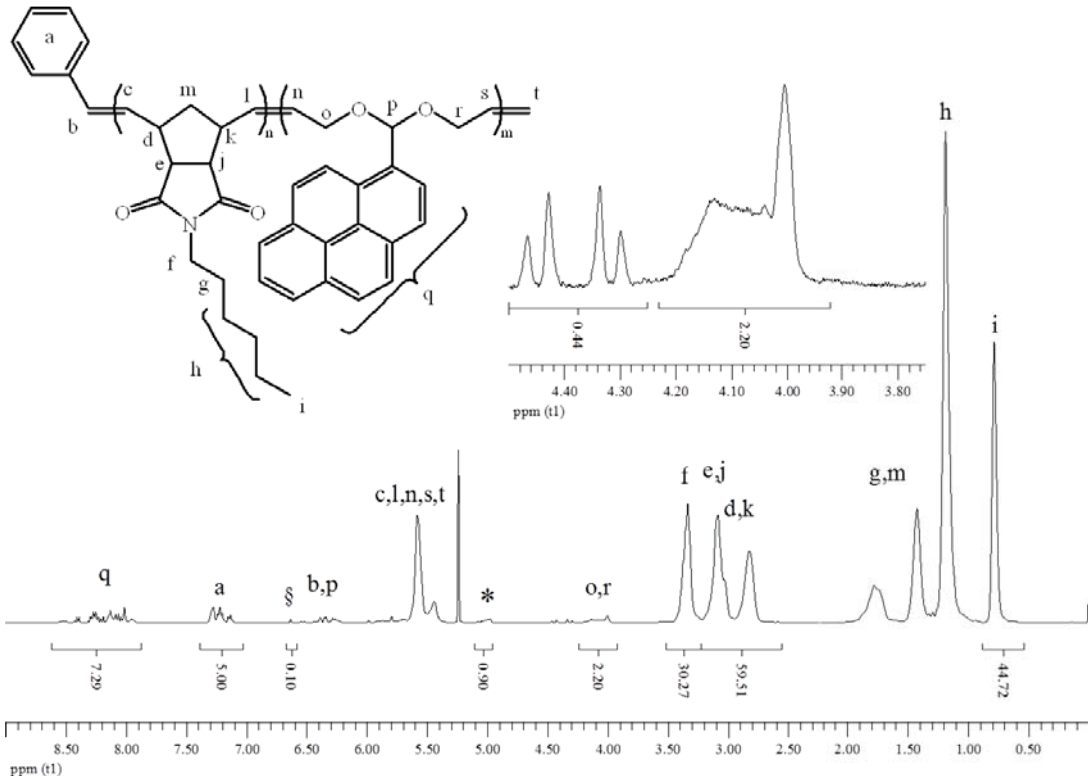

FIGURE S1. Assigned ^{1}H NMR spectrum of the polymer obtained from the polymerization of *endo*NbHex 300 min after the addition of DxpPyr. The inset shows the 4.5-3.8 ppm region expanded. The signal marked with a star corresponds to the unfunctionalized poly(NbHex) chain-end protons, while the signal marked with § corresponds to the acetal of the unreacted DxpPyr (CD_2Cl_2, 400 MHz). Note that the calculated ratio of protons corresponding to intact acetals and pyrene is 0.36 as opposed to the expected 0.44.

Reactivity ratios

The reactivity ratios of two monomers are defined by their relative rates of polymerization (eq.1).

$$r_1 = \frac{k_{11}}{k_{12}} \qquad r_2 = \frac{k_{22}}{k_{21}} \qquad \text{eq.1}$$

These ratios express the probability of each monomer (namely M_1 and M_2) to react with a polymer chain, if the final monomer on the chain is the same (k_{11} and k_{22} respectively), or the other (k_{12} and k_{21} respectively). In a random copolymerization, r_1 and r_2 are both equal to 1, while in an alternating copolymerization both values are close to zero. Additionally, if r_1 (or r_2) is greater than 1, homopolymerization of M_1 (or M_2 respectively) is favored. It should, however, be noted that these are derivations from the differential Mayo-Lewis model for a copolymer composition (eq.2).

