Supporting Information

Benzyl Bispidine as an Efficient Replacement for (-)-Sparteine in Ring Opening Polymerisation.

Richard Todd,[a] Gabriel Rubio,[a,b] Daniel J. Hall,[a] Sarah Tempelaar[a] and Andrew P. Dove[*a]

Department of Chemistry, University of Warwick, Coventry, CV4 7AL, UK

General Experimental

All reactions with air and/or sensitive compounds were carried out under a dry nitrogen atmosphere using standard Schlenk line techniques or undertaken in a glovebox. Solvents were purchased from Fisher and Aldrich. Tetrahydrofuran and dichloromethane were purified over Innovative Technology SPS alumina solvent columns and then degassed. Chemicals were purchased from Aldrich or Alfa and used as received unless noted otherwise. $CDCl_3$ was dried over 4Å molecular sieves and obtained using vacuum transfer. (-)-Sparteine was dried over calcium hydride and then distilled under an inert atmosphere. Benzyl bispidine was dried over calcium hydride in THF, filtered under inert conditions and the solvent then removed. All hydrogen bond donor co-catalysts were prepared as reported in literature and either dried over 4Å molecular sieves in DCM, calcium hydride in THF or distilled over calcium hydride.[1] Lactide, kindly donated by PURAC, was purified using the following procedure: *L* or *D*-Lactide was dissolved in DCM, passed through a silica plug and dried over magnesium sulphate, after which the solvent was removed. The lactide was dissolved in hot toluene which was removed before being transferred into a Schlenk flask under inert conditions. This procedure was repeated using dry toluene before further drying over 3Å molecular sieves in DCM (x2). *rac*-Lactide was formulated by dissolving equal amounts of dried *L*-lactide and *D*-lactide in DCM and removing the solvent. ^{1}H NMR and ^{13}C NMR spectra were recorded using a Bruker DPX-300 or a Bruker DPX-400 spectrometer. Gel permeation chromatography (GPC) analysis was used to determine the molecular weights and polydispersities of the synthesized polymers, with respect to poly(styrene) standards (chloroform GPC) or poly(methyl methacrylate) standards (DMF GPC) from Polymer Laboratories. The system was equipped with a guard column and two mixed D columns

(Polymer Laboratories). Mass spectra were acquired by MALDI-ToF mass spectrometry using a Bruker Daltonics Ultraflex II MALDI-ToF (matrix-assisted laser desorption and ionisation time-of-flight) mass spectrometer, equipped with a nitrogen laser delivering 3 ns laser pulses at 337 nm. Solutions of DCTB as matrix, NaTFA as cationization agent and polymer were prepared by preparing DCM solutions at a concentration of 10 g/L. 10 μL aliquots of matrix, polymer and NaTFA solutions were applied sequentially to the target followed by solvent evaporation to prepare a thin matrix/analyte film. The samples were measured in linear ion mode.

Propane-1,1,3,3-tetracarboxylic acid tetramethylester (4):[2]

Dimethylmalonate (80 g, 0.6055 mol, 4 eq.) and paraformaldehyde (4.6 g, 0.1514 mol, 1 eq.) were heated to 60 °C before potassium hydroxide (10% in ethanol) was added dropwise (1.5 g of the KOH solution), resulting in the mixture becoming clear. The temperature was increased to 95 °C and the solution stirred for 16 h. The excess dimethylmalonate was removed under vacuum before the product was dissolved in dichloromethane and filtered to yield a clear oil that crystallised on standing, (40 g, 96%). Characterizing data was consistent with those reported previously.[2] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.69 (s, 12 H, CH_3), 3.46 (t, *J* = 7.4 Hz, 2 H, CH), 2.42 (t, *J* = 7.4 Hz, 2 H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.9, 52.8, 49.0, 27.4.

1,5-Dihydroxy-2,4-di(hydroxymethyl)pentane (5):[2]

$LiAlH_4$ (10.88 g, 0.2570 mol, 2 eq.) was suspended in dry THF (650 mL). The mixture was cooled to 0 °C before a solution of propane-1,1,3,3-tetracarboxylic acid tetramethylester (35.5 g, 0.1285 mol, 1 eq.) in THF (100 mL) was added dropwise over several hours and then refluxed for 16 hours. The solid was collected by filtration and the product extracted with soxhlet apparatus with THF as the solvent. The THF was removed under reduced pressure to yield white crystals, (8.52 g, 40%). Characterizing data was consistent with those reported previously.[2] Mp: 130-132 °C (Lit: 130°C); ^{1}H NMR (400 MHz, CD_3OD): δ = 3.59 (d, *J* = 5.6 Hz, 8 H, CH_2O), 1.76 (m, 2 H, CH), 1.30 (t, *J* = 6.9 Hz, 2 H, CH_2); ^{13}C NMR (100 MHz, CD_3OD): δ = 64.0, 41.8, 27.4.

1,5-Dibromo-2,4-bis(bromomethyl)pentane (6b):

1,5-Ddihydroxy-2,4-di(hydroxymethyl)pentane (4.2 g, 0.0256 mol, 3 eq.) was heated to 80 °C with stirring before PBr_3 (4.8 ml, 0.0512 mol, 6 eq.) was slowly added dropwise. NOTE fumes of HBr are produced that should be neutralized through a base scrubber prior to emission. After complete addition, the temperature was increased to 100 °C and left stirring for 16 hours. Careful addition of H_2O was undertaken in small quantities to neutralise any remaining PBr_3 before the product was extracted with CH_2Cl_2 and passed through a silica plug. Removal of the solvent under reduced pressure yielded white crystals, (6.45 g, 61%). Mp: 45-48 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.6 (dd, *J* = 10.5, 4.0 Hz, 4 H, CH_2Br), 3.46 (dd, *J* = 10.5, 6.2 Hz, 4 H, CH_2Br), 2.08 (m, 2 H, CH), 1.64 (t, *J* = 7.0 Hz, 2 H, CH_2); ^{13}C NMR (100 MHz, CD_3OD): δ = 10.8, 7.4, 5.5; Elemental Analysis %calcd (%found) for $C_7H_{12}Br_4$: C 20.2 (20.3), H 2.9 (2.8).

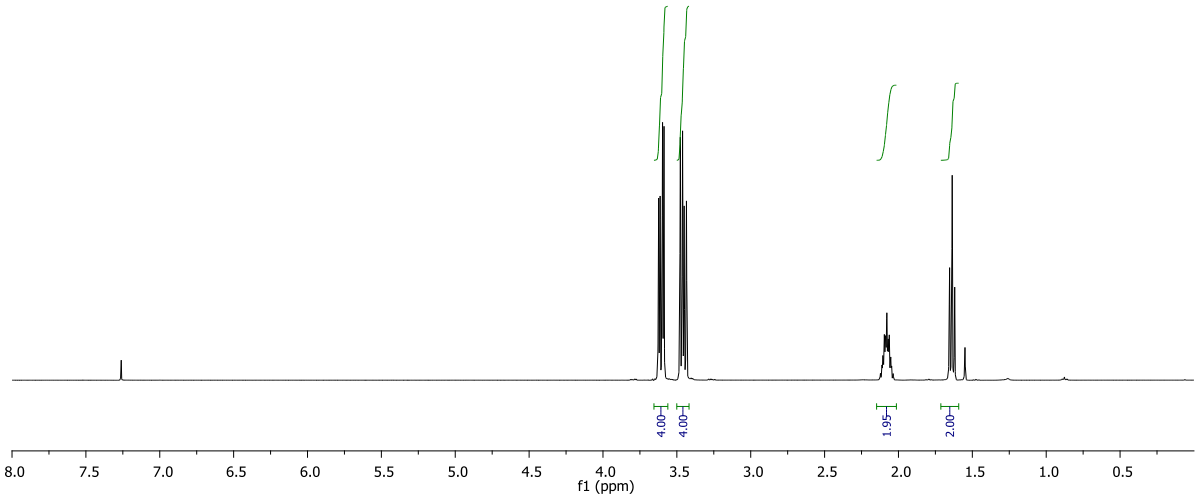


Figure S1 ^{1}H NMR spectrum of **6b** (MeOD, 400 MHz).

