Supporting Information

Cooperative Heterometallic Catalysts: Balancing Activity and Control in PCL-*block*-PLA Copolymer Synthesis

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General experimental details

All manipulations involving air or moisture sensitive compounds were performed either in a glove box or using standard Schlenk techniques under an argon atmosphere. $Ca(HMDS)_2(THF)_2$[1] and complexes **1**—**3**[2,3] were synthesised using previously reported procedures and were based on a commercially available (*S,S*)-(+)-2,6-bis[2-(hydroxydiphenylmethyl)-1-pyrrolidinyl-methyl]-4-methylphenol (ProPhenol) ligand, developed by Trost *et al.*[4] All reagents and solvents were obtained from Sigma-Aldrich, Fischer Scientific, Honeywell or Acros Organics and used as received unless stated otherwise. Dry toluene solvent was collected from a solvent purification system (Innovative Technologies). Anhydrous NMR solvents ($CDCl_3$ and THF-d_8) used for NMR spectroscopic analysis of air- and moisture-sensitive compounds were dried overnight over CaH_2, degassed three times by freeze-pump-thaw and vacuum transferred under reduced pressure. All dry solvents were stored in the presence of activated 4 Å molecular sieves under an argon atmosphere. L- and *rac*-lactide (L-LA and *rac*-LA) monomers were purified by double recrystallisation from toluene followed by sublimation. Benzyl alcohol (BnOH) and ε-caprolactone (CL) were dried over CaH_2 and distilled under reduced pressure prior to use.

NMR spectroscopy

1D NMR (^1H, $^1H\{^1H\}$, ^{13}C) and 2D NMR (DOSY) spectra were recorded on a Bruker AVA500 spectrometer at 298 K operating at 500 MHz. Chemical shifts (δ) are given in parts per million (ppm), and coupling constants (*J*) are reported in Hertz (Hz). ^1H and ^{13}C NMR spectra were referenced with respect to the residual peaks of deuterated solvents ($CDCl_3$: 7.27 ppm, 77.00 ppm; THF-d_8: 3.58 ppm, 25.31 ppm).

Diffusion-Ordered Spectroscopy (DOSY) NMR experiments were performed at 298 K on a Bruker Ascend 2 channel instrument operating at a frequency of 500 MHz for proton resonance under TopSpin (version 4.1.3, Bruker Biospin, Karlsruhe) and equipped with a z-gradient DCH/5mm tuneable "CryoProbe"™ probe and a GRASP II gradient spectroscopy accessory providing a maximum gradient output of 53.5 G/cm (5.35G/cmA). Diffusion ordered NMR data was acquired using the Bruker pulse program dstebpgp3s with a spectral width of 10330 Hz (centred on 6.175 ppm) and 32768 data points.[5] A relaxation delay of 2 s was employed along with a diffusion time (Δ) of 100 ms and a longitudinal eddy current delay (LED) of 5 ms. Bipolar gradients pulses (δ/2) of 1.5 ms and homospoil gradient pulses of 0.6 ms were used. The gradient strengths of the 3 homospoil pulses were -13.17%, -17.13%, -15.37%. 16 experiments were collected with the bipolar gradient strength, initially at 5% (1st experiment), linearly increased to 95% (16th experiment). All gradient pulses were smooth-square shaped (SMSQ10.100) and after each application a recovery delay of 200 μs used. The experiment was run with 16 scans per increment, employing one stimulated echo with two spoiling gradients.

DOSY NMR spectra were formatted in TopSpin. Parameters were optimised empirically to find the best quality of data for presentation purposes. Diffusion coefficients were calculated by fitting intensity data to the Stejskal-Tanner expression.

SEC analysis

Polymer samples (2 – 10 mg) were dissolved in GPC grade THF (1 mL) and filtered using a 0.2 µm PTFE syringe filter. SEC analyses of the filtered polymer samples were carried out in GPC grade THF at a flow rate of 1 mL min^{-1} at 35 °C on a 1260 Infinity II GPC/SEC single detector system with mixed bed C PLgel columns (300 x 7.5 mm). The RI detector was calibrated using narrow molecular weight polystyrene standards.

DSC analysis

DSC experiments were performed using a DSC (DSC 2500, TA Instruments) with a refrigerated cooling accessory (RCS90). In all experiments, the DSC cell was purged with nitrogen at 50 mL/min. Indium was used to calibrate the cell constant. Materials were sealed in Tzero aluminium pans with a pierced hole on the lid. Runs were performed at a ramp rate of 5°C/min from -80 °C to 200 °C.

The relative degree of crystallisation (x_c) can be measured by following equation:[6]

$$x_c = \frac{\Delta H_m}{\Delta H_f} \times 100$$

where ΔH_m is the enthalpy change associated with melting the sample and ΔH_f the is the theoretical enthalpy of melting for a 100% crystalline sample.

General procedure for polymer syntheses

General experimental procedure for the synthesis of PCL

In a glovebox, CL (100 eq., 2.5 mmol, 277.0 µL) was dissolved in dry toluene (1.5 mL) in an air-tight vial equipped with a magnetic stirrer bar. In a separate vial, catalyst **1**, **2** or **3** (1 eq., 25 µmol) was dissolved in toluene solvent, and BnOH was added (1 eq., 25 µmol, total volume = 1.0 mL). Both solutions were stirred at 70 °C for 1 h using DrySyn heating blocks. The polymerisation of CL was initiated by the addition of the catalyst/BnOH solution to the CL solution ([CL] = 1.0 M; combined volume = 2.5 mL). Aliquots of propagating PCL chains were taken periodically over the reaction time to monitor monomer conversion and polymer growth. Upon completion, PCL was quenched by the addition of chloroform and purified by precipitation from cold acidified methanol to remove any residual unconverted monomer and traces of metal catalyst.

General experimental procedure for the synthesis of PCL-*b*-PL(L)A

The copolymerisation to prepare PCL-*b*-PL(L)A diblock copolymers was carried out *via* a sequential addition of L- or *rac*-LA after the full conversion of CL to PCL (using the homopolymerisation procedure presented above). In a separate air-tight vial equipped with a magnetic stirrer bar, LA (100 eq., 2.5 mmol, 360.3 mg) was dissolved in toluene (2.5 mL) and stirred at 70 °C for 1 h. Subsequently, the LA solution was added to the propagating PCL* chain in toluene (total volume = 5.0 mL, [LA] = 0.5 M). Please note that the CL polymerisation was allowed to proceed for one minute beyond the time determined for high conversion by ^{1}H NMR analysis (**1**: 5 min, **2**: 2.5 min, **3**: 2 min; refer to Table S1, *vide infra*), prior to the addition of the LA solution, to help ensure that only traces of unreacted CL were present from the homopolymerisation step. Aliquots of the PCL-P(L)LA copolymerisation were taken periodically to monitor monomer conversion and polymer growth (Figure S1). Upon completion (**1**: 2.5 h, **2**: 2 h, **3**: 20 mins), the PCL-PL(L)A copolymerisation was quenched by the addition of chloroform and purified by precipitation from cold acidified methanol to remove any residual unconverted monomer and traces of metal catalyst.

