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Effective synthetic approach to copolymers of glycolic and lactic acids for biomedical applications

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Supplementary Information

S1. Synthetic procedures

S1.1. General

All of the synthetic experiments were conducted under argon atmosphere. Diethyl ether and THF were refluxed with Na/benzophenone and distilled prior to use. DMF was distilled under reduced pressure. 3,6-Dimethyl-1,4-dioxane-2,5-dione (*rac*-lactide, Sigma-Aldrich, 99%) was purified prior to use by sublimation and subsequent recrystallization from dry toluene followed by drying *in vacuo*. 1,4-Dioxane-2,5-dione was purified by sublimation under reduced pressure.

$CDCl_3$ (Cambridge Isotope Laboratories, Inc., D 99.8 %) and DMSO-d_6 (Aldrich, ≥99.5 atom %D) were used as purchased. Toluene-d_8 and benzene-d_6 were distilled from Na/K alloy. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AVANCE 400 spectrometer (400 MHz) and on a Bruker Avance III 600 spectrometer (600 MHz) at 20 °C. The chemical shifts are reported in ppm relative to the solvent residual signals. Size exclusion chromatography (SEC) analysis of polymer samples was performed at 40 °C using an Agilent PL-GPC 220 gel permeation chromatograph equipped with PLgel column, with DMF as eluent (1 mL min^{-1}) and poly(ethylene oxide) standards. DSC experiments were performed on a TGA/DSC1 apparatus (Mettler Toledo). Elemental analysis (C, H) was carried out on a Perkin Elmer Series II CHNS/O Analyzer 2400.

S1.2. Catalyst preparation

BHT complexes [(μ-BHT)ZnEt]$_2$[1] and (BHT)$_2$AlMe[2] were prepared according to the known procedures.

(2,6-Di-*tert*-butyl-4-methylphenoxy)(2-ethoxy-2-oxoethoxy)magnesium (**Mg1**). A solution of BHT-H (220 mg, 1 mmol) in THF (1 mL) was added dropwise to a stirred solution of Bu_2Mg in heptane (1.0 mL, 1.0 M, 1 mmol). After 30 min, a solution of $HOCH_2COOEt$ (104 mg, 1 mmol) in THF (1 mL) was added dropwise to the stirred reaction mixture. The stirring was stopped after 30 min. Hexane (8 mL) was slowly layered on a top of the formed solution. After 14 days, the mother liquor was decanted. The remaining crystals were washed with toluene (2×1 mL), hexane (2×5 mL), and dried under vacuum. Total product yield was 360 mg (61%, 0.31 mmol). ^{1}H NMR (600 MHz, $CDCl_3$, 20 °C), δ: 6.93 (s, 4H, m-$\underline{H}_{BHT}$); 4.40 (br.s, 4H, OC$\underline{H}_2$COO); 4.27 (q, 4H, ^3J = 7.15 Hz, $CH_3C\underline{H}_2O$-); 3.90 (m, 12H, OC$\underline{H}_{2\ THF}$); 2.24 (s, 6H, C$\underline{H}_{3\ BHT}$); 1.89 (m, 12H, C$\underline{H}_{2\ THF}$); 1.38 (s, 36H, (C$\underline{H}_3$)$_3$C $_{BHT}$); 1.29 (t, ^3J = 7.15 Hz, 6H, C$\underline{H}_3CH_2O$-). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$, 20 °C), δ: 187.0 (C=O); 161.6 (ipso-$\underline{C}$-O_{BHT}); 136.9; 125.4; 118.6; 69.0 (THF); 63.1; 62.6; 34.8 ((CH$_3$)$_3\underline{C}_{BHT}$); 30.1 ((C$\underline{H}_3$)$_3C_{BHT}$); 25.5 (THF); 21.3 (CH_3-$_{BHT}$) ; 14.2 (CH_3CH_2O-).

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[1] C. Descour, T.J.J. Sciarone, D. Cavallo, T. Macko, M. Kelchtermans, I. Korobkov and R. Duchateau, *Polym. Chem.*, 2013, **4**, 4718.

[2] R. A. Stapleton, B. R. Galan, S. Collins, R. S. Simons, J. C. Garrison and W. J. Youngs, *J. Am. Chem. Soc.*, 2003, **125**, 9246.