Benzyl Bispidine (2):

Under a nitrogen atmosphere, 1,5-dibromo-2,4-bis(bromomethyl)pentane (4.81 g, 0.01157 mol, 1 eq.) was transferred into an ampoule and dissolved in dry toluene (30 mL). Benzylamine (6 eq.) was added to the ampoule before it was sealed. The solution was refluxed for three days resulting in the formation of a white solid. The mixture was washed with NaOH 15% in water (60 mL) and the aqueous phase re-extracted with toluene (2 × 50

mL). The organic phases were combined, and the solvent removed under reduced pressure to yield an oil. The crude product was purified by first passing through a silica plug using CH_2Cl_2:MeOH (90:10) to remove the impurities and then CH_2Cl_2:MeOH:NEt_3 (80:10:10) to obtain **2** as a pure oil, (1.1 g, 31%). Spectroscopic data was found to be the same as previous literature reports for this compound.[3] ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.32 (m, 10H), 3.47 (s, 4H), 2.80 (d, *J* = 10.7 Hz, 4H), 2.33 (dd, *J* = 10.8, 4.0 Hz, 4H), 1.89 (m, 2H), 1.55 (n, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 139.95, 128.97, 128.16, 126.63, 63.49, 58.06, 31.10, 29.99.

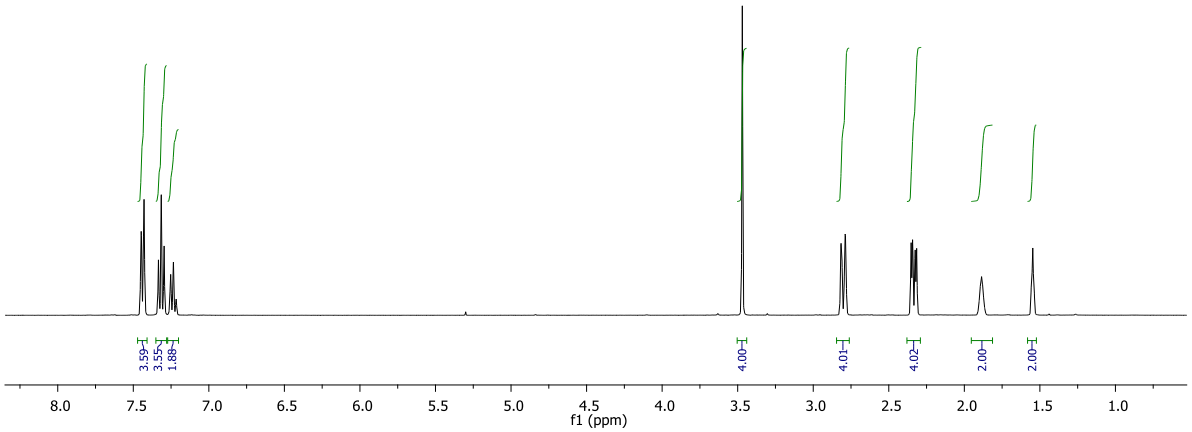


Figure S2 ^{1}H NMR spectrum of **2** ($CDCl_3$, 400 MHz).

Example polymerisation procedure:

In a typical experiment, the alcohol initiator, tertiary amine (5 mol% to monomer), and co-catalyst (10 mol% to monomer) were dissolved in dry $CDCl_3$. A separate solution of lactide was added to the initiator/catalyst solution (0.7 M lactide in total). Polymerisations were monitored by ^{1}H NMR spectroscopy until approximately 90% monomer conversion before being precipitated directly into hexanes. The solution was decanted from the precipitated polymer before addition of diethyl ether. Following stirring the polymer was recovered by filtration.

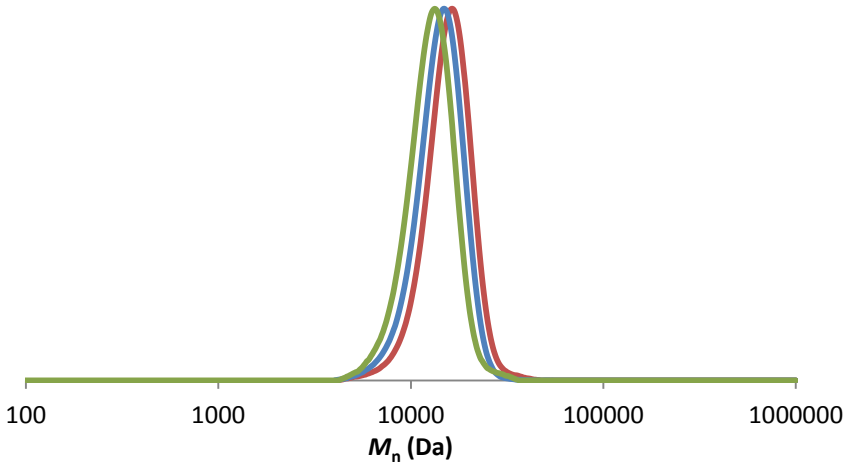


Figure S3 GPC traces of PLLA prepared by the ROP of *L*-LA ([LA] = 0.7 M), initiated from 1-phenylethanol ($[M]_0/[I]_0$ = 50), catalysed by 10 mol% TU and 5 mol% tertiary amine. Order from left to right: Me_6TREN (green), benzyl bispidine (blue), (-)-sparteine (red).

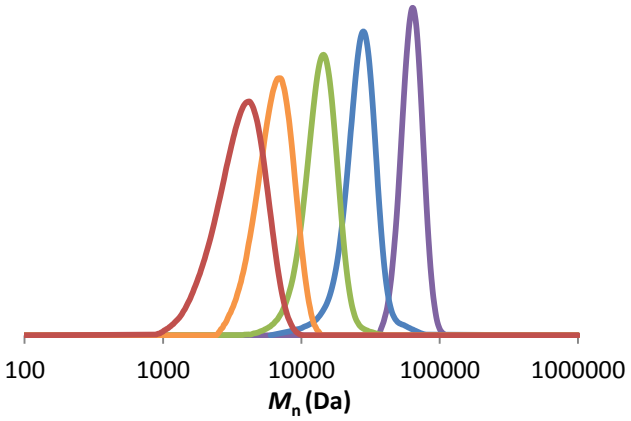


Figure S4 GPC traces of PLLA prepared by the ROP of *L*-LA ([LA] = 0.7 M), initiated from 1-phenylethanol, catalysed by 10 mol% TU and 5 mol% **2**. $[M]_0/[I]_0$ in order from left to right: 10, 20, 50, 100, 250.