General experimental procedure for PCL-PLA-PCL copolymer synthesis

In a glovebox, in an air-tight vial equipped with a magnetic stirrer bar, catalyst **1**, **2** or **3** (1 eq., 25 µmol) was dissolved in toluene solvent, and BnOH was added (1 eq., 25 µmol, total volume = 1.0 mL). In a separate air-tight vial with a magnetic stirrer bar, CL (100 eq., 2.5 mmol, 277.0 µL) was dissolved in toluene (total volume = 1.42 mL or 1.25 mL, for respective [CL] = 1.76 M or 2.0 M in the first step *i.e.* CL homopolymerisation). The polymerisation of CL was initiated by the addition of catalyst/BnOH solution, and was allowed to proceed for one minute beyond the time determined for high conversion

by ^{1}H NMR analysis (**1**: 5 min, **2**: 2.5 min, **3**: 2 min; refer to Table S1, *vide infra*) prior to LA addition. Subsequently, the LA solution (100 eq., 2.5 mmol, 360.3 mg in 1.42 mL or 1.25 mL of toluene) was added to the propagating PCL* chain in toluene to give a respective total volume = 2.84 mL or 2.50 mL ([LA] = 0.88 M or 1.0 M) in the second step of PCL-PLA copolymerisation). The reaction mixture was stirred for a set period of time (see above protocol for the synthesis of PCL-*b*-PLA for details), prior to the addition of neat CL_2 (100 eq., 2.5 mmol, 277.0 µL) as the third "block". Note that the LA polymerisation was also allowed to react for 1 minute beyond the time point in which each catalyst achieved ≥95% LA conversion (**1**: 2.5 h, **2**: 2 h, **3**: 20 mins), prior to the addition of CL_2 for the third "block", to help ensure complete conversion of the LA monomer. In all cases, the polymerisation of CL_2 was allowed to proceed for 24 h. Upon completion of each polymerisation step, aliquots of PCL, PCL-PLA diblock and PCL-PLA-PCL (co)polymers were taken and quenched by the addition of excess chloroform. The final resultant copolymers were purified by precipitation from cold acidified methanol to remove any residual unconverted monomer and traces of metal catalyst.

Comparison of CL monomer conversion generated by catalysts 1 – 3

Table S1 Catalyst activity of 1 – 3 for CL homopolymerisation in toluene at 70 °C at different time points.

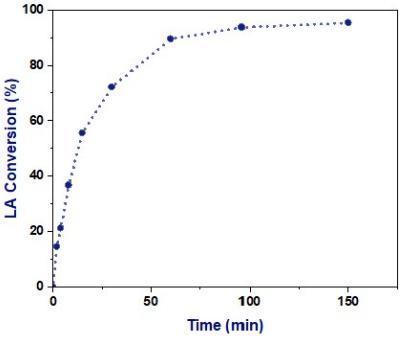
Catalyst **1**		Catalyst **2**		Catalyst **3**	
Time (s)	**CL conv. (%)**	**Time (s)**	**CL conv. (%)**	**Time (s)**	**CL conv. (%)**
30	30	30	87	30	91
60	54	60	94	60	95
90	72	90	97	120	98
120	82	100	97	180	98
150	89	120	98		
180	93	130	98		
240	96				
300	98				

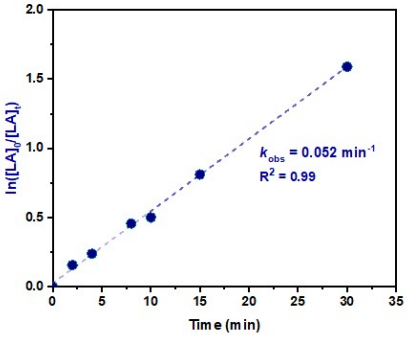
Note: Fewer time points are presented for CL conversion using catalysts **2** and **3** due to high catalyst activity, achieving essentially full CL conversion in 2 minutes.

Conversion and kinetic plots of *rac*-LA copolymerisation from a living PCL* chain to prepare PCL-*block*-PLA copolymers using catalysts 1 – 3

(a)

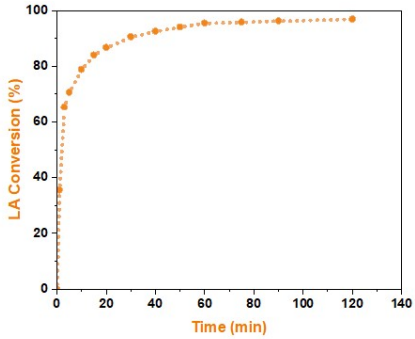
Time (min)	*Rac*-LA conv. (%)
2	15
4	21
8	37
15	56
30	72
60	89
96	94
150	95

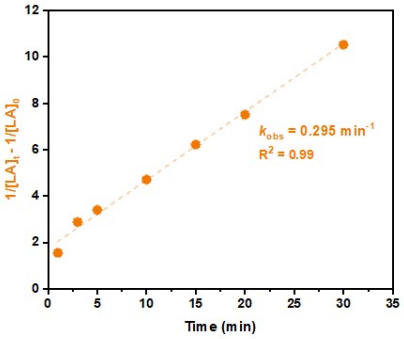




(b)

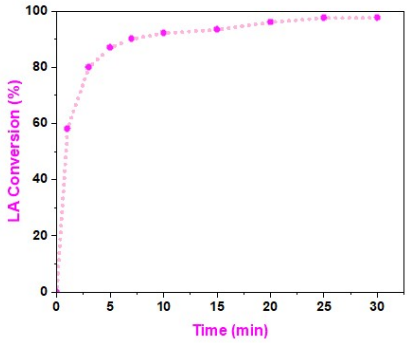
Time (min)	*Rac*-LA conv. (%)
1	35
3	65
5	71
10	79
15	84
20	87
30	91
40	93
50	94
60	95
75	96
90	96
120	97





(c)

Time (min)	*Rac*-LA conv. (%)
1	58
3	80
5	87
7	90
10	92
15	93
20	96
25	98
30	98



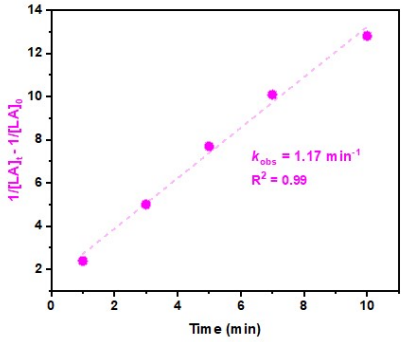


Figure S1 Conversion and kinetic plots of *rac*-LA copolymerisation from a living PCL* chain generated by catalysts (**a**) **1** (first-order) (**b**) **2** (second-order) and (**c**) **3** (second-order). Polymerisation conditions: [cat.]:[BnOH]:[CL]:[LA] = 1:1:100:100, [CL] = 1.0 M, [LA] = 0.5 M in toluene at 70 °C.

SEC traces of PCL homopolymers and the resultant PCL-*b*-PL(L)A copolymers catalysed by 1 – 3