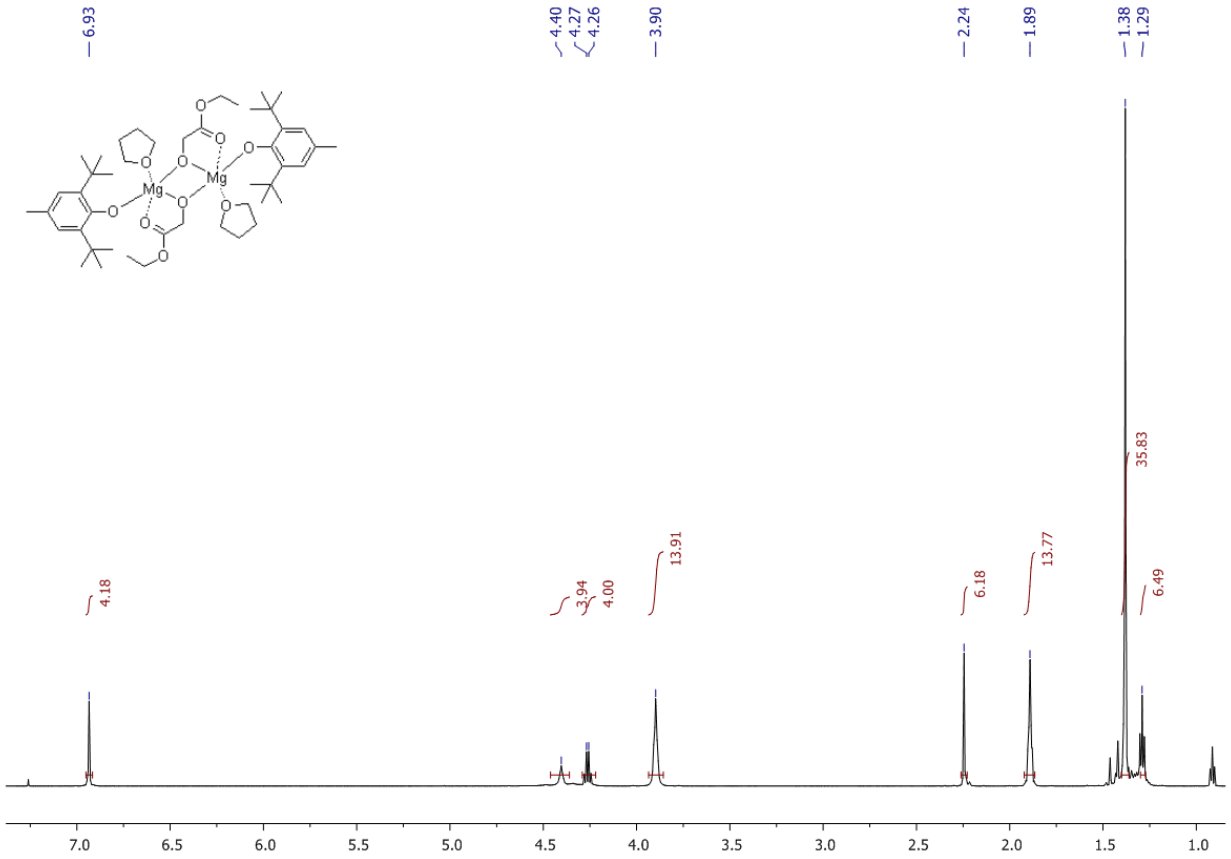

Figure S1 ^{1}H NMR spectrum (600 MHz, $CDCl_3$, 20 °C) of **Mg1** catalyst.

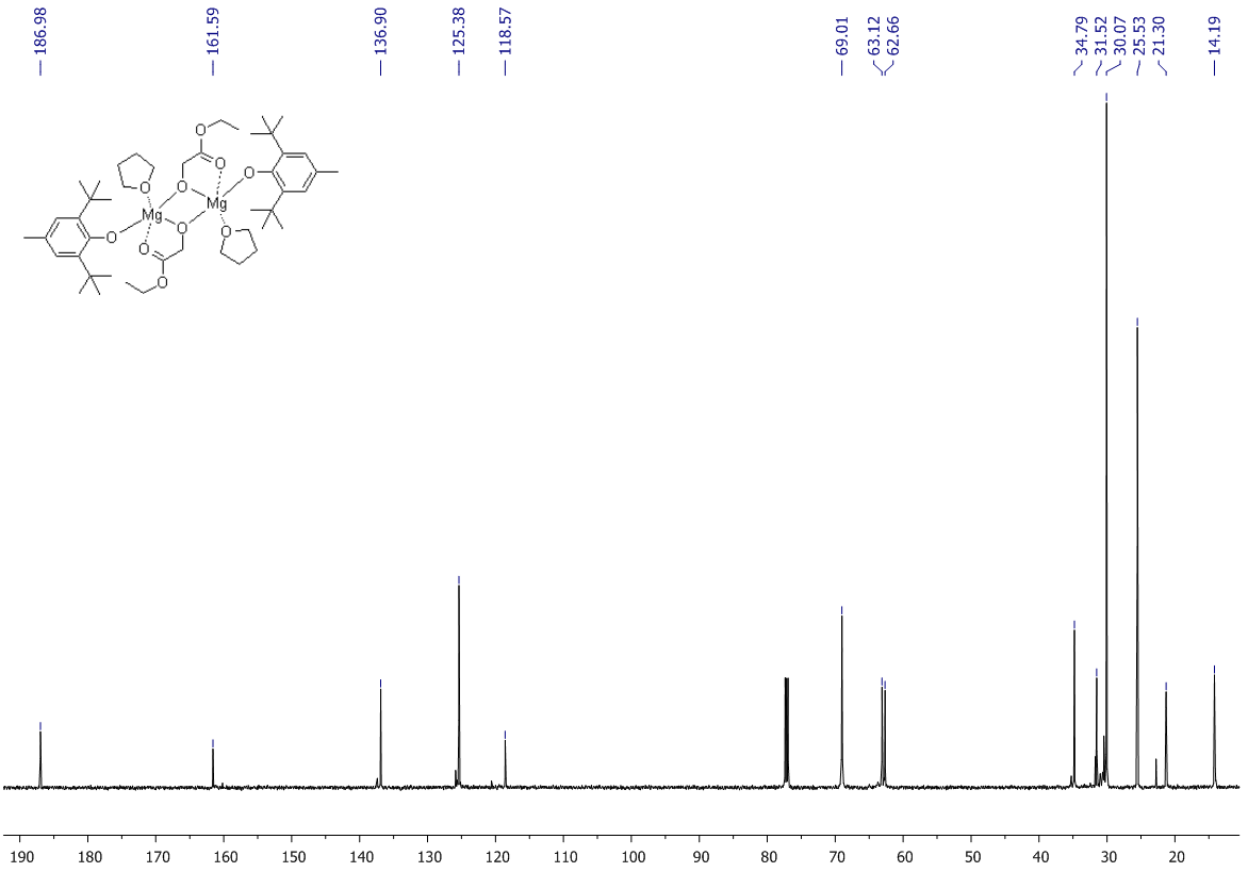

Figure S2 $^{13}C\{^{1}H\}$ NMR spectrum (151 MHz, $CDCl_3$, 20 °C) of **Mg1** catalyst.

Magnesium 2-ethoxy-2-oxoethanolate (**Mg2**). $MgBu_2$ (1.0 M in *n*-heptane, 5 mL, 5 mmol) was added dropwise to stirred solution of $HOCH_2COOEt$ (1.041 g, 10 mmol) in toluene (6 mL). The mixture was stirred for 3 h, the solvents were evaporated under reduced pressure. The residue (viscous yellow oil) was washed with *n*-hexane (3×10 mL) and dried *in vacuo*. The yield was 1.072 g (4.65 mmol, 93%), yellow powder. Elemental analysis for $C_8H_{14}MgO_6$, 230.50: Calc. (%) C 41.69, H 6.12, O 41.65; Found (%) C 41.55, H 6.30, O 41.81.