Determination of P_m values for the polymerisation of *rac*-lactide:

Homonuclear decoupled ^{1}H NMR spectra of poly(*rac*-lactide) were run on a 400 MHz NMR instrument using $CDCl_3$ as solvent. The decoupling pulse was focused in the methyl region, at around 1.6 ppm. The resulting spectra were resolved using NMR software deconvolution algorithms and the peaks assigned according to literature.[4]

Tetrad	Probability
mmm	$(P_m)^2 + 0.5P_rP_m$
mmr	$0.5P_rP_m$
rmm	$0.5P_rP_m$
rmr	$0.5(P_r)^2$
mrm	$0.5((P_m)^2 + P_rP_m)$

Where $P_m + P_r = 1$

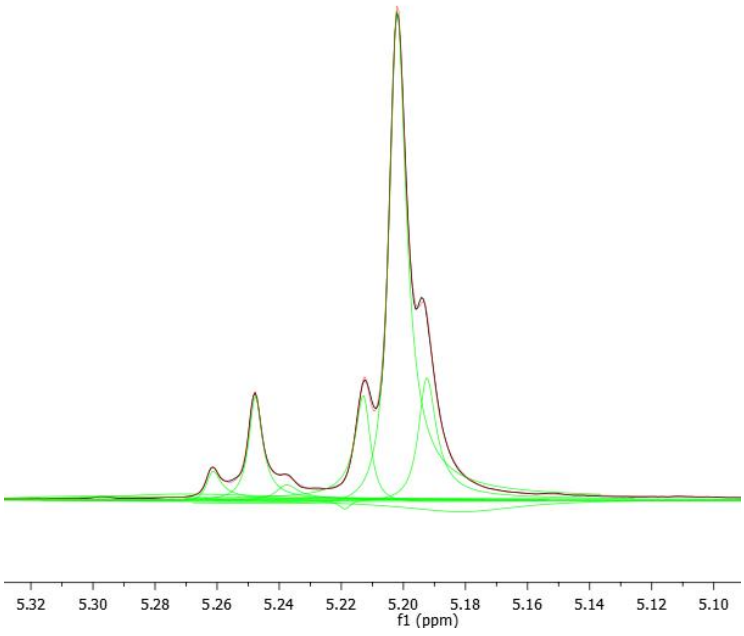


Figure S5 Homonuclear decoupled ^{1}H NMR spectra (in $CDCl_3$, focussed around methine region) of poly(rac-lactide) prepared by the ROP of *rac*-LA ([LA] = 0.7 M), initiated from 1-phenylethanol ($[M]_0/[I]_0$ = 100), catalysed by 10 mol% TU and 5 mol% **2**.

Table S1 Calculated P_m values for the binary catalyst systems **2**/TU and (-)-sparteine/TU

Catalyst			rmr	rmm	mmr	mmm	mrm	Difference of Squares
Benzyl Bispidine + TU	Experimental Intensities		0.0301	0.0967	0.0913	0.6430	0.1388	
	P_m	0.73	0.0365	0.0986	0.0986	0.6315	0.1350	0.0180
		0.74	0.0338	0.0962	0.0962	0.6438	0.1300	0.0046
		0.75	0.0313	0.0938	0.0938	0.6563	0.1250	0.0219
(-)-Sparteine + TU	Experimental Intensities		0.0252	0.0994	0.0723	0.6456	0.1575	
	P_m	0.73	0.0365	0.0986	0.0986	0.6315	0.1350	0.0300
		0.74	0.0338	0.0962	0.0962	0.6438	0.1300	0.0154
		0.75	0.0313	0.0938	0.0938	0.6563	0.1250	0.0280
Benzyl Bispidine + TU (0 °C)	Experimental Intensities		0.0254	0.1031	0.0911	0.6299	0.1506	
	P_m	0.72	0.0392	0.1008	0.1008	0.6192	0.1400	0.0197
		0.73	0.0365	0.0986	0.0986	0.6315	0.1350	0.0094
		0.74	0.0338	0.0962	0.0962	0.6438	0.1300	0.0263

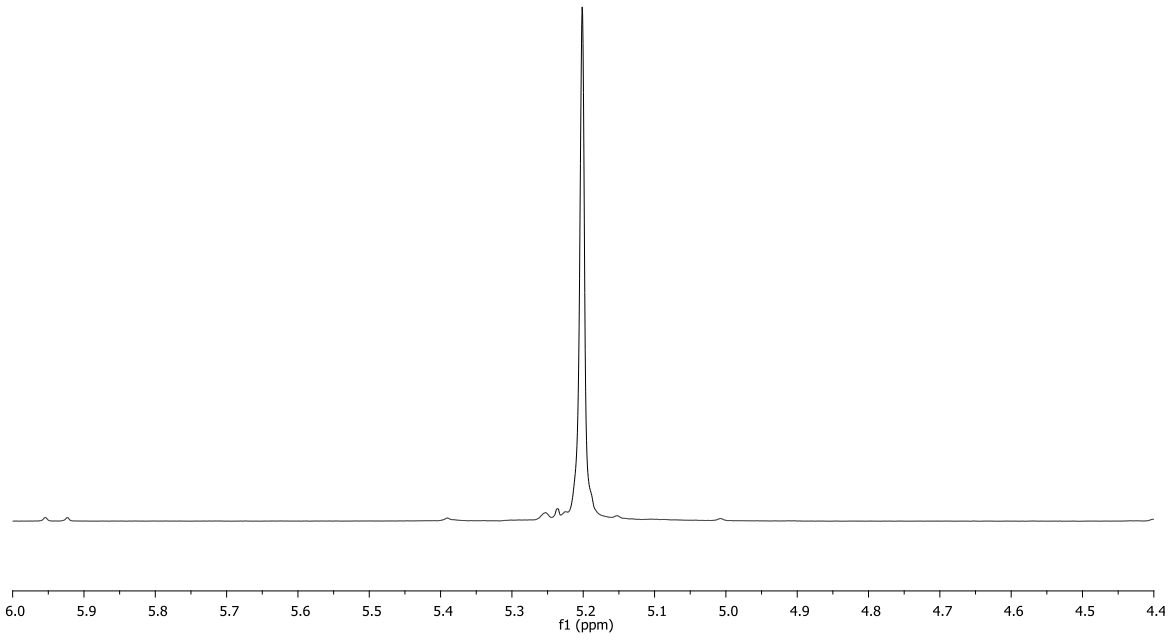


Figure S6 Homonuclear decoupled ^{1}H NMR spectrum (in $CDCl_3$, focussed around the methine region) of PLLA prepared by the ROP of *L*-LA ([LA] = 0.7 M), initiated from 1-phenylethanol ($[M]_0/[I]_0$ = 50), catalysed by 10 mol% TU and 5 mol% **2**.

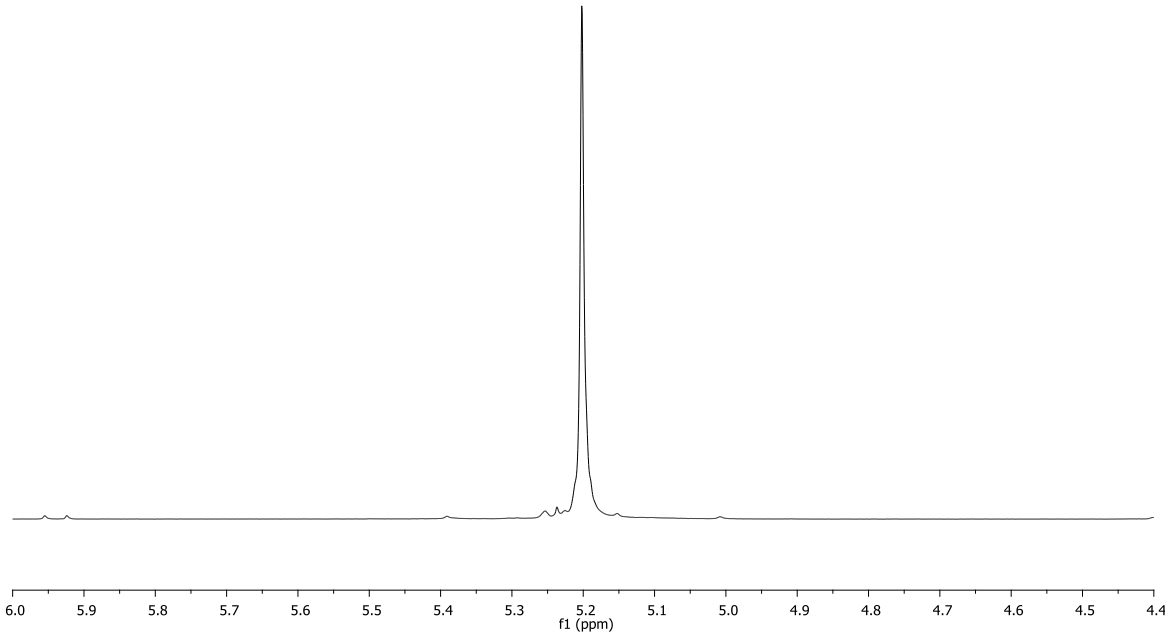


Figure S6 Homonuclear decoupled ^{1}H NMR spectrum (in $CDCl_3$, focussed around the methine region) of PLLA prepared by the ROP of *L*-LA ([LA] = 0.7 M), initiated from 1-phenylethanol ($[M]_0/[I]_0$ = 50), catalysed by 10 mol% TU and 5 mol% (-)-sparteine.