$$F_1 = \frac{r_1 f_1^2 + f_1 f_2}{r_1 f_1^2 + 2 f_1 f_2 + r_2 f_2^2} \qquad \text{eq.2}$$

The assumptions that lead to this equation be used for the determination of the relative reactivity ratios of two monomers do not necessarily apply to ROMP. For example, ROMP is theoretically a reversible process. However, as one of the monomers used here is a bulky norbornene, it can be assumed that de-polymerization, as well as back-biting is negligible.[1] Additionally, it has been postulated that "chain editing" is possible *via* cross-metathesis with a backbone alkene and the incoming monomer.[2]

To evaluate the reactivity ratio, the copolymerizations of DxpPhe and *endo*NbHex, with monomer feed ratios (f_i) ranging from 0.1 up to 0.9, were studied by ^{1}H NMR spectroscopy. The polymerizations were monitored by ^{1}H NMR spectroscopy and upon reaching overall monomer conversion of ~10%, the polymer composition in dioxepin was measured and plotted against the dioxepin monomer feed ratio (FIGURE S2).

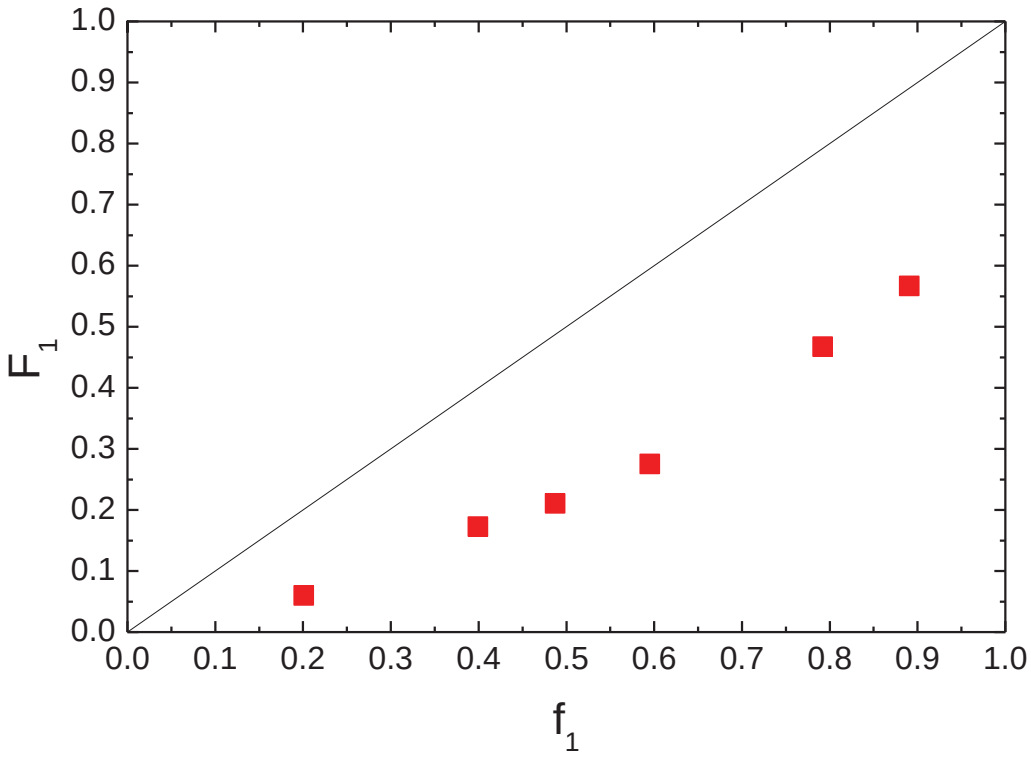

FIGURE S2 Polymer DxpPhe content (F_1) with respect to monomer DxpPhe feed ratio (f_1) in the copolymerization with *endo*NbHex determined by ^{1}H NMR spectroscopy. Line shows ideal random copolymerization.