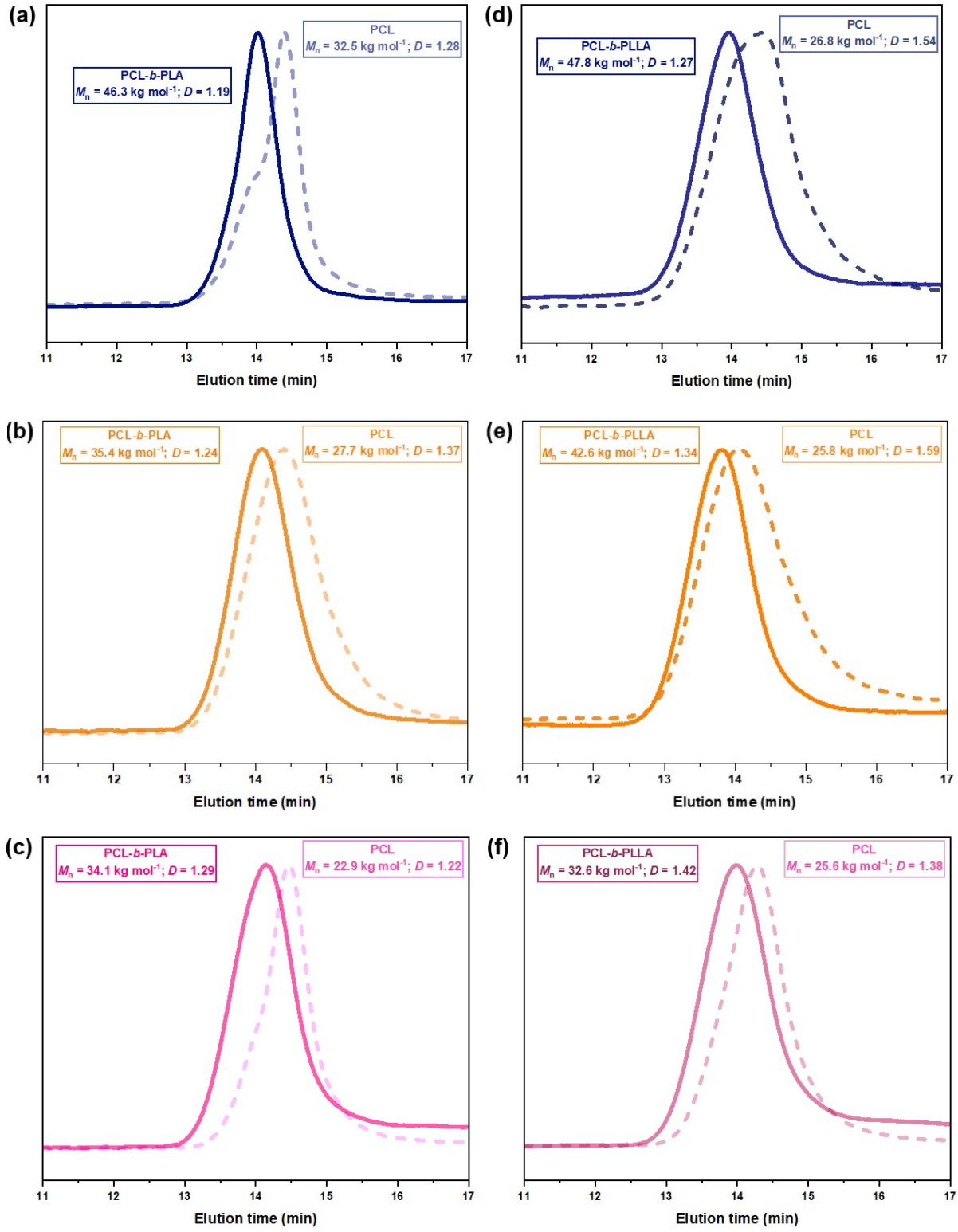


Figure S2 Overlay of SEC traces of PCL and PCL-*b*-PLA (**a–c**) and PCL-*b*-PLLA (**d–f**) catalysed by **1** (top), **2** (middle) and **3** (bottom) in toluene at 70 °C (Table 1).

DOSY NMR of PCL-*b*-PLA copolymer

The formation of diblock PCL-PLA copolymers produced by **1—3** was analysed by DOSY NMR. Using a 100:100 ratio of CL:LA ratio, the two blocks gave very similar diffusion coefficients (**Figure S3 a—c**), and the SEC traces further confirmed the presence of copolymers through an increase in M_n as well as a monomodal peak for the PCL-*b*-PLA copolymer (**Figure S2 a—c**). To provide further evidence for the formation of PCL-*b*-PLA diblock copolymers, a copolymerisation was performed with 200 eq. of CL and 50 eq. of LA with catalyst **2** (reaching essentially full monomer conversions of >98% for both blocks). DOSY NMR analysis of this copolymer exhibited a single diffusion coefficient for both the PCL and PLA blocks (**Figure S3d**). With such a large difference in the number of monomers, the observation of a single diffusion coefficient gives additional confidence in the formation of PCL-*b*-PLA copolymers.

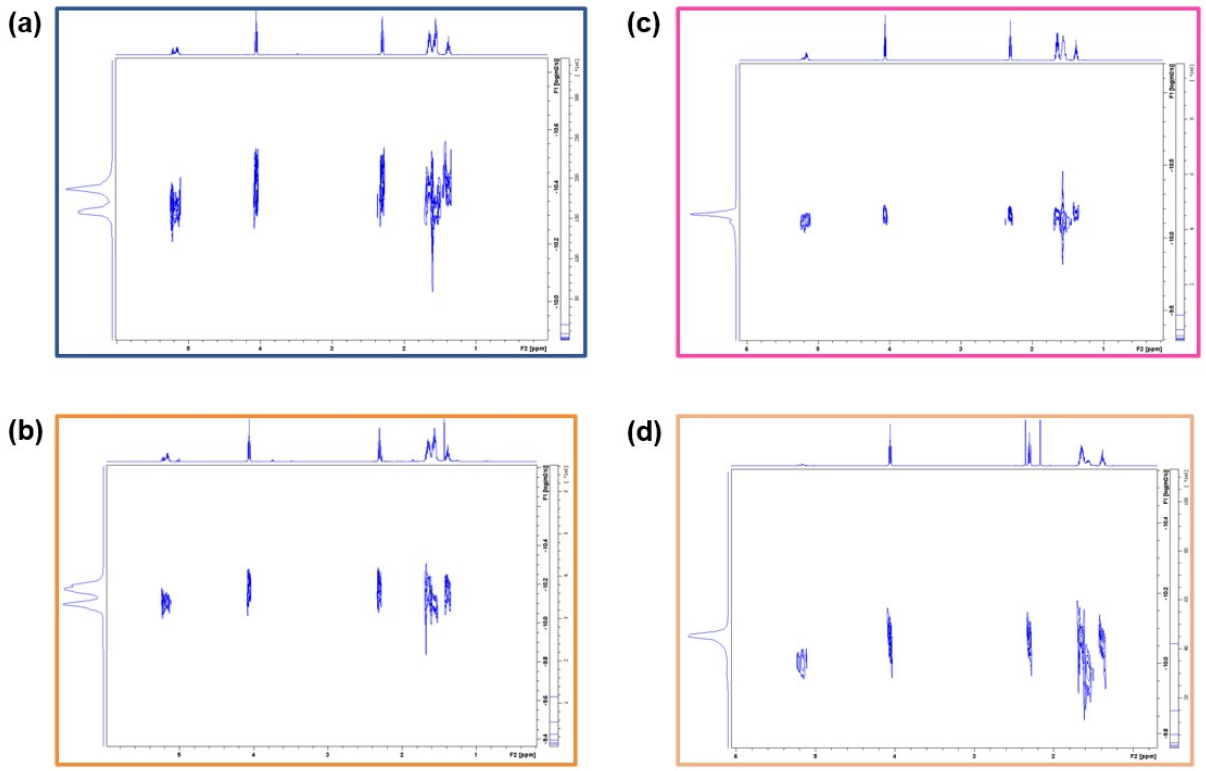


Figure S3 DOSY NMR spectra of PCL-*b*-PLA catalysed by (**a**) **1**, (**b**) **2** and (**c**) **3** at 100:100 CL:LA equivalents, and (**d**) PCL-*b*-PLA catalysed by **2** at 200:50 CL:LA equivalents, in $CDCl_3$.

Block copolymer structure analysis

Calculations for randomness factor, *R*, and number-average sequence length, *l*

The relative integrals (*i*) of CL-CL, LA-LA, CL-LA and LA-CL ^{1}H NMR diad resonances of the copolymer structure were used to quantify the degree of randomisation resulting from transesterification.