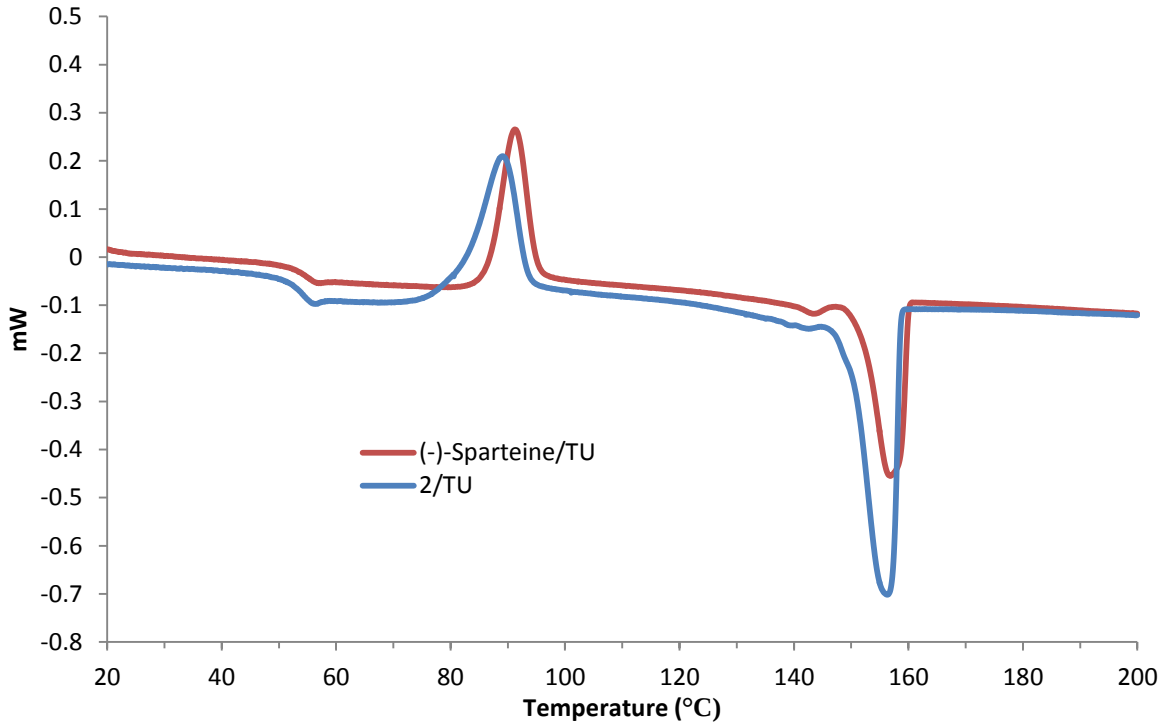


Figure S7 DSC thermogram of PLLA prepared by the ROP of *L*-LA ([LA] = 0.7 M), initiated from 1-phenylethanol ($[M]_0/[I]_0$ = 100), catalysed by 10 mol% TU and 5 mol% tertiary amine.

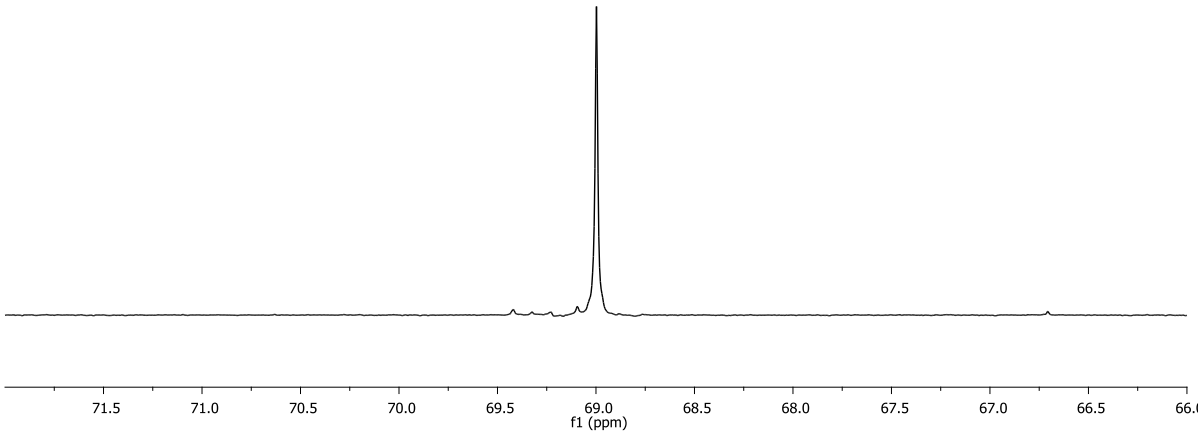


Figure S8 ^{13}C NMR spectrum (in $CDCl_3$, focussed around δ = 69 ppm) of PLLA prepared by the ROP of *L*-LA ([LA] = 0.7 M), initiated from 1-phenylethanol ($[M]_0/[I]_0$ = 50), catalysed by 10 mol% TU and 5 mol% (-)-sparteine.