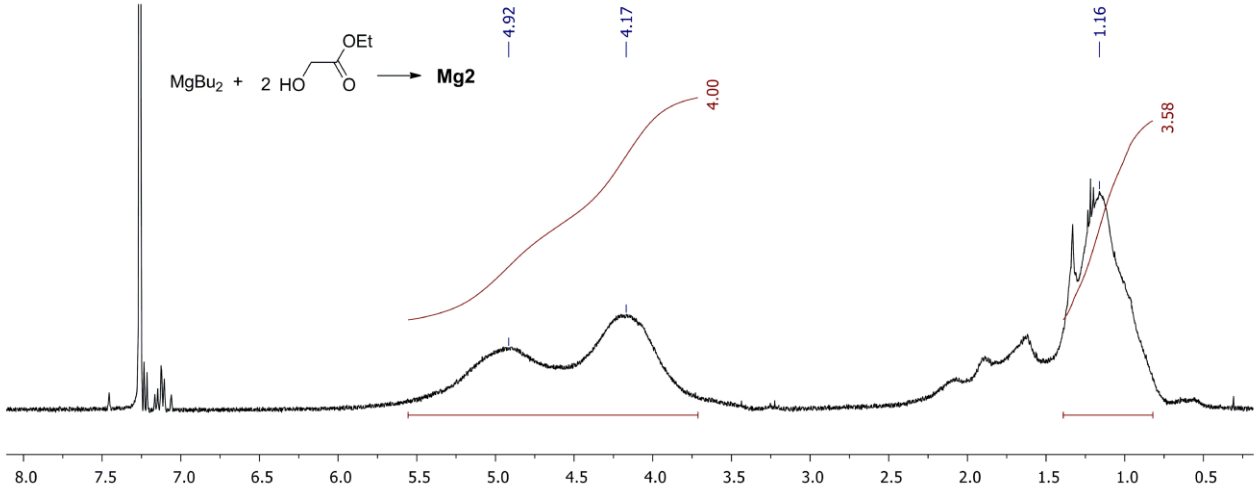

Figure S3 ^1H NMR spectra (C_6D_6, 20 °C, 400 MHz) of **Mg2** catalyst.

(2,6-Di-*tert*-butyl-4-methylphenoxy)(2-ethoxy-2-oxoethoxy)zinc (**Zn1**). $HOCH_2COOEt$ (104 mg, 1 mmol) was added to solution of $[(\mu\text{-BHT})ZnEt]_2$ (320 mg, 0.5 mmol) in toluene (8 mL). The mixture was stirred for 1 h and used as a ROP catalyst.

Bis(2-ethoxy-2-oxoethoxy)zinc (**Zn2**). $ZnEt_2$ (1.0 M in *n*-heptane, 4 mL, 4 mmol) was added dropwise to stirred solution of $HOCH_2COOEt$ (0.833 g, 8 mmol) in toluene (7 mL). After 2 h of stirring, the solvents were removed under reduced pressure. The residue (viscous yellow oil) was washed with *n*-hexane (3×10 mL) and dried *in vacuo*. The yield was 0.987 g (3.63 mmol, 91%), pale yellow powder. Elemental analysis for $C_8H_{14}ZnO_6$, 271.57: Calc. (%) C 35.38, H 5.20, O 35.35; Found (%) C 35.55, H 5.29, O 35.52.

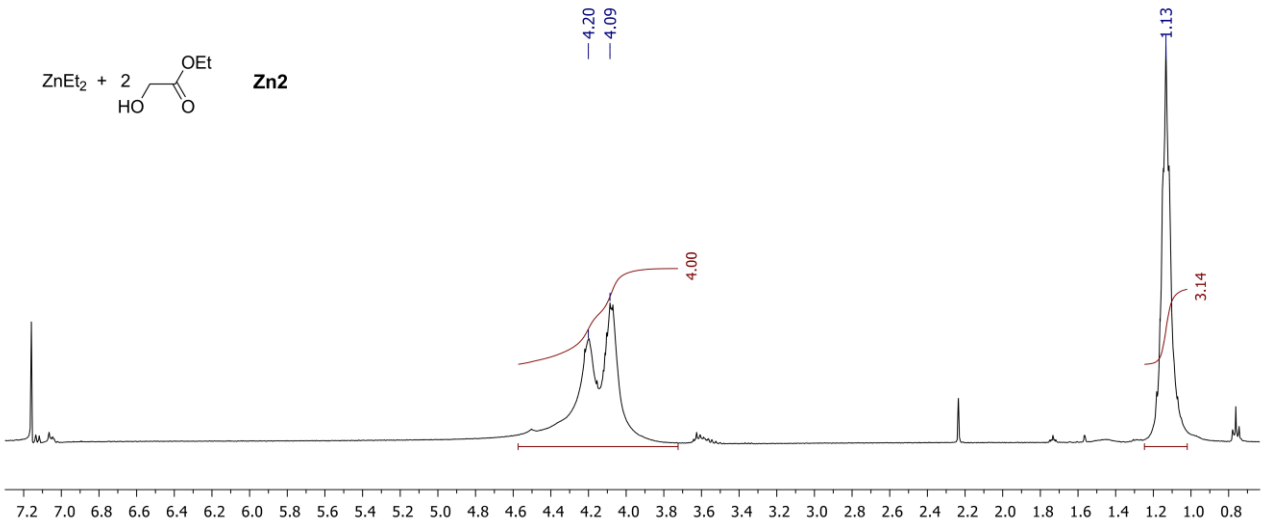

Figure S4 ^{1}H NMR spectra ($CDCl_3$, 20 °C, 400 MHz) of **Zn3** catalyst.

Dimer of (2,6-di-*tert*-butyl-4-methylphenoxy)(2-ethoxy-2-oxoethoxy)(methyl)aluminum (**Al1**). $HOCH_2COOEt$ (11 mg, 0.1 mmol) was added to stirred solution of $(BHT)_2AlMe$ (48 mg, 0.1 mmol) in toluene (0.8 mL). The mixture was stirred for 1 h and used as a ROP catalyst.