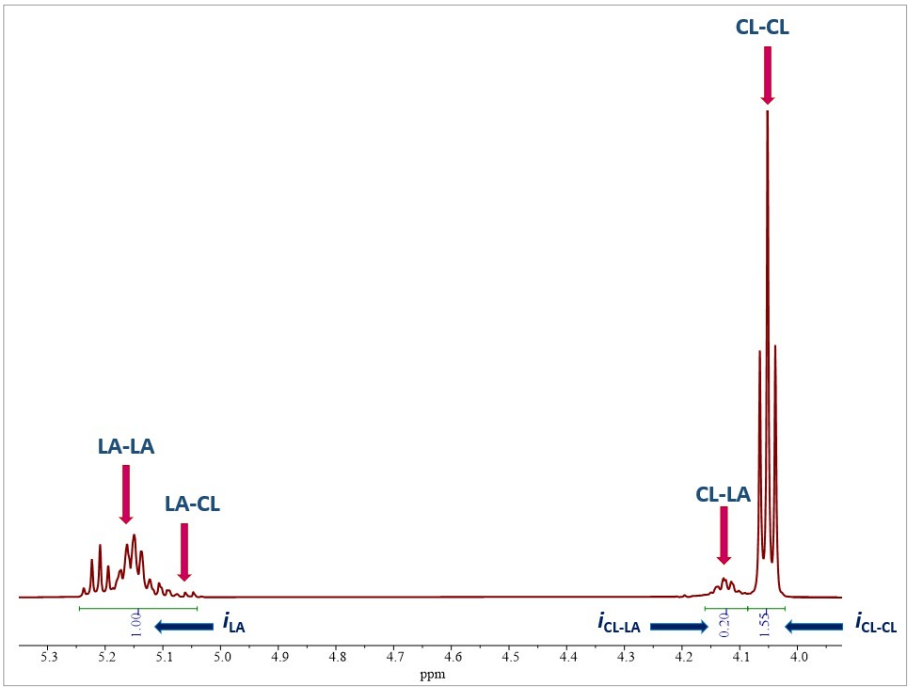


Figure S4 Example ^{1}H NMR spectrum of PCL-PLA-PCL copolymer generated with catalyst **1** (Table 2, entry 1); where the relative integrals of diad resonances at 5.0 – 5.3 and 4.0 – 4.2 ppm were used for quantifying the randomness factor, *R*, and number-average sequence lengths, *l*. Note that another set of CL-LA linkage resonance resulting from transesterification appears at 2.37 ppm, which further confirmed these *R* and *l* values.[7]

The randomness factor, *R*, and number-average sequence lengths (*l*) for CL and LA chain were calculated using the following equations:[7]

$$i_{CL} = i_{CL-CL} + i_{CL-LA} \quad \text{and} \quad i_{LA} = i_{LA-LA} + i_{LA-CL}$$

Where f_{CL} and f_{LA} are relative mole fractions of PCL and PLA in the copolymer, respectively.

$$f_{CL} = \frac{i_{CL}}{i_{LA} + i_{CL}} \quad \text{and} \quad f_{LA} = \frac{i_{LA}}{i_{LA} + i_{CL}}$$

Following this, the average diad relative molar fractions $f_{C\text{-}C}$, $f_{C\text{-}L}$, and $f_{L\text{-}L}$, were calculated:

$$f_{C-C} = f_{CL} \times f_{C-C/CL}$$

$$f_{C-L} = f_{CL} \times f_{C-L/CL}$$

$$f_{L-L} = 1 - (f_{C-C} + f_{C-L})$$

Where,

$$f_{C-C/CL} = \frac{i_{CL-CL}}{i_{CL}} \quad \text{and} \quad f_{C-L/CL} = \frac{i_{CL-LA}}{i_{CL}}$$

Randomness factor, *R* and the number-average sequence length for CL and LA chain (l_{CL} and l_{LA}) are calculated using the following equations:[7]

$$R = \frac{f_{C-L}}{2 \times f_{LA} \times f_{CL}}$$

$$l_{CL} = \frac{2f_{CL}}{f_{CL-LA}} \qquad l_{LA} = \frac{2f_{LA}}{f_{CL-LA}}$$

Table S2 Thermal properties of PCL-*b*-PLA and PCL-*b*-PLLA copolymers analysed by DSC.

Entry	Cat	Polymer	PCL		PL(L)A		Degree of crystallinity, χ_{PCL} (%)[6]	Degree of crystallinity, χ_{PLA} (%)[6]
			T_g (°C)	T_m (°C)	T_g (°C)	T_m (°C)		
1	**1**	PCL-**PLA**	-62.6	56.3	25.1	-	20	-
2	**2**		-62.2	55.8	30.4	-	16	-
3	**3**		-60.4	55.7	29.9	-	23	-
4	**1**	PCL-**PLLA**	-62.8	55.3	26.0	156.5	18	23
5	**2**		-62.2	54.7	-	163.2	15	28
6	**3**		-59.8	55.8	-	-	24	-

DSC thermogram traces for PCL-*b*-PLA and PCL-*b*-PLLA copolymers

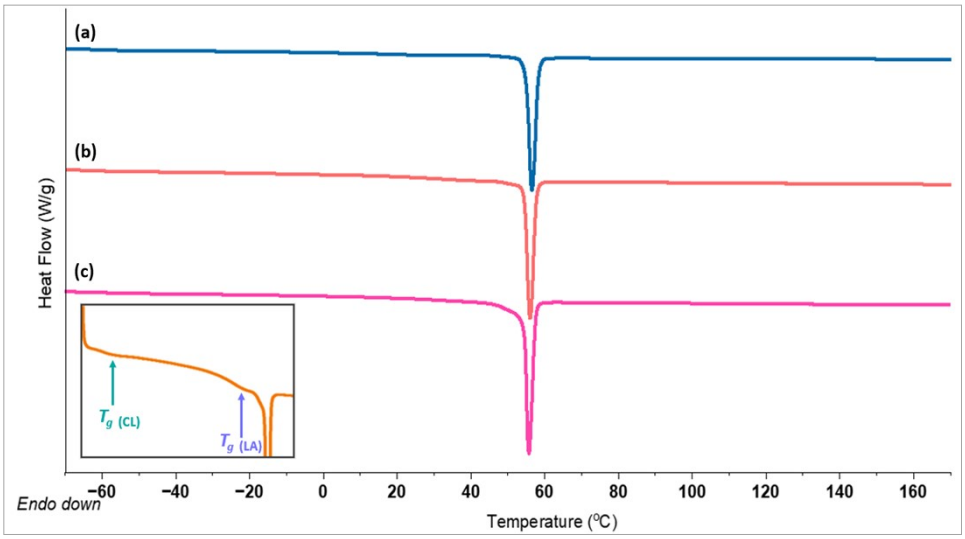


Figure S5 DSC thermograms for PCL-*b*-PLA copolymers catalysed by (**a**) **1**, (**b**) **2** and (**c**) **3**.

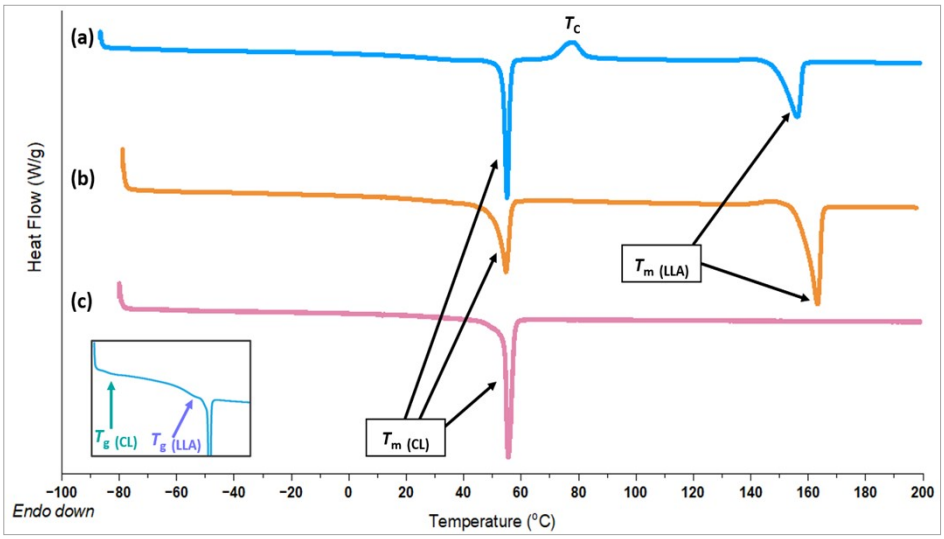


Figure S6 DSC thermograms for PCL-*b*-PLLA copolymers catalysed by (**a**) **1**, (**b**) **2** and (**c**) **3**.