From these results, the calculation of the reactivity ratios r_1 and r_2 were possible using Contour, a software developed by van Herk which applies a non-linear least squares (NLLS) method.[3] The reactivity ratios were found to be 0.19 for DxpPhe (r_1) and 3.48 for *endo*NbHex (r_2) with the confidence intervals shown in FIGURE S3.

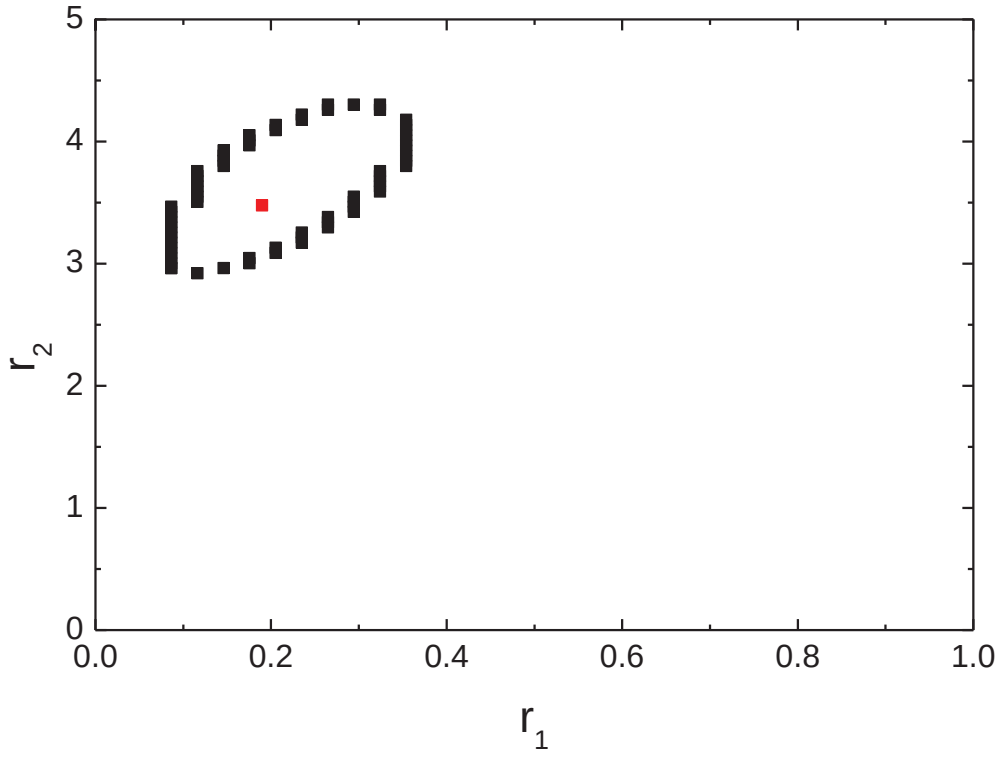

FIGURE S3 Plot of joint confidence intervals (95%) of the reactivity ratios for DxpPhe (r_1) and *endo*NbHex (r_2).

While the margins of error are quite broad, it is concluded that r_2 is significantly larger than unity, and thus k_{22} is greater than k_{21} (see eq.1) which further suggests that *endo*NbHex is more likely to react with itself than with DxpPhe. However, r_1 is much smaller than unity which suggests that k_{11} is smaller than k_{12} and therefore DxpPhe is more likely to react with *endo*NbHex than with itself.

While determination of the reactivity ratios of the monomers in the copolymerization of *exo*NbHex and dioxepins was not possible using the aforementioned method due to the high conversion of *exo*NbHex, we employed the method used for the determination of the reactivity ratios of monomers that reach high conversions in anionic polymerization.[4, 5] As such, in the copolymerization with DxpMe the reactivity ratio of *exo*NbHex was found to be 7.8, while in the copolymerization with DxpPhe it was 6.8, thus suggesting the highly preferential homopolymerization of norbornene ($k_{11}>>k_{12}$).