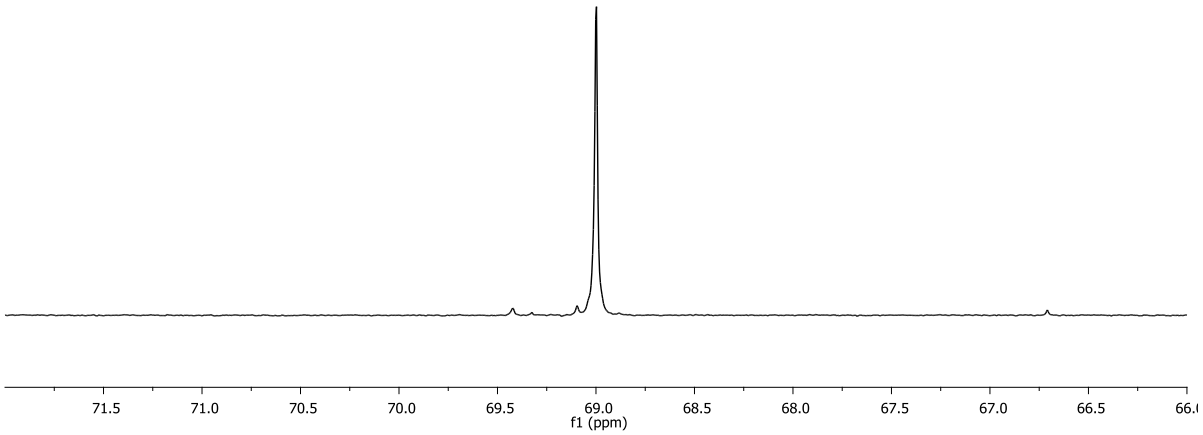
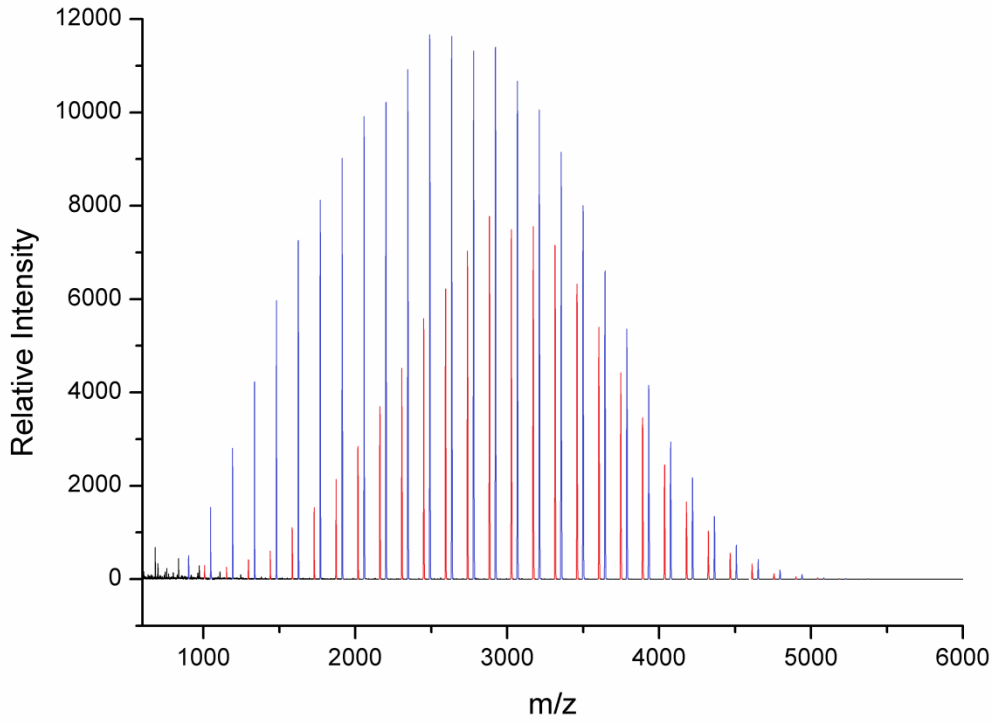
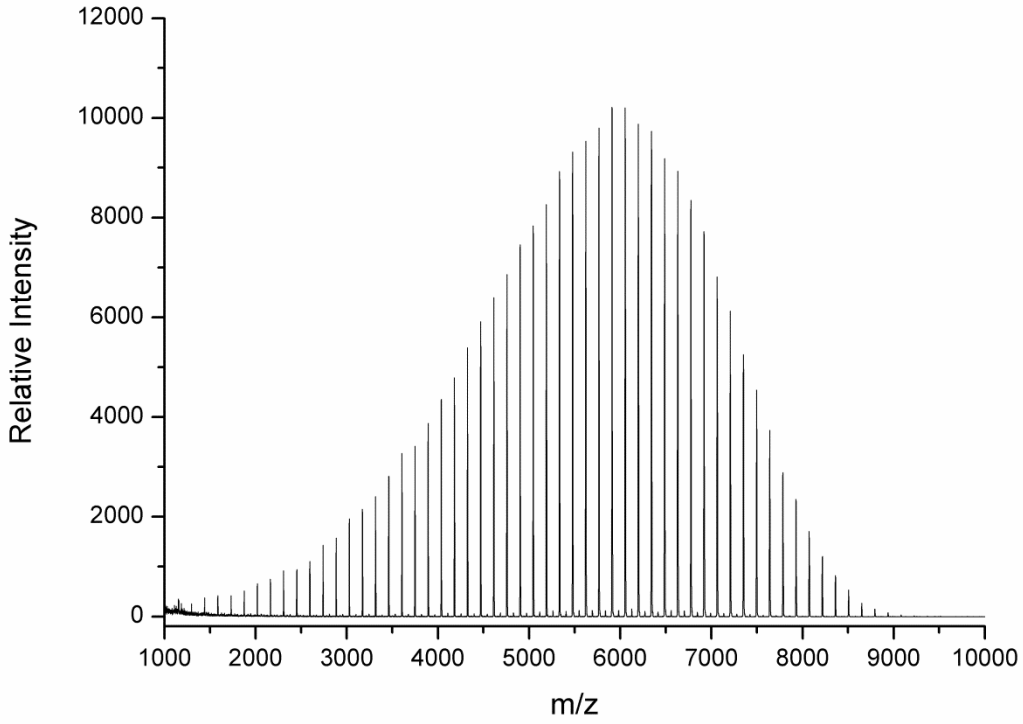


Figure S9 ^{13}C NMR spectrum (in $CDCl_3$, focussed around δ = 69 ppm) of PLLA prepared by the ROP of *L*-LA ([LA] = 0.7 M), initiated from 1-phenylethanol ($[M]_0/[I]_0$ = 50), catalysed by 10 mol% TU and 5 mol% **2**.



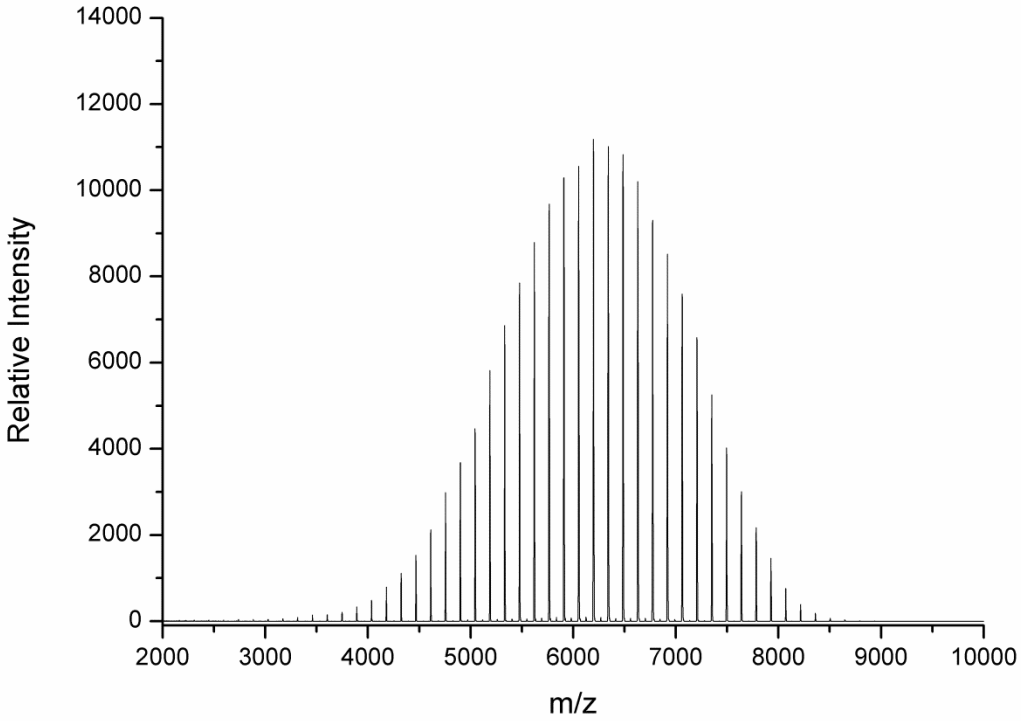
n	Calc. m/z Initiated from 1-phenylethanol	Exp. m/z Initiated from 1-phenylethanol (Red distribution)	Calc. m/z Initiated from **12**	Exp. m/z Initiated from **12** (Blue distribution)
20	3027.8	3027.1	3067.7	3067.0
21	3171.9	3171.2	3211.8	3211.1
22	3316.0	3315.3	3356.0	3355.4
23	3460.1	3459.4	3500.1	3499.5

Figure S10 MALDI-ToF MS of PLLA prepared by the ROP of *L*-LA ([LA] = 0.7 M), initiated from 1-phenylethanol ($[M]_0/[I]_0$ = 50), catalysed by 10 mol% **12** and 5 mol% **2**.