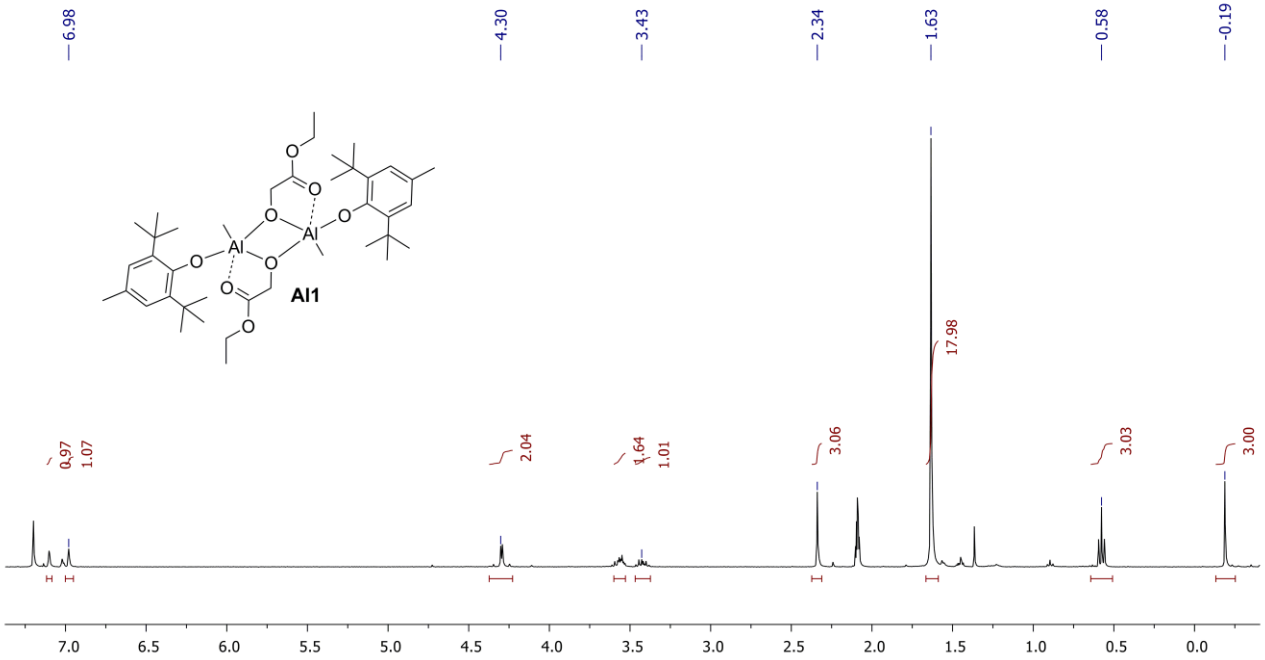

Figure S5 ^{1}H NMR spectra ($CDCl_3$, 20 °C, 400 MHz) of **Al1** catalyst.

Bis(2-ethoxy-2-oxoethoxy)(methyl)aluminum (**Al2**). $AlMe_3$ (1.0 M in *n*-hexane, 10.3 mL, 10.3 mmol) was added dropwise to stirred solution of $HOCH_2COOEt$ (2.082 g, 20 mmol) in toluene (7 mL). After 2 h of stirring, the solvents were removed under reduced pressure. The residue (viscous yellow oil) was washed with *n*-hexane (3×10 mL) and dried *in vacuo*. The yield was 1.90 g (7.7 mmol, 77%), colorless viscous oil. Elemental analysis for $C_9H_{17}AlO_6$, 248,21: Calc. (%)C 43.55, H 6.90, O 38.68; Found (%) C 35.55, H 5.29, O 35.52.

S1.3. Polymerization procedure

Monomers (10 mmol) and toluene (monomers/toluene ratio ~70 : 30 by volume) were placed under argon atmosphere into a flame-dried vial and heated under stirring at a given temperature. The catalyst (0.8 mL of 0.125 M solution in toluene) was added, and the mixture was stirred within a specified period of time. The resulting polymers were dissolved in hot DMSO (or in hot toluene for polymers containing up to 50% glycolide), precipitated by methanol, filtered, and dried *in vacuo*. Glycolide/lactide ratios were calculated using comparative integration of signals at 5.21–5.28 ppm (C***H***-CH_3) and 4.85–4.95 ppm (C***H₂***) in ^{1}H NMR spectra of copolymer solutions in DMSO-d_6.

S2. NMR spectra of polymers

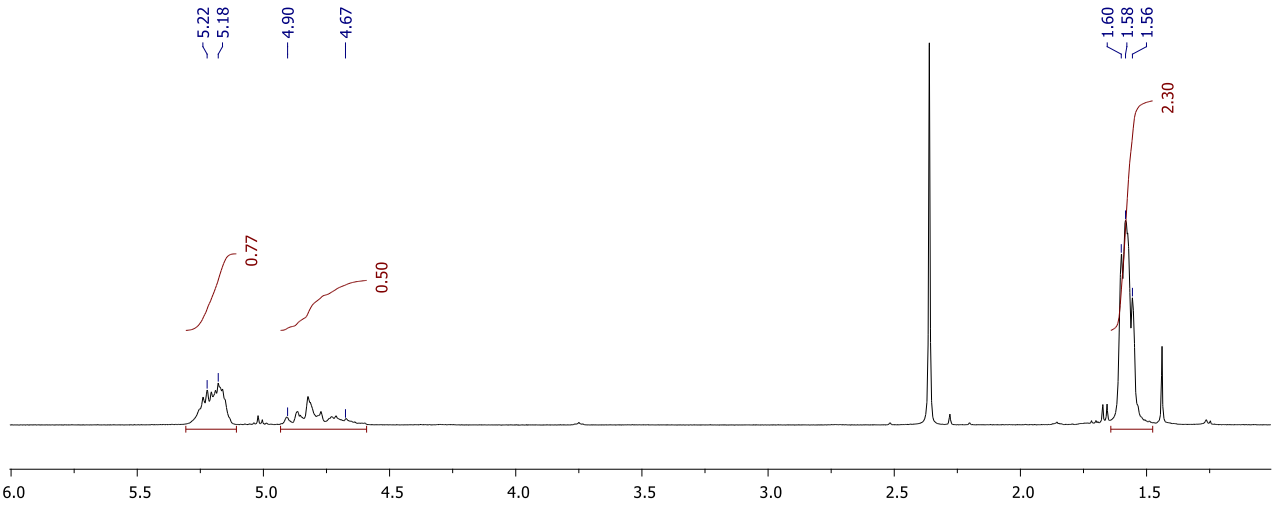

Figure S6 ^{1}H NMR spectra ($CDCl_3$, 20 °C, 400 MHz) of PGLA obtained by copolymerization of 75 : 25 LA/GL mixture with **Mg1** catalyst (110 °C, toluene, Table S1, entry *1*).