Sequential polymerization of *endo*NbHex in the presence of large excess of DxpPhe

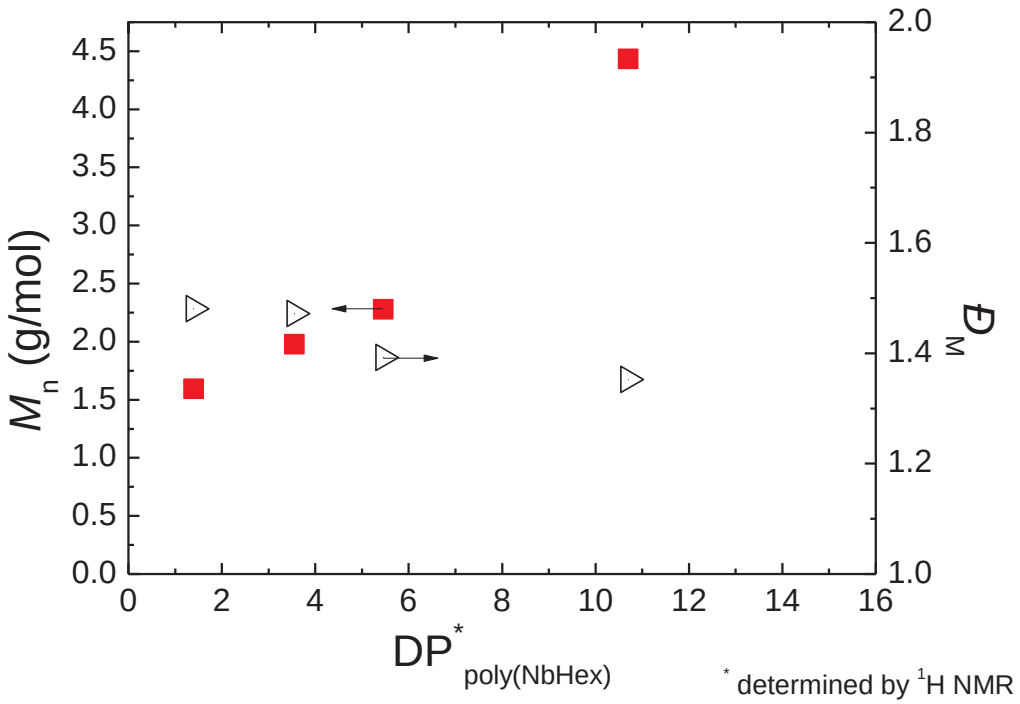

FIGURE S4 Molecular weight and dispersity evolution of the polymers synthesized by the sequential addition of *endo*NbHex into excess DxpPhe, in the presence of **G1**.

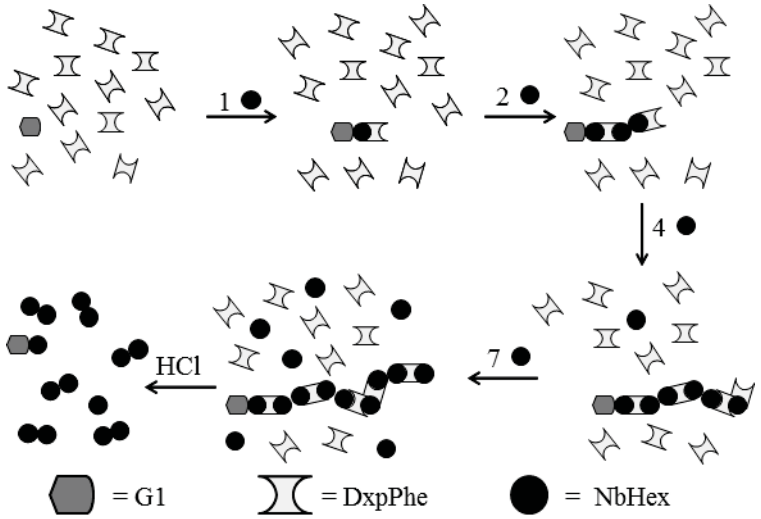

FIGURE S5 Cartoon representation of the proposed reaction pathway from the sequential addition of *endo*NbHex into a large excess of DxpPhe.