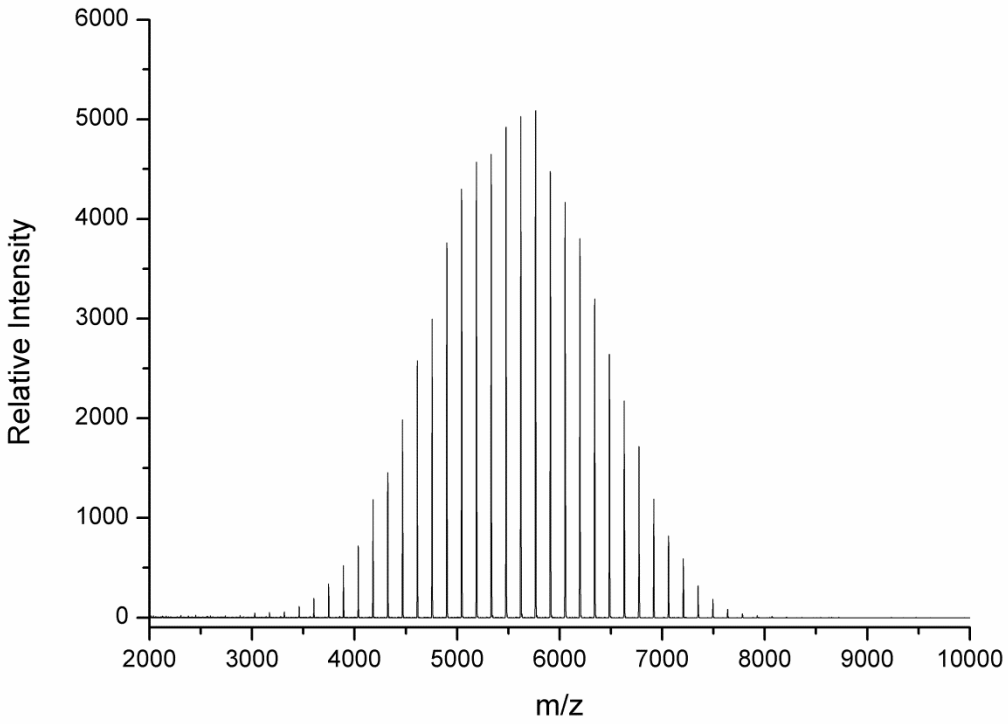
n	Calc. m/z Initiated from 1-phenylethanol	Exp. m/z Initiated from 1-phenylethanol
47	6919.3	6918.9
48	7063.4	7063.2
49	7207.5	7207.2
50	7351.7	7351.4

Figure S11 MALDI-ToF MS of PLLA prepared by the ROP of *L*-LA ([LA] = 0.7 M), initiated from 1-phenylethanol ($[M]_0/[I]_0 = 50$), catalysed by 10 mol% **10** and 5 mol% **2**.



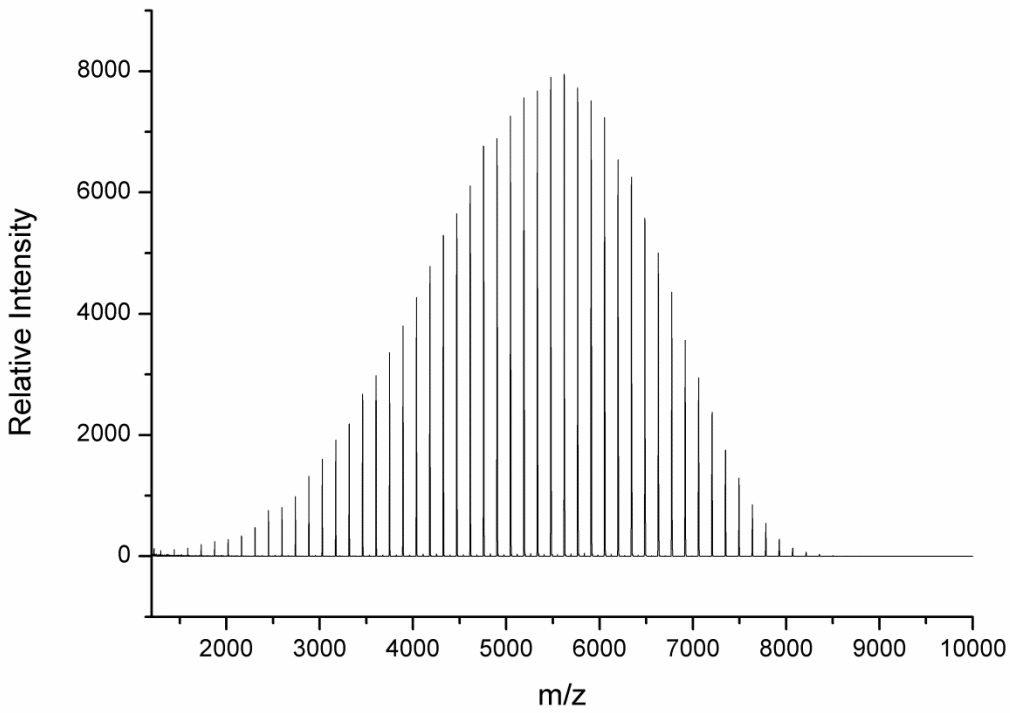
n	Calc. m/z Initiated from 1-phenylethanol	Exp. m/z Initiated from 1-phenylethanol
47	6919.3	6917.7
48	7063.4	7061.9
49	7207.5	7206.1
50	7351.7	7350.3

Figure S12 MALDI-ToF MS of PLLA prepared by the ROP of *L*-LA ([LA] = 0.7 M), initiated from 1-phenylethanol ($[M]_0/[I]_0$ = 50), catalysed by 10 mol% **8** and 5 mol% **2**.



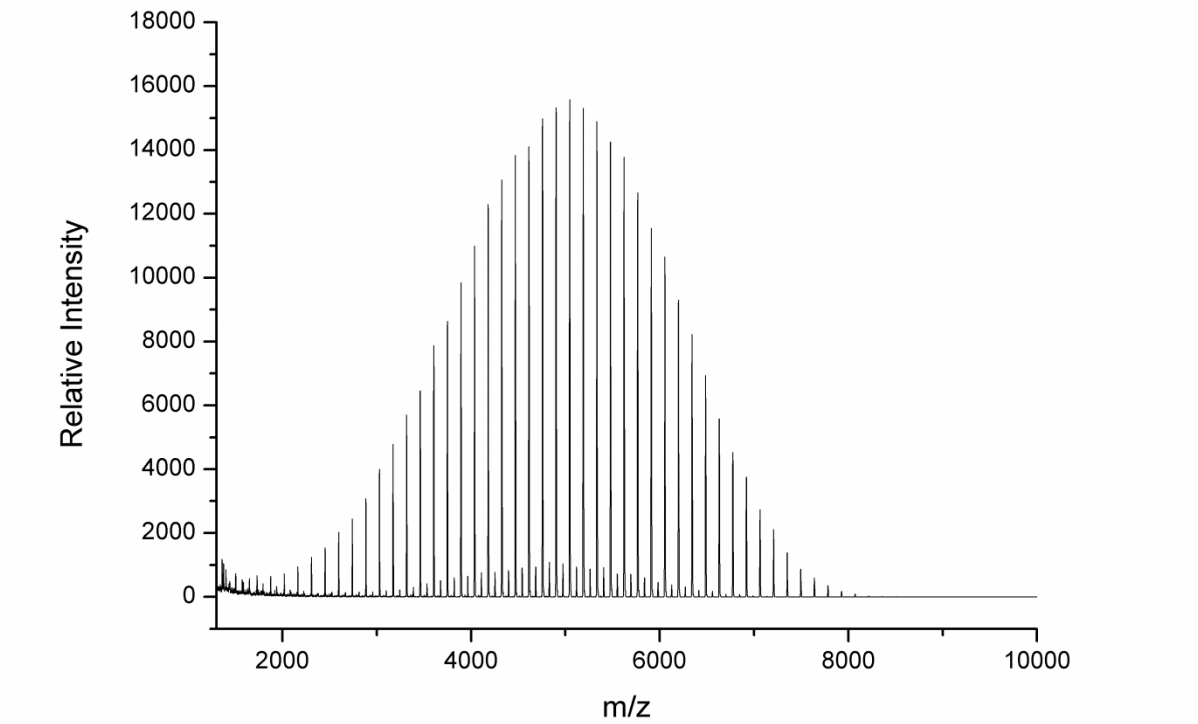
n	Calc. m/z Initiated from 1-phenylethanol	Exp. m/z Initiated from 1-phenylethanol
47	6919.3	6917.3
48	7063.4	7061.4
49	7207.5	7205.2
50	7351.7	7349.3