Table S3 Investigations into the synthesis of PCL-PLA-PCL copolymers using catalysts **1 – 3**.

	Cat	Polymer	CL_2 conv. (%)[a]	$M_{n,obs}$ (kg/mol)[b]	$M_{n,calc}$ (kg/mol)[c]	$Đ$[b]	Compos-ition (PCL:PLA)[d]	I_{CL}, I_{LA}[d,e]	R[d,f]
1[g]	**1**	PCL-PLA	-	49.7	25.4	1.23	53:47	100, 112	0.02
		PCL-PLA-PCL	73	56.3	33.8	1.48	64:36	9, 5	0.31
2[g]	**2**	PCL-PLA	-	32.6	25.4	1.37	50:50	96, 95	0.02
		PCL-PLA-PCL	42	31.3	30.1	1.56	53:47	9, 8	0.23
3[g]	**3**	PCL-PLA	-	28.9	25.4	1.43	50:50	51, 50	0.04
		PCL-PLA-PCL	16	28.9	27.3	1.44	63:37	21, 13	0.13
4[h]	**2**	PCL-PLA	-	31.0	25.3	1.43	49:51	96, 100	0.02
		PCL-PLA-PCL	90	31.5	35.6	1.55	67:33	4, 2	0.76
5[h]	**3**	PCL-PLA	-	26.4	25.1	1.60	45:55	83, 100	0.02
		PCL-PLA-PCL	48	22.8	30.6	1.62	63:37	7, 4	0.38

[*a*] Determined from PCL/PLA signal integrals with respect to CL/LA monomer signals *via* ^{1}H NMR spectroscopy; [*b*] Determined by SEC analysis using polystyrene standard in THF, values uncorrected to enable comparisons between crude homopolymers and copolymers; [*c*] Calculated from monomer conversions, $M_{n,calc}$ = ((M_{CL}×([M]/[I])×CL conv.) + M_{LA}×([M]/[I])×LA conv.) + (M_{CL}×([M]/[I])×CL_2 conv.)), assuming 1 chain per catalyst. [*d*] Determined from PCL/PLA signal integrals by ^{1}H NMR spectroscopy of copolymer samples, using crude aliquots for PCL-PLA precursors and purified samples for the final PCL-PLA-PCL copolymers; [*e*] *I:* number average sequence length; [*f*] Randomness factor, *R*: *R* = 0 (blocky structure), *R* = 1 (fully random); [*g*] 100:100:100:1:1 [CL_1]:[LA]:[CL_2]:[cat.][BnOH] where [CL_1] = 1.76 M, [LA] = 0.88 M solution in toluene and CL_2 was added neat, at 70 °C; [*h*] 100:100:100:1:1 [CL_1]:[LA]:[CL_2]:[cat.][BnOH] where [CL_1] = 2 M, [LA] = 1 M solution in toluene and CL_2 was added neat, at 100 °C.

SEC traces of PCL homopolymer, PCL-*b*-PLA and PCL-PLA-PCL copolymers catalysed by 1 – 3 under different conditions

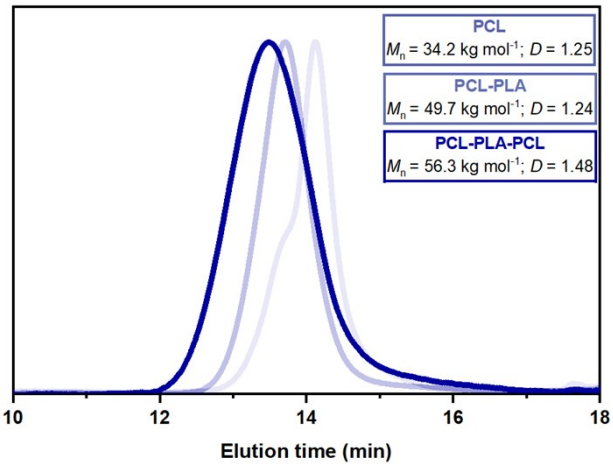


Figure S7 SEC traces of PCL homopolymer, PCL-*b*-PLA and PCL-PLA-PCL copolymers catalysed by **1** (Table 2, entry 1; Table S3, entry 1).

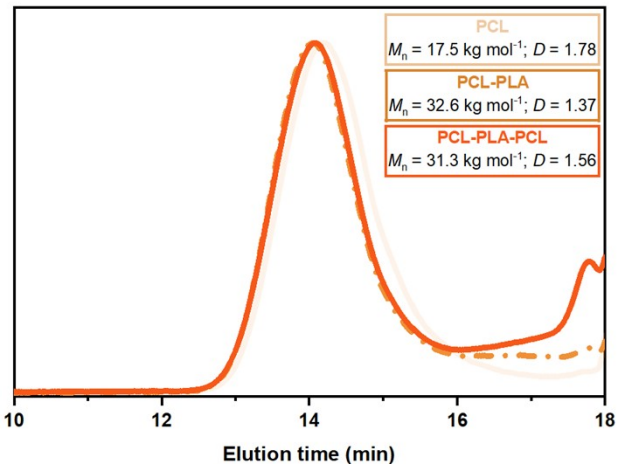


Figure S8 SEC traces of PCL homopolymer, PCL-*b*-PLA and PCL-PLA-PCL copolymers catalysed by **2** (Table 2, entry 2; Table S3, entry 2).

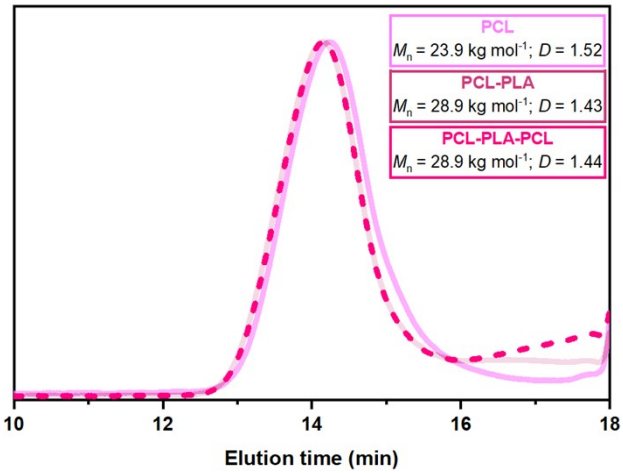


Figure S9 SEC traces of PCL homopolymer, PCL-*b*-PLA and PCL-PLA-PCL copolymers catalysed by **3** (Table 2, entry 4; Table S3, entry 3).

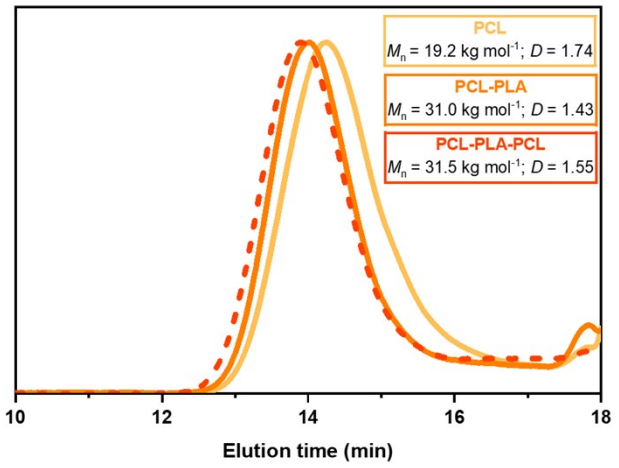


Figure S10 SEC traces of PCL homopolymer, PCL-*b*-PLA and PCL-PLA-PCL copolymers catalysed by **2** at elevated temperature (100 °C) and increased monomer concentration (Table 2, entry 3; Table S3, entry 4).