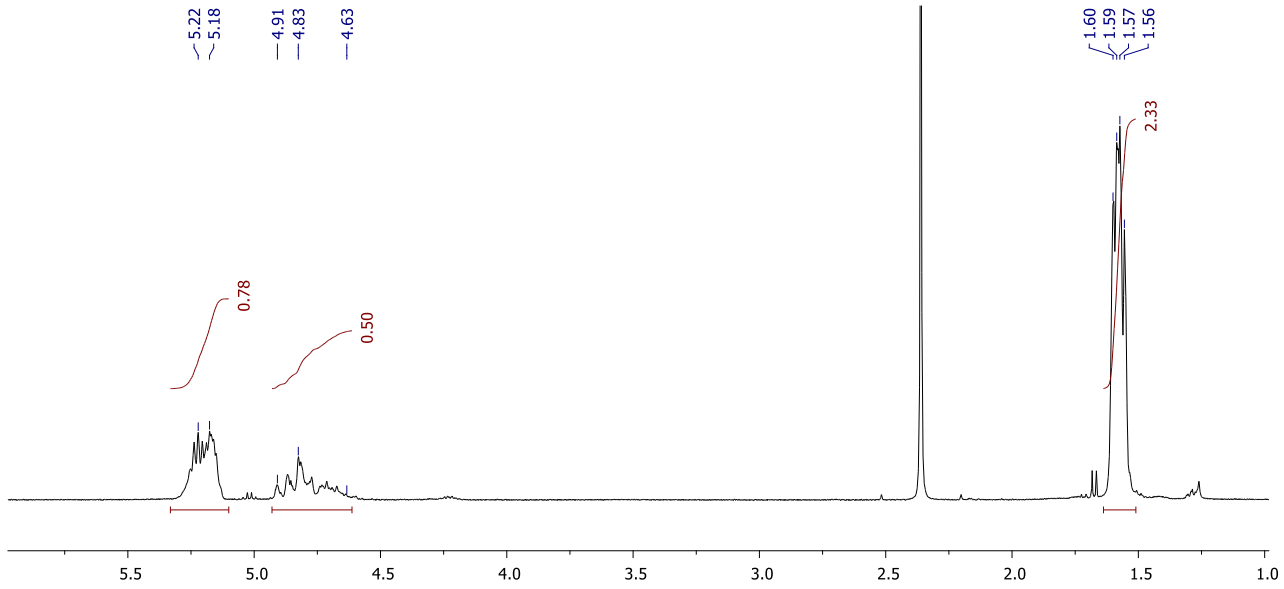

Figure S7 ^{1}H NMR spectra ($CDCl_3$, 20 °C, 400 MHz) of PGLA obtained by copolymerization of 75 : 25 LA/GL mixture with **Al1** catalyst (110 °C, toluene, Table S1, entry *5*).

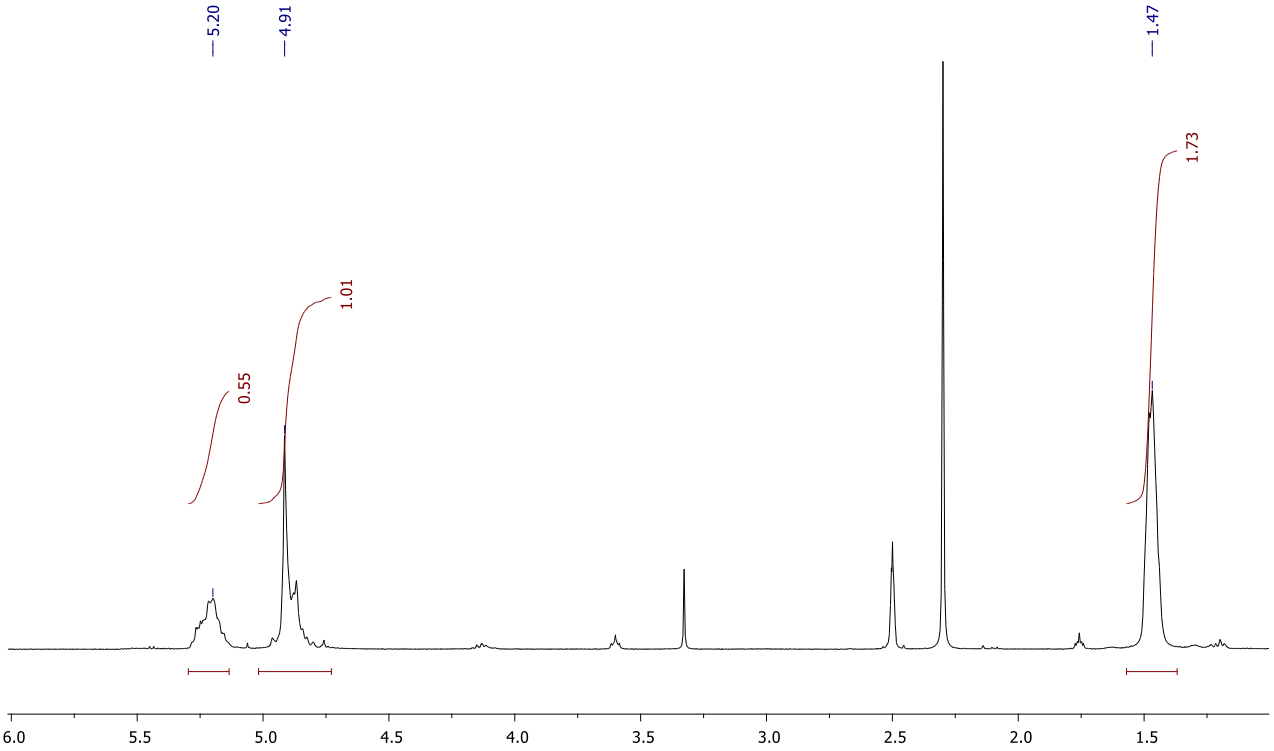

Figure S8 ^{1}H NMR spectra (DMSO-d_6, 20 °C, 400 MHz) of PGLA obtained by copolymerization of 50 : 50 LA/GL mixture with **Al2** catalyst (110 °C, toluene, Table S1, entry *12*).