Sequential polymerization of *exo*NbHex in the presence of large excess of DxpPhe

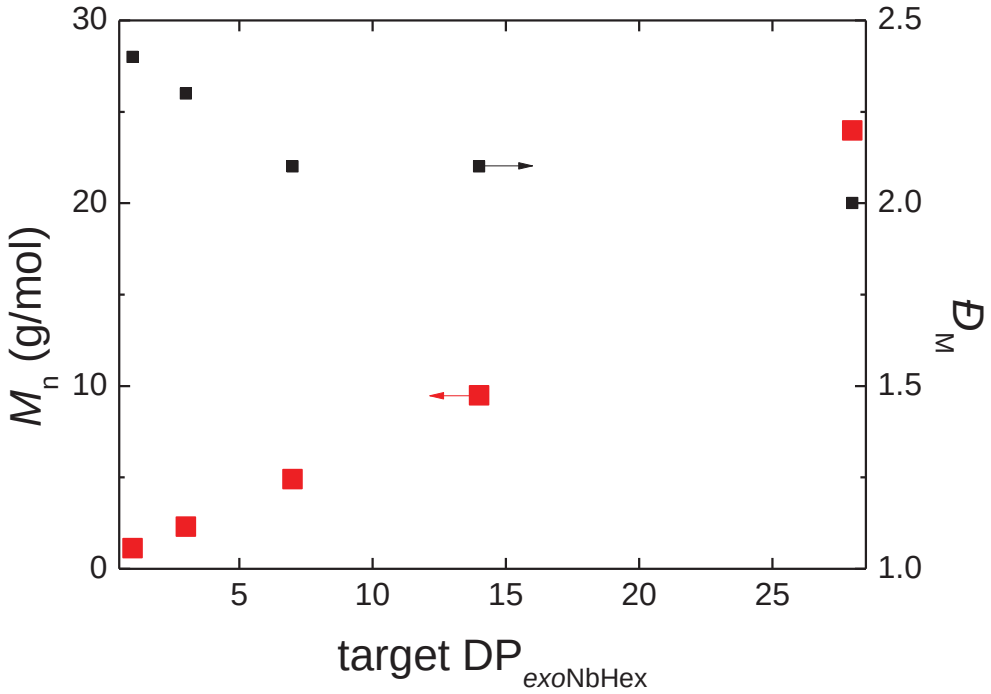

FIGURE S6 Molecular weight and dispersity evolution of the polymers synthesized by the sequential addition of *exo*NbHex into excess DxpPhe, in the presence of **G1**.

For the deconvolution of the multimodal peaks obtained by SEC characterization of the hydrolyzed polymers, each trace was fitted with multiple Gaussian distributions (Figure S7).