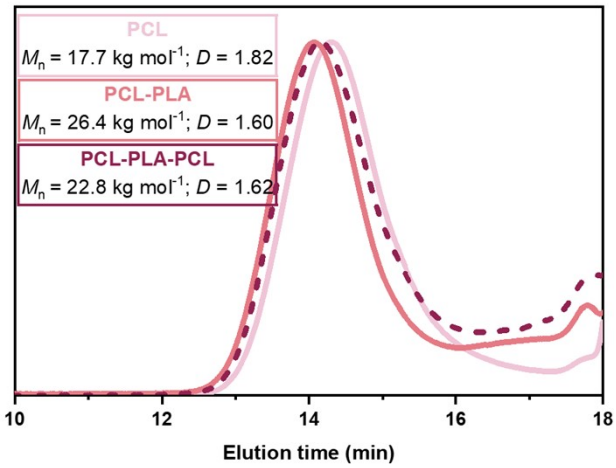


Figure S11 SEC traces of PCL homopolymer, PCL-*b*-PLA and PCL-PLA-PCL copolymers catalysed by **3** at elevated temperature (100 °C) and increased monomer concentration (Table 2, entry 5; Table S3, entry 5).

DOSY NMR spectrum of PCL-PLA-PCL copolymers catalysed by 3

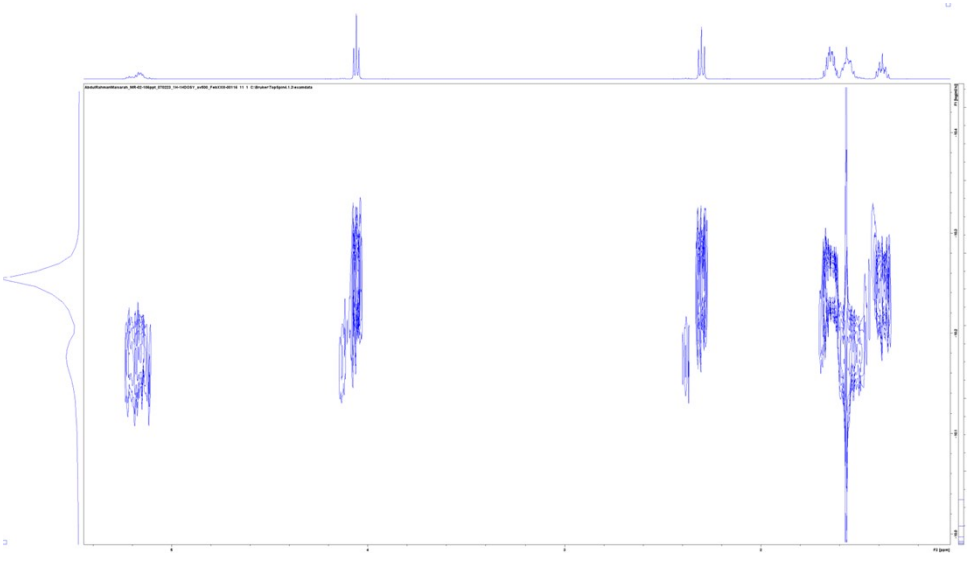


Figure S12 DOSY NMR spectrum of the purified PCL-PLA-PCL copolymer catalysed by **3** at elevated temperature (100 °C) and increased monomer concentration (Table 2, entry 5) (NMR in $CDCl_3$, 298 K).

Determination of polymer tacticity

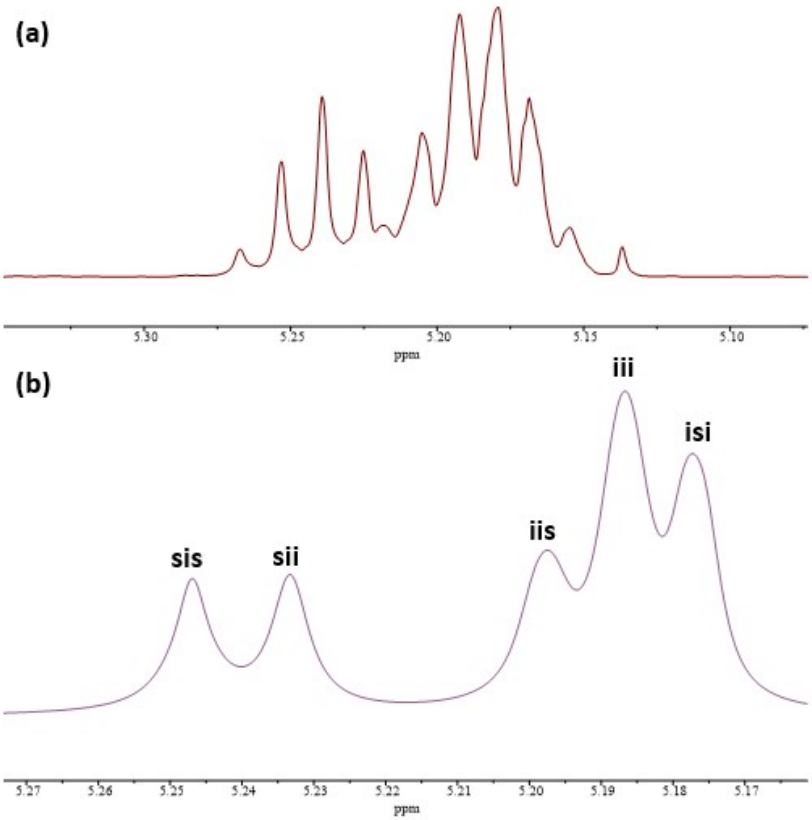


Figure S13 Example of ^{1}H (top) and $^{1}H\{^{1}H\}$ (bottom) NMR spectra in $CDCl_3$ used to determine tacticity of PLA backbone within the PCL-PLA block copolymer (500 MHz, 298 K).[8] PCL-P(L)LA spectra for diblock copolymers catalysed by **3** include an additional signal (Table 1, entries 3 and 6), attributed to stereochemical scrambling from LA epimerisation.[9]