Figure S13 MALDI-ToF MS of PLLA prepared by the ROP of *L*-LA ([LA] = 0.7 M), initiated from 1-phenylethanol ($[M]_0/[I]_0$ = 50), catalysed by 10 mol% **9** and 5 mol% **2**.



n	Calc. m/z Initiated from 1-phenylethanol	Exp. m/z Initiated from 1-phenylethanol
47	6919.3	6917.0
48	7063.4	7061.2
49	7207.5	7205.1
50	7351.7	7349.2

Figure S14 MALDI-ToF MS of PLLA prepared by the ROP of *L*-LA ([LA] = 0.7 M), initiated from 1-phenylethanol ($[M]_0/[I]_0 = 50$), catalysed by 5 mol% **11** and 5 mol% **2**.



n	Calc. m/z Initiated from 1-phenylethanol	Exp. m/z Initiated from 1-phenylethanol
47	6919.3	6918.5
48	7063.4	7062.7
49	7207.5	7206.9
50	7351.7	7351.2

Figure S15 MALDI-ToF MS of PLLA prepared by the ROP of *L*-LA ([LA] = 0.7 M), initiated from 1-phenylethanol ($[M]_0/[I]_0 = 50$), catalysed by 10 mol% TU and 5 mol% Me_6TREN.

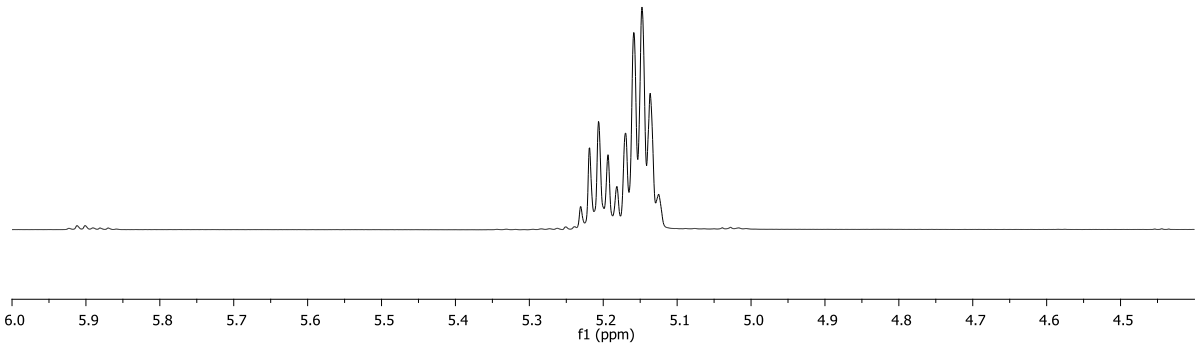


Figure S16 ^{1}H NMR spectrum (in $CDCl_3$, focussed around the methine region) of PLLA prepared by the ROP of *L*-LA ([LA] = 0.7 M), initiated from 1-phenylethanol ($[M]_0/[I]_0$ = 50), catalysed by 10 mol% **8** and 5 mol% **2**.

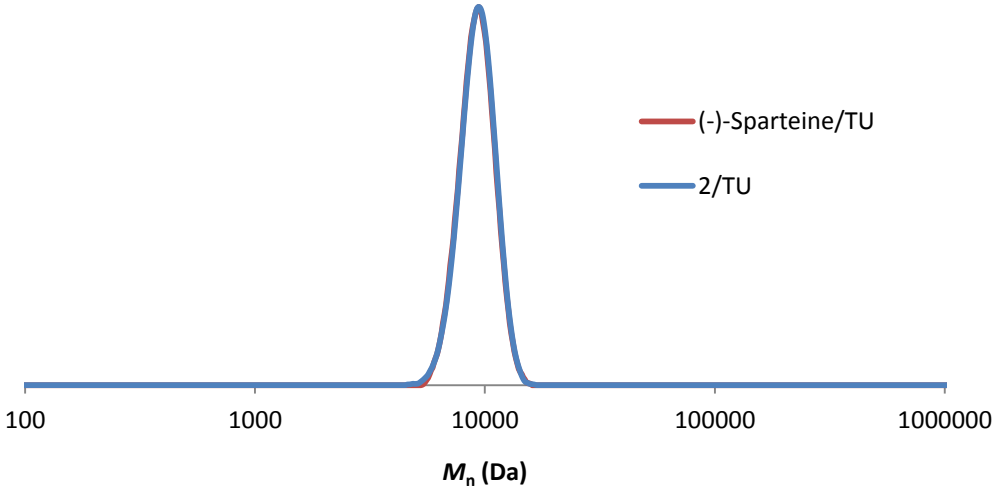
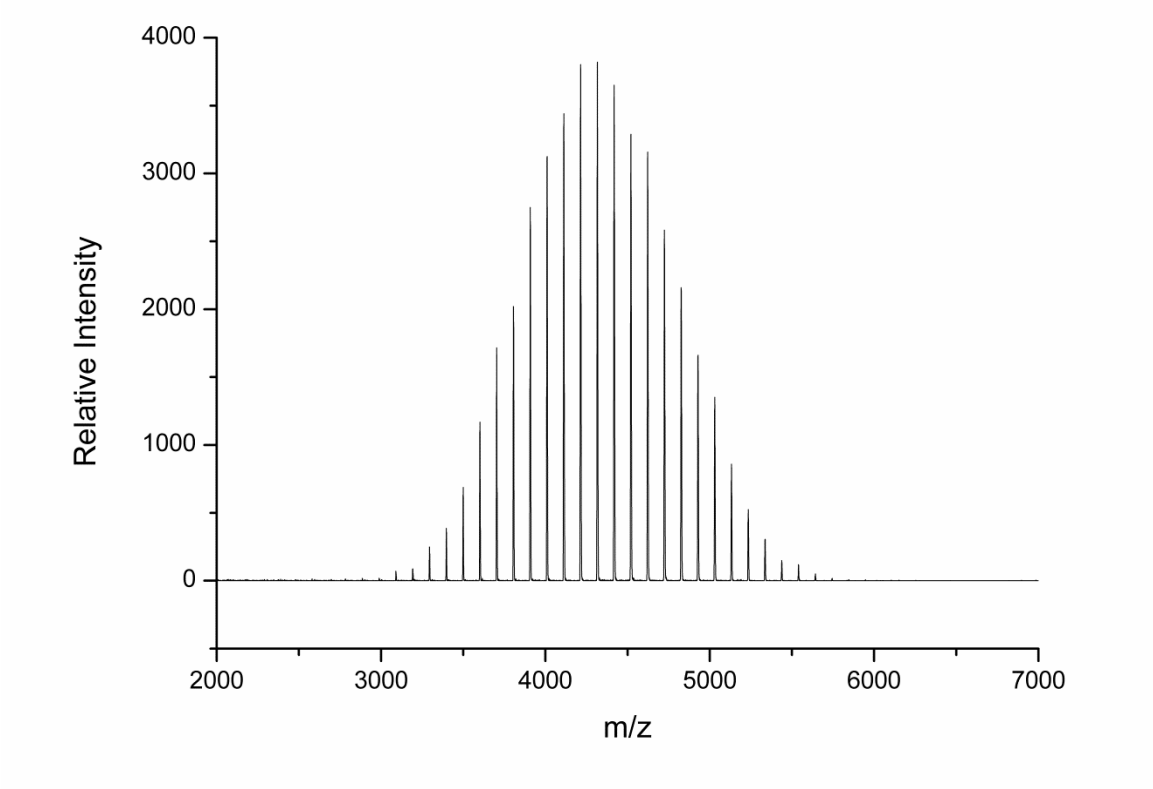