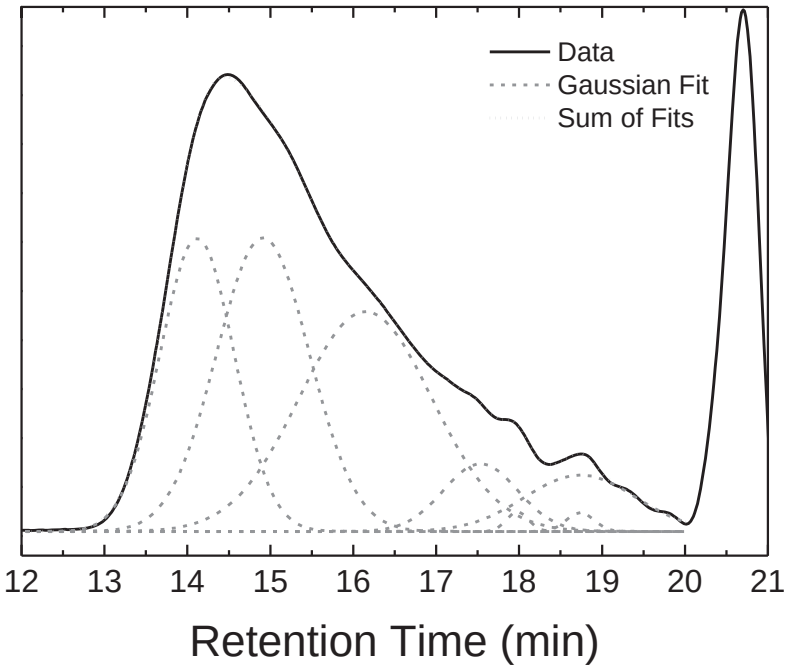

FIGURE S7 Example of the SEC trace obtained from the multiblock copolymer of *exo*NbHex and DxpPhe after hydrolysis of the acetal groups, and the multiple Gaussian distributions used to fit the curve.

The Gaussian distributions from each sample trace were then compared in order to identify the different polymer blocks (Figure S7).

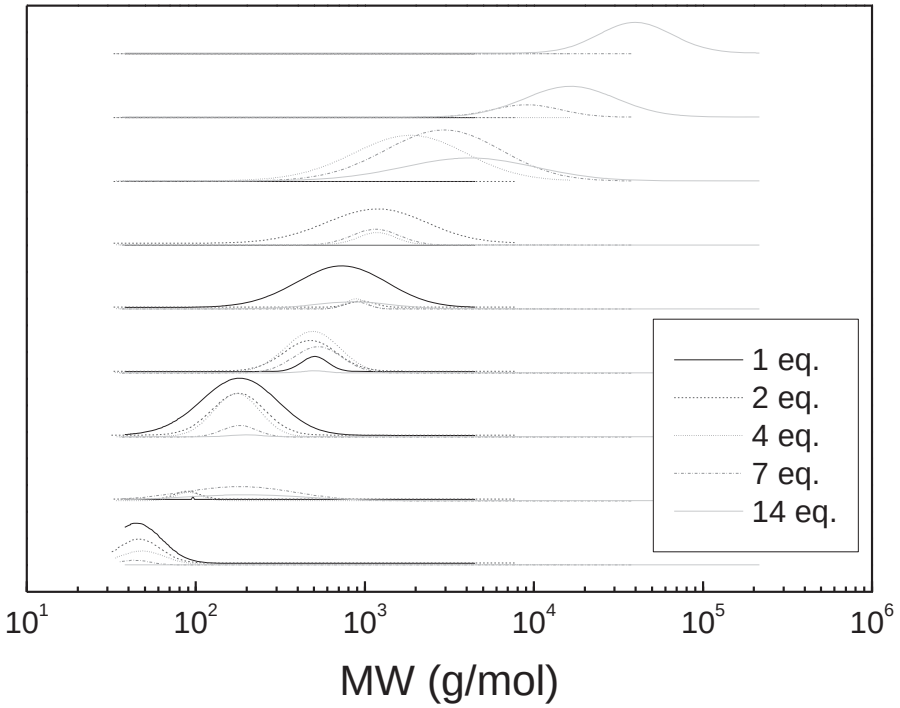

FIGURE S8 Deconvoluted Gaussian peaks from the fitting of the SEC distributions of the hydrolyzed polymers of *exo*NbHex in the presence of DxpPhe.

It is apparent that in all samples some low molecular weight peaks are present which are attributed to small molecules (such as monomer, benzaldehyde, residual catalyst, etc.) and are consistently present in all samples. Higher molecular weight peaks were attributed to the individual poly(NbHex) blocks, however direct comparison is not possible as they vary in intensity and width.

Chain extension of poly(NbHex) with DxpMe

*Exo*NbHex (200 mg, 0.808 mmol, 10 eq.) was dissolved in $CDCl_3$ (1 mL) in a dry ampoule, while **G1** (66.5 mg, 0.081 mmol, 1 eq.) was dissolved in $CDCl_3$ (1 mL) in another ampoule. Both solutions were degassed *via* three freeze-pump-thaw cycles before their contents were combined with cannula transfer under N_2. The polymerization was allowed to proceed under a nitrogen blanket for one hour, when an aliquot was removed, quenched with 100-fold excess of EVE and used for further characterization. A solution of DxpMe (23.1 mg, 0.202 mmol, 5 eq.) previously degassed by three freeze-pump-thaw cycles, was added to the reaction mixture. The reaction was allowed to proceed for 16 hours before quenching with EVE.