NMR characterisation

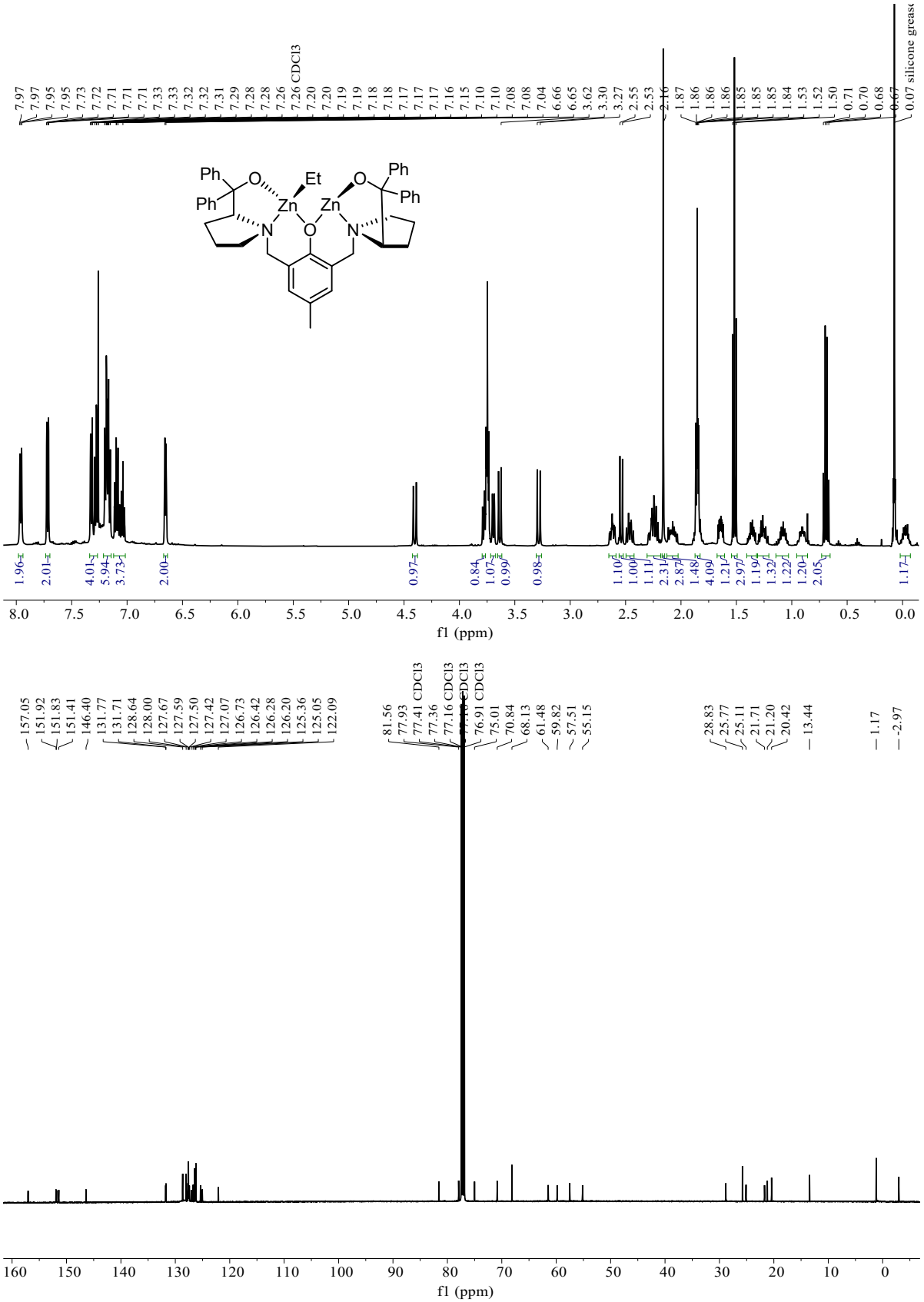


Figure S14 ^{1}H (top) and ^{13}C (bottom) NMR spectra of catalyst **1** in $CDCl_3$ (298 K). NMR spectra are in good agreement with previously reported literature.[2]

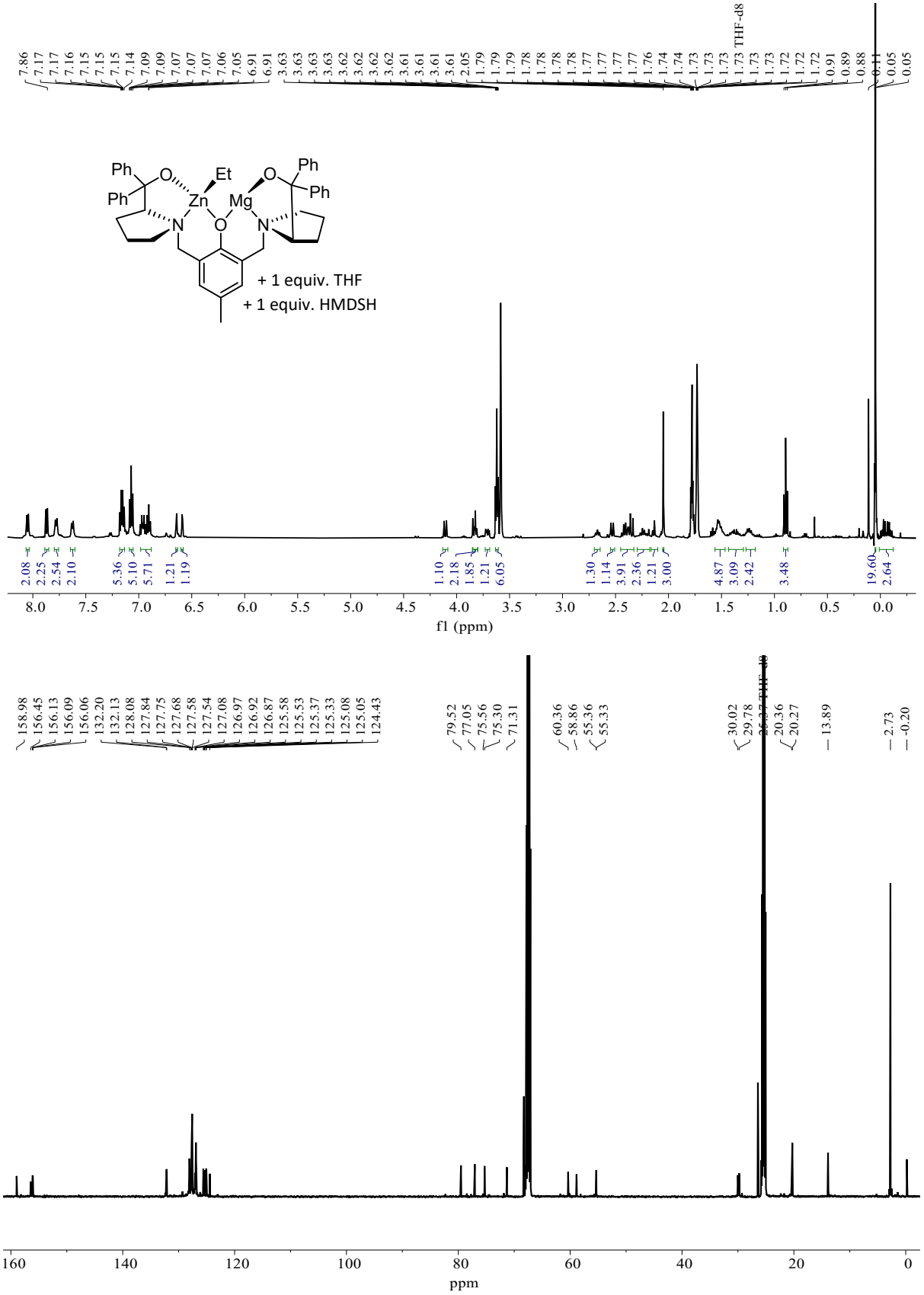


Figure S15 ^{1}H (top) and ^{13}C (bottom) NMR spectra of catalyst **2** in THF-d_8 (298 K). NMR spectra are in good agreement with previously reported literature.[3]