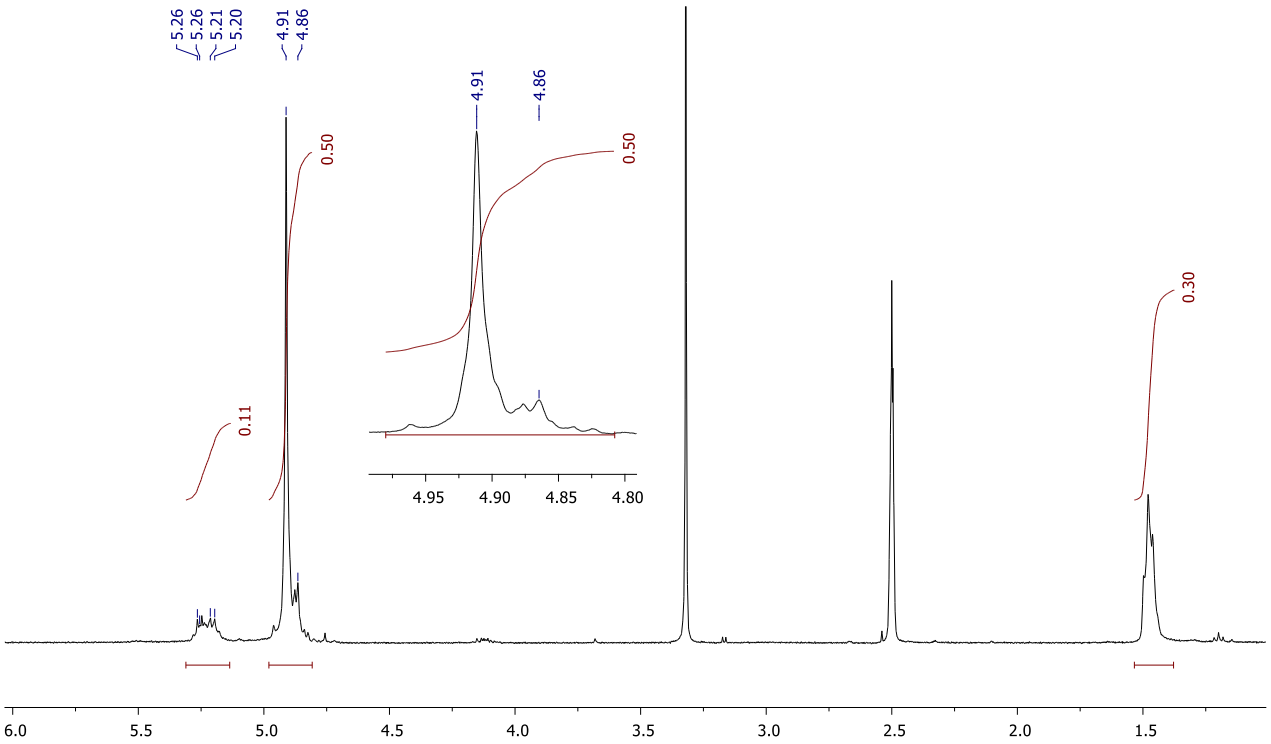

Figure S9 ^{1}H NMR spectra (DMSO-d_6, 20 °C, 400 MHz) of PGLA obtained by copolymerization of 25 : 75 LA/GL mixture with **Al2** catalyst (110 °C, toluene, Table S1, entry *18*).

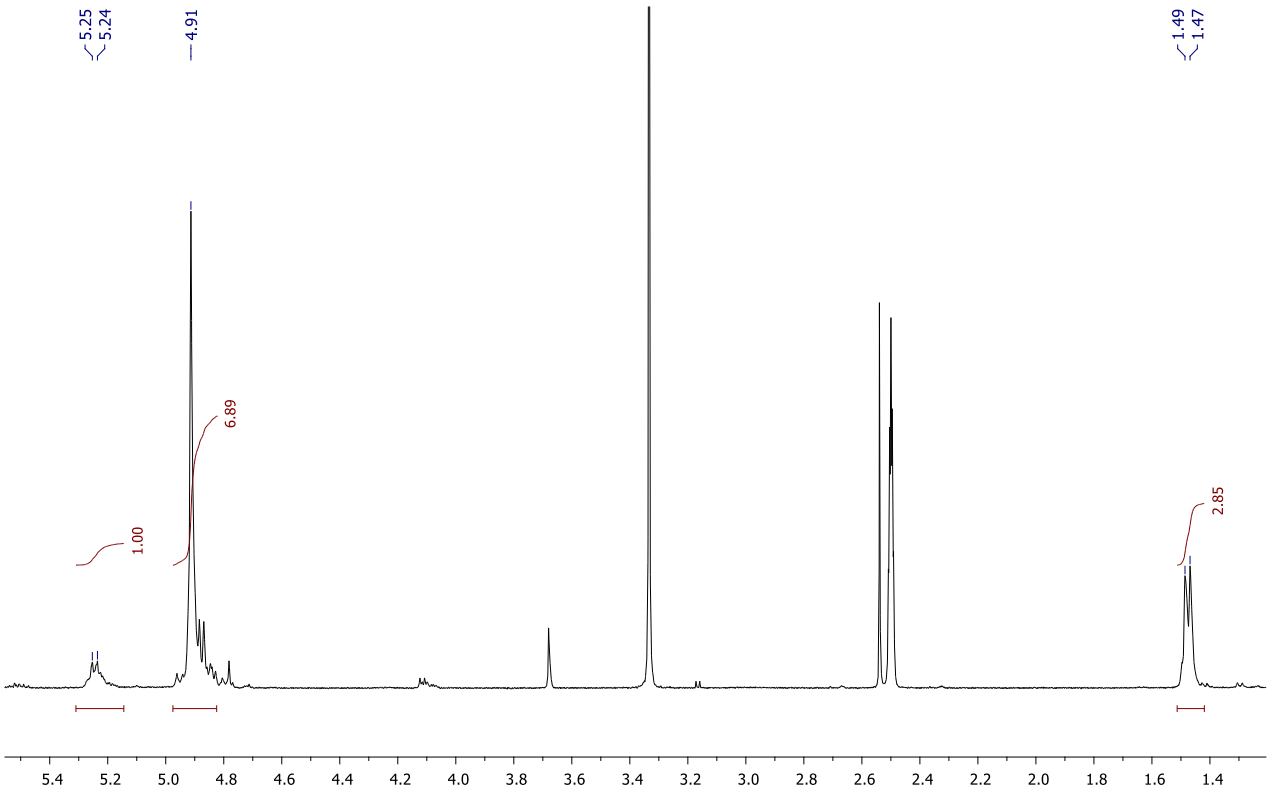

Figure S10 ^{1}H NMR spectra (DMSO-d_6, 20 °C, 400 MHz) of PGLA obtained by copolymerization of 50 : 50 MeGL/GL mixture with **Mg1** catalyst (110 °C, toluene, Table S1, entry *28*).