Synthesis of poly(NbHex)-*b*-poly(DxpMe)-*b*-poly(NbPyr)

Initially, *exo*NbHex (226 mg, 1.075 mmol, 5 eq.) was dissolved in chloroform (1 mL) in a dry ampoule, while in a different ampoule **G1** (177 mg, 0.215 mmol, 1 eq.) was also dissolved in chloroform (1 mL). After degassing *via* three freeze-pump-thaw cycles the contents of the ampoules were combined *via* cannula transfer under N_2 and the reaction was allowed to proceed for two hours under a nitrogen blanket. An aliquot was removed (450 µL) and quenched with 100-fold excess EVE and further characterized. A solution of DxpMe (95.1 mg, 0.833 mmol, 5 eq.) in chloroform (775 µL), previously degassed by three freeze-pump-thaw cycles, was added to the reaction and the polymerization was allowed to proceed for two

hours at room temperature. Then, an aliquot was removed (450 µL), quenched with 100-fold excess EVE, and further characterized. A previously degassed solution of *exo*NbPyr (237.3 mg, 0.673 mmol, 5 eq.) in chloroform (905 µL) was added to the reaction mixture and the polymerization was allowed to proceed for two hours before quenching with 100-fold excess EVE. The polymer was isolated by precipitation in methanol containing potassium 2-isocyanoacetate (5 eq.) to remove insoluble ruthenium species.[6]

Hydrolysis of dioxepin-containing polymers

In a typical procedure the polymer (10 mg) was dissolved in THF (5 mL) and HCl (35%, 1 mL) was added. The reaction was stirred for two hours at room temperature before removing volatiles under reduced pressure. The hydrolysis products were characterized without further purification.

Addition of DxpPyr to a living ROMP of *endo*NbHex

In a dry ampoule, *endo*NbHex (500 mg, 2.022 mmol, 20 eq.) and **G1** (83.1 mg, 0.101 mmol, 1 eq.) were dissolved in DCM (4 mL) and were then degassed by three freeze-pump-thaw cycles. The polymerization was allowed to proceed at room temperature under N_2 for 18 hours. Then, an aliquot was removed and quenched with 100-fold excess EVE. To the polymerization, a previously degassed *via* three freeze-pump-thaw cycles solution of DxpPyr (121.6 mg, 0.405 mmol, 5 eq. with respect to the remaining catalyst) in DCM (1 mL) was added. Aliquots of the reaction were withdrawn after 0.5, 1, 2, and 5 hours and quenched.

Determination of reactivity ratios

For copolymerizations with *exo*NbHex, the two monomers (see tables below for amounts) were dissolved in DCM (200 µL) and placed in an NMR tube fitted with a Young's tap. The solution was degassed *via* three freeze-pump-thaw cycles before a previously degassed stock solution in CD_2Cl_2 of Grubbs 1st generation catalyst (50 µL, 0.041 M) was added. The mixture was degassed once more and the tube was filled with nitrogen. The reaction was monitored by NMR spectroscopy.

Table S2. Quantities of reagents used for the copolymerizations of DxpMe and *exo*NbHex towards the calculation of their reactivity ratios.

	DxpMe		*exo* NbHex		**G1**	
	m (mg)	n (mmol)	m (mg)	n (mmol)	m (mg)	n (nmol)
10:90	1.87	0.016	36.43	0.147	3.37	4.095
20:80	3.74	0.033	32.38	0.131	3.37	4.095
30:70	5.61	0.049	28.33	0.115	3.37	4.095
40:60	7.47	0.065	24.28	0.098	3.37	4.095
50:50	9.34	0.082	20.24	0.082	3.37	4.095
60:40	11.21	0.098	16.19	0.065	3.37	4.095
70:30	13.08	0.115	12.14	0.049	3.37	4.095
80:20	14.95	0.131	8.09	0.033	3.37	4.095
90:10	16.82	0.147	4.05	0.016	3.37	4.095

Table S3. Quantities of reagents used for the copolymerizations of DxpPhe and *exo*NbHex towards the calculation of their reactivity ratios.