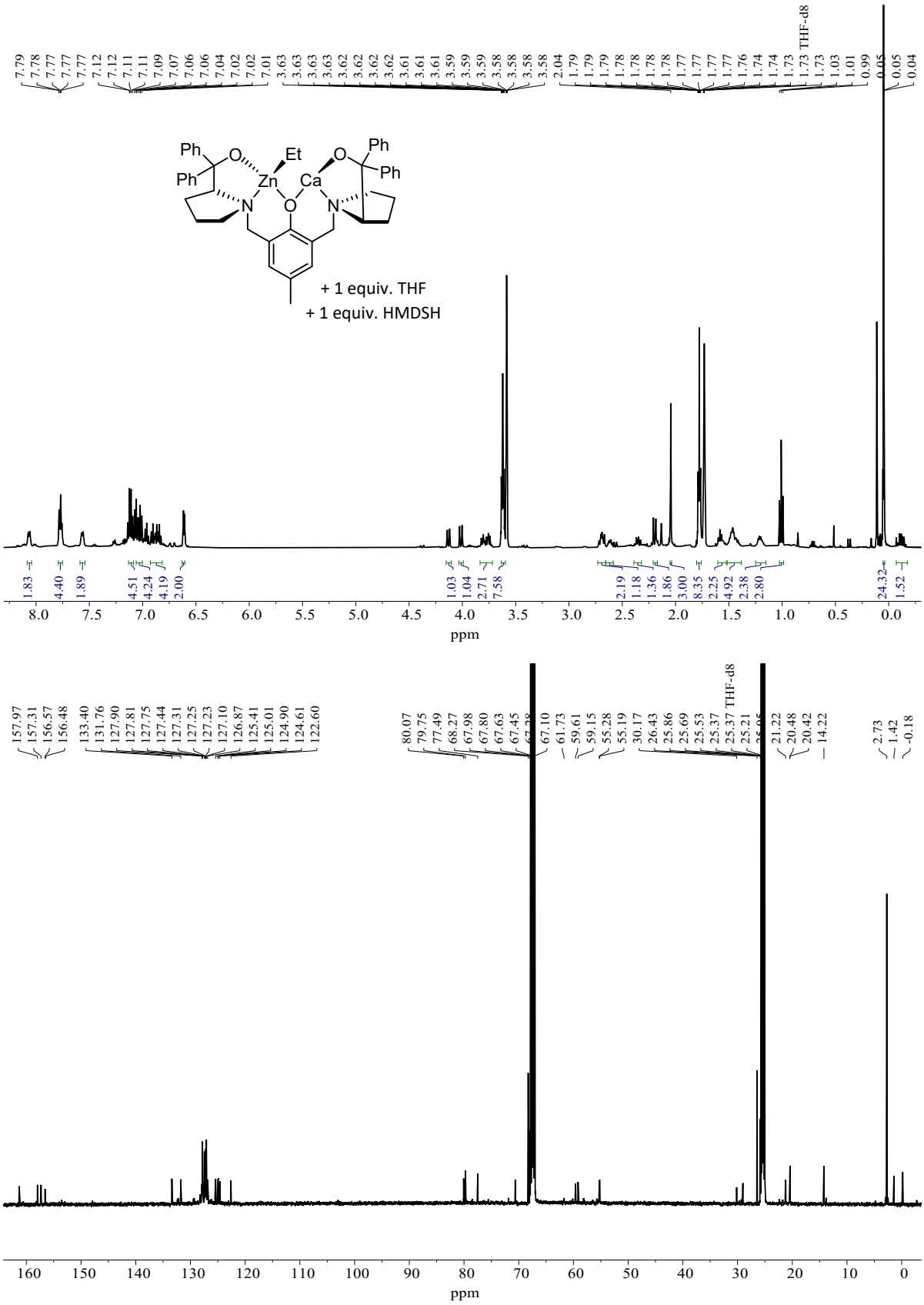


Figure S16 ^{1}H (top) and ^{13}C (bottom) NMR spectra of catalyst **3** in THF-d_8 (298 K). NMR spectra are in good agreement with previously reported literature.[3]

Possible reaction pathways following CL insertion to produce block (*via* propagation) or random (*via* transesterification) copolymers

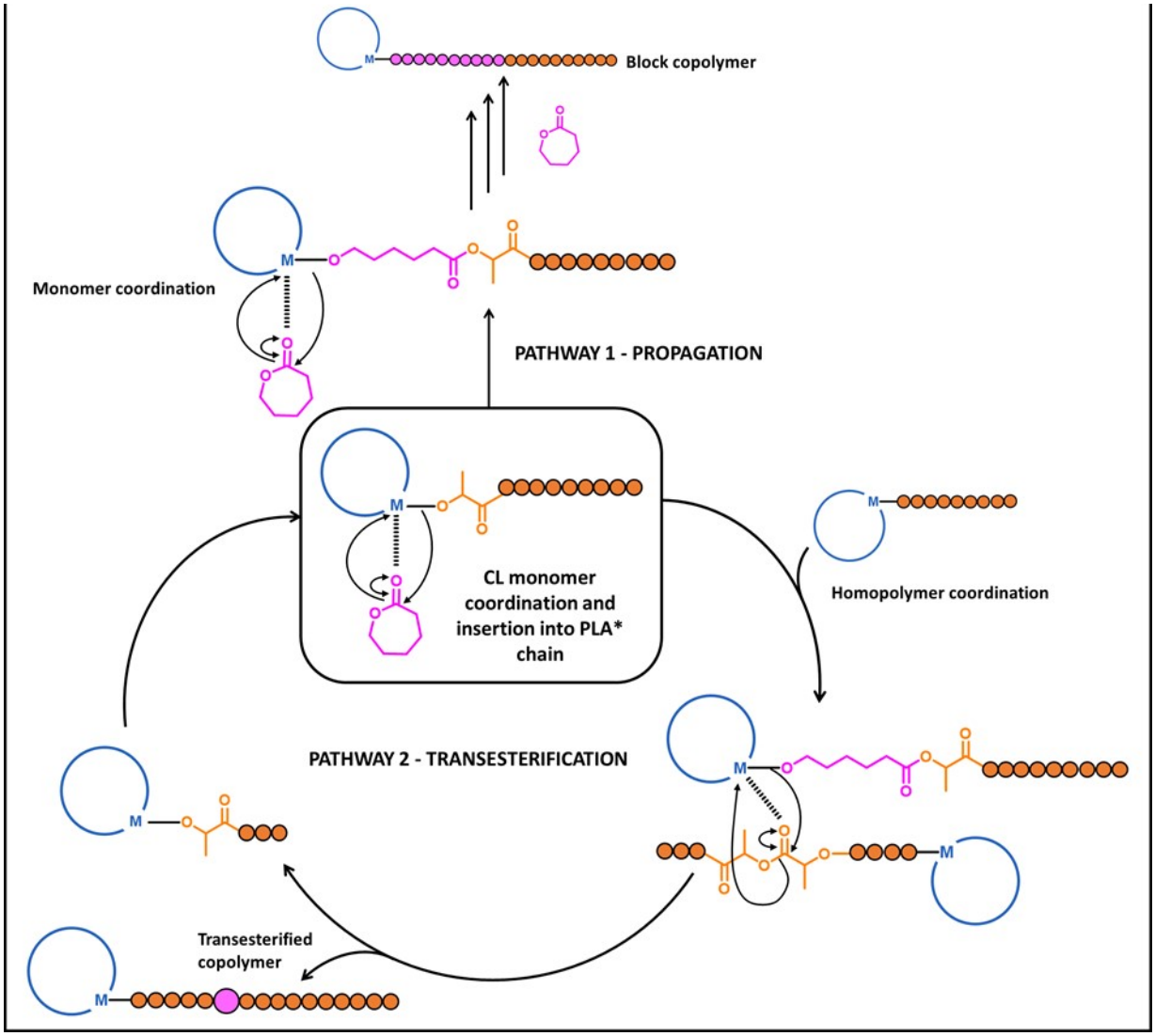


Figure S17 Reaction pathways available following *ε*-caprolactone (CL) insertion, either 1) propagation to produce block copolymers (top) or 2) transesterification to give random copolymers.[10] The competition between propagation and transesterification is controlled by the nature of the (hetero)metal (refer to Scheme 1 for further details).

References

1. X. He, B. C. Noll, A. Beatty, R. E. Mulvey and K. W. Henderson, *J. Am. Chem. Soc.*, 2004, **126**, 7444–7445.
2. W. Gruszka, L. C. Walker, M. P. Shaver and J. A. Garden, *Macromolecules*, 2020, **53**, 4294–4302.
3. W. Gruszka, H. Sha, A. Buchard and J. A. Garden, *Catal. Sci. Technol.*, 2022, **12**, 1070–1079.
4. B. M. Trost and H. Ito, *J. Am. Chem. Soc.*, 2000, **122**, 12003–12004.
5. D. H. Wu, A. D. Chen and C. S. Johnson, *J. Magn. Reson. A*, 1995, **115**, 260–264.
6. Y. Kong and J. N. Hay, *Polymer*, 2002, **43**, 3873–3878.
7. J. Fernández, A. Etxeberria and J.-R. Sarasua, *J. Mech. Behav. Biomed. Mater.*, 2012, **9**, 100–112.
8. T. M. Ovitt and G. W. Coates, *J. Am. Chem. Soc.*, 2002, **124**, 1316–1326.
9. S. Singha Roy, S. Sarkar and D. Chakraborty, *Chem. Rec.*, 2021, **21**, 1968–1984.
10. T. J. Neal, E. D. Neal, J. Cumby and J. A. Garden, *Polym. Chem.*, 2024, **15**, 1704–1713.