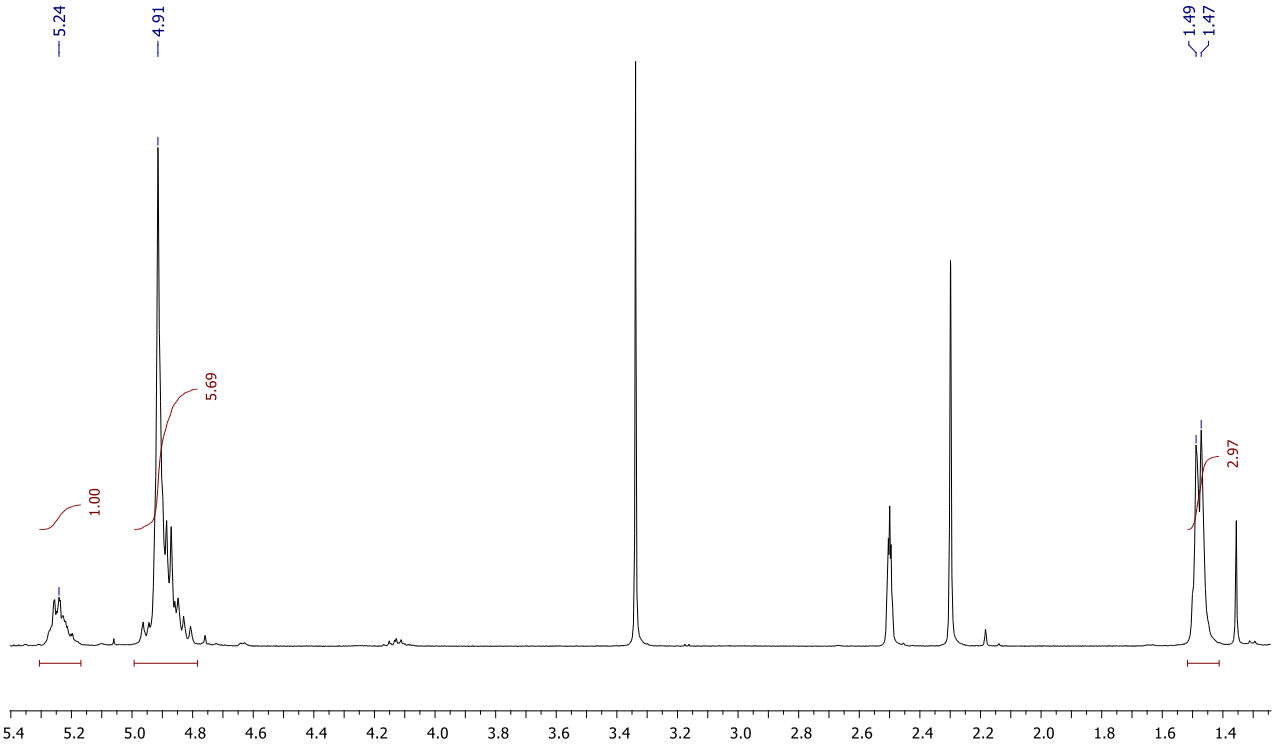

Figure S11 ^{1}H NMR spectra (DMSO-d_6, 20 °C, 400 MHz) of PGLA obtained by copolymerization of 50 : 50 MeGL/GL mixture with **Al1** catalyst (110 °C, toluene, Table S1, entry *30*).

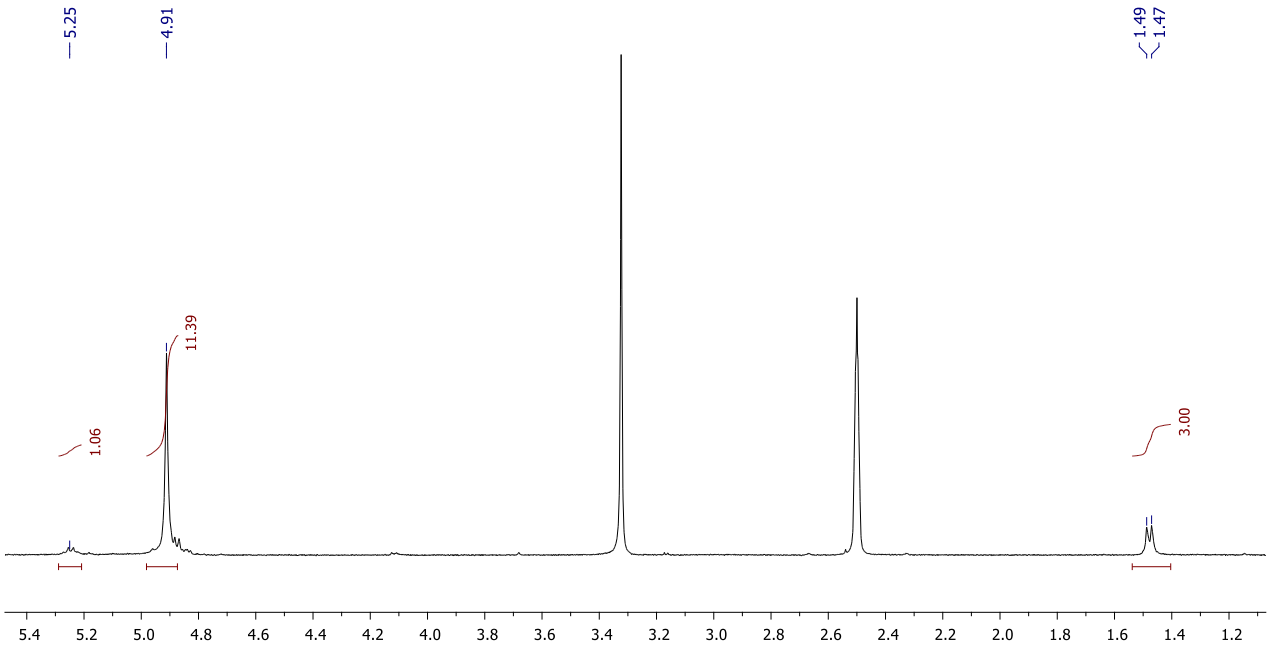

Figure S12 ^{1}H NMR spectra (DMSO-d_6, 20 °C, 400 MHz) of PGLA obtained by copolymerization of 20 : 80 MeGL/GL mixture with **Mg1** catalyst (110 °C, toluene, Table S1, entry *31*).