	DxpPhe		*exo* NbHex		**G1**	
	m (mg)	n (mmol)	m (mg)	n (mmol)	m (mg)	n (nmol)
10:90	2.06	0.012	25.96	0.105	3.37	4.095
20:80	4.11	0.023	23.08	0.093	3.37	4.095
30:70	6.17	0.035	20.19	0.082	3.37	4.095
40:60	8.22	0.047	17.31	0.070	3.37	4.095
50:50	10.28	0.058	14.43	0.058	3.37	4.095
60:40	12.34	0.070	11.54	0.047	3.37	4.095
70:30	14.39	0.082	8.65	0.035	3.37	4.095
80:20	16.45	0.093	5.77	0.023	3.37	4.095
90:10	18.51	0.105	2.88	0.012	3.37	4.095

For copolymerizations with *endo*NbHex, the two monomers (see table below for amounts) were dissolved in CH_2Cl_2 (310 µL) and placed in an NMR tube fitted with a Young's tap. The solution was degassed *via* three freeze-pump-thaw cycles before a previously degassed stock solution in CD_2Cl_2 of **G1** (300 µL, 0.024 M) was added. The mixture was degassed once more and the tube was filled with nitrogen. The reaction was monitored by NMR spectroscopy.

Table S4. Quantities of reagents used for the copolymerizations of DxpPhe and *endo*NbHex towards the calculation of their reactivity ratios.

	DxpPhe		*endo* NbHex		**G1**	
	m (mg)	n (mmol)	m (mg)	n (mmol)	m (mg)	n (nmol)
20:80	11.13	0.063	62.48	0.253	6.50	7.898
40:60	22.27	0.126	46.86	0.190	6.50	7.898
50:50	27.84	0.158	39.05	0.158	6.50	7.898
60:40	33.40	0.190	31.24	0.126	6.50	7.898
80:20	44.54	0.253	15.62	0.063	6.50	7.898
90:10	50.11	0.284	7.81	0.032	6.50	7.898

Sequential polymerization of *endo* norbornenes

Initially, stock solutions of all reagents were prepared and degassed *via* three freeze-pump-thaw cycles. DxpPhe (214 mg, 1.215 mmol, 20 eq.) was dissolved in DCM (500 µL), *endo*NbHex (250 mg, 1.011 mmol) was dissolved in DCM (2.5 mL), and **G1** (50 mg, 0.061 mmol, 1 eq.) was dissolved in 500 µL DCM. The solutions containing DxpPhe and **G1** were combined *via* cannula transfer under N_2 and stirred for 30 minutes before *endo*NbHex solution (150 µL, 1 eq.) was added under N_2 to the reaction mixture. The polymerization was allowed to proceed for two hours before an aliquot (250 µL) was removed and quenched with 100-fold excess EVE, while *endo*NbHex solution (235 µL, 2 eq.) was added under N_2 to the reaction mixture. The polymerization was allowed to proceed for four hours before an aliquot (300 µL) was removed and quenched with 100-fold excess EVE, while *endo*NbHex solution (346 µL, 4 eq.) was added under N_2 to the reaction mixture. The polymerization was allowed to proceed for another ten hours before an aliquot (400 µL) was removed and quenched with 100-fold excess EVE , while endoNbHex solution (400 µL, 7 eq.) was added under N_2 to the reaction mixture. The polymerization was stirred for another 20 hours before quenching with 100-fold excess EVE. All samples were dried and characterized without further purification.

Sequential polymerization of *exo* norbornenes

This procedure was carried out in a similar manner to the sequential polymerization of *endo* norbornenes, using *exo*NbHex. Each batch was only allowed to react for 1 hour before removing a sample for characterization and adding the next. Additionally, an extra batch containing 14 equivalents of *exo*NbHex (with respect to the catalyst) were added.

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