Figure S17 Two overlapping GPC traces of poly(TMC) prepared by the ROP of TMC ($[TMC]_0$ = 2.0 M), initiated from benzyl alcohol ($[M]_0/[I]_0$ = 50), catalysed by 5 mol% TU and 5 mol% **2**.



n	Calc. m/z Initiated from benzyl alcohol	Exp. m/z Initiated from benzyl alcohol
47	4929.4	4928.3
48	5031.5	5030.6
49	5133.5	5132.5
50	5235.6	5234.7

Figure S18 MALDI-ToF MS of PLLA prepared by the ROP of TMC ($[TMC]_0$ = 2.0 M), initiated from benzyl alcohol ($[M]_0/[I]_0$ = 50), catalysed by 5 mol% TU and 5 mol% **2**.

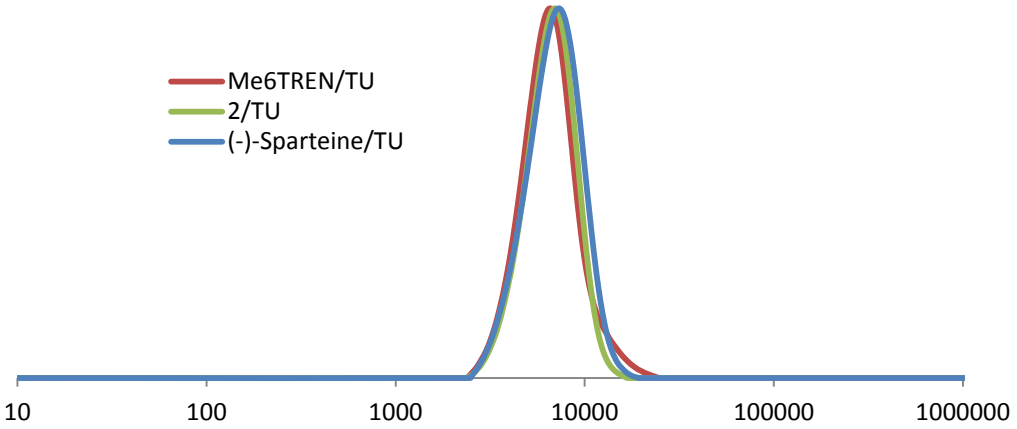
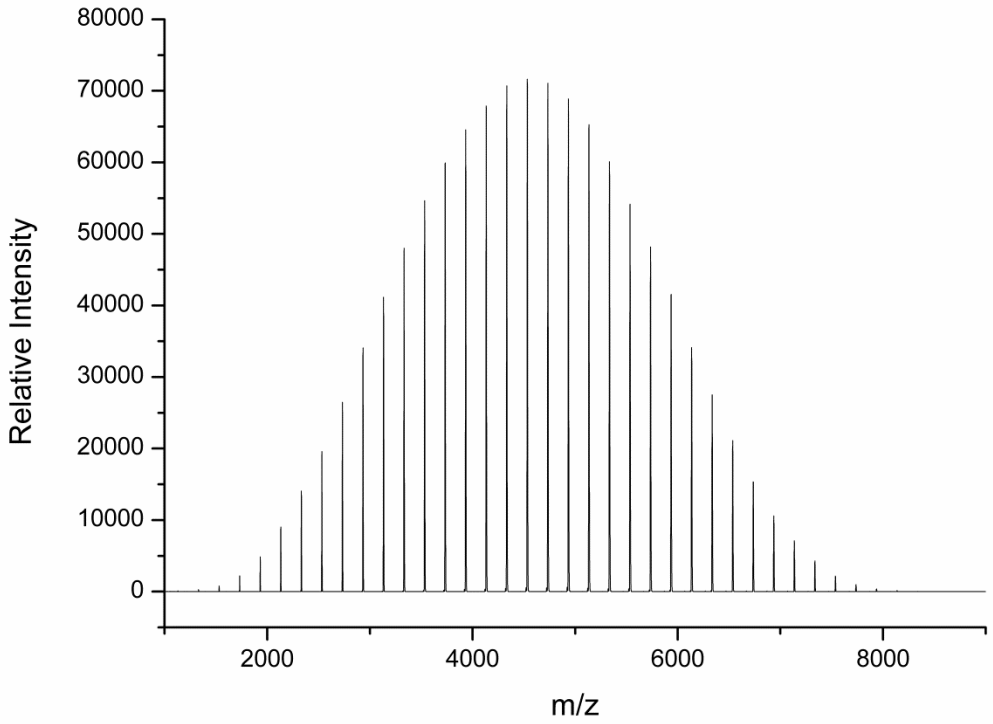


Figure S19 Three overlapping GPC traces of poly(MAC) prepared by the ROP of MAC ($[MAC]_0$ = 0.5 M), initiated from benzyl alcohol ($[M]_0/[I]_0$ = 20), catalysed by 10 mol% TU and 5 mol% **2**.



n	Calc. m/z Initiated from benzyl alcohol	Exp. m/z Initiated from benzyl alcohol
17	3534.4	3533.4
18	3734.6	3733.5
19	3934.7	3933.7
20	4134.9	4133.8

Figure S20 MALDI-ToF MS of PLLA prepared by the ROP of MAC ($[MAC]_0$ = 0.5 M), initiated from benzyl alcohol ($[M]_0/[I]_0$ = 20), catalysed by 10 mol% TU and 5 mol% **2**.

References:

(1) (a) Koeller, S.; Kadota, J.; Peruch, F.; Deffieux, A.; Pinaud, N.; Pianet, I.; Massip, S.; Leger, J. M.; Desvergne, J. P.; Bibal, B. *Chem. Eur. J.* **2010**, *16*, 4196(b) Thomas, C.; Peruch, F.; Deffieux, A.; Milet, A.; Desvergne, J. P.; Bibal, B. *Adv. Synth. Catal.* **2011**, *353*, 1049(c) Coulembier, O.; Sanders, D. P.; Nelson, A.; Hollenbeck, A. N.; Horn, H. W.; Rice, J. E.; Fujiwara, M.; Dubois, P.; Hedrick, J. L. *Angew. Chem. Int. Ed.* **2009**, *48*, 5170(d) Alba, A.; Schopp, A.; Delgado, A. P. D.; Cherif-Cheikh, R.; Martin-Vaca, B.; Bourissou, D. *J. Polym. Sci. Part A: Polym. Chem.* **2010**, *48*, 959(e) Varga, S.; Jakab, G.; Drahos, L.; Holczbauer, T.; Czugler, M.; Soós, T. *Org Lett* **2011**, *13*, 5416.

(2) Gogoll, A.; Johansson, C.; Axén, A.; Grennberg, H. *Chem. Eur. J.* **2001**, *7*, 396.

(3) Toom, L.; Kutt, A.; Kaljurand, I.; Leito, I.; Ottosson, H.; Grennberg, H.; Gogoll, A. *J. Org. Chem.* **2006**, *71*, 7155.

(4) Zell, M. T.; Padden, B. E.; Paterick, A. J.; Thakur, K. A. M.; Kean, R. T.; Hillmyer, M. A.; Munson, E. J. *Macromolecules*, **2002**, *35*, 7700.