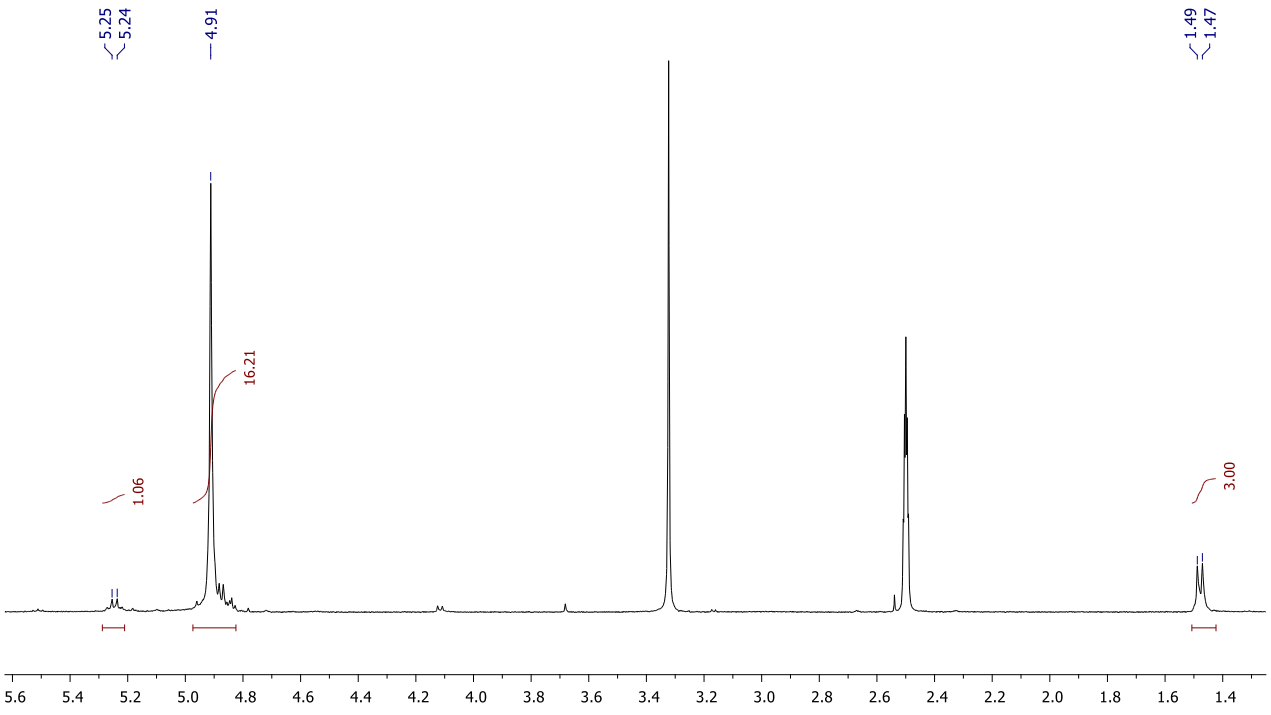

Figure S13 ^{1}H NMR spectra (DMSO-d_6, 20 °C, 400 MHz) of PGLA obtained by copolymerization of 20 : 80 MeGL/GL mixture with **Zn1** catalyst (110 °C, toluene, Table S1, entry *32*).

S3. Copolymerization experiments and product characteristics

Table S1 Copolymerization of GL and LA catalyzed by 'biometal' complexes .

entry	Catalyst	*T*/°C	*t*/h	Initial comonomer ratio	Ratio of LA/GL units in the polymer.	Yield (%)[a]	M_n calc./ kDa	M_n[b] exp./ kDa	$Đ_M$[b]
Lactide-Glycolide copolymerization									
1	Mg1	110	1	75:25	75:25	92	12.7	10.1	1.69
2	Mg2	110	1	75:25	75:25	92	12.7	7.7	1.76
3	Zn1	110	1	75:25	75:25	93	12.8	6.4	1.94
4	Zn2	110	1	75:25	75:25	93	12.8	9.4	1.85
5	Al1	110	1	75:25	76:24	93	12.8	11.1	2.12
6	Al2	110	1	75:25	75:25	92	12.7	9.4	2.27
7	Mg1	110	1	50:50	53:47	87	11.3	7.5 [c]	1.78
8	Mg2	110	1	50:50	53:47	87	11.3	7.5	1.67
9	Zn1	110	1	50:50	52:48	89	11.6	8.2	1.78
10	Zn2	110	1	50:50	51:49	91	11.8	11.8	1.91
11	Al1	110	1	50:50	53:47	94	12.2	10.5	2.20
12	Al2	110	1	50:50	53:47	94	12.2	8.8	2.04
13	Mg1	110	1	25:75	30:70	83	10.2	n.d.	n.d.
14	Mg2	110	1	25:75	35:65	73	9.0	n.d.	n.d.
15	Zn1	110	1	25:75	23:77	66	8.1	5.3 [c]	1.62
16	Zn2	110	1	25:75	24:76	55	6.8	n.d.	n.d.
17	Al1	110	1	25:75	23:77	93	11.4	5.8 [c]	1.83
18	Al2	110	1	25:75	23:77	94	11.6	4.5 [c]	2.20
19	Mg1	110	4	10:90	21:79	80	9.5	n.d.	n.d.
20	Mg2	110	4	10:90	17:83	63	7.5	-	-
21	Zn1	110	4	10:90	14:86	78	9.3	-	-
22	Zn2	110	4	10:90	6:94	44	5.2	-	-
23	Al1	110	4	10:90	12:88	92	10.9	-	-
24	Al2	110	4	10:90	10:90	94	11.2	-	-
25	Zn2	150	4	10:90	10:90	81	9.7	-	-
26	Al2	150	4	10:90	10:90	96	11.4	-	-
27	$SnOct_2$	150	4	10:90	10:90	99	11.8	-	-
Methylglycolide-Glycolide copolymerization									

28	Mg1	110	1	50:50	26:74	81	11.1	-	-
29	Zn1	110	1	50:50	25:75	68	9.3	-	-
30	Al1	110	1	50:50	27:73	91	12.5	-	-
31	Mg1	110	1	20:80	14:86	84	10.1	-	-
32	Zn1	110	1	20:80	11:89	78	9.3	-	-
33	Al1	110	1	20:80	11:89	95	11.3	-	-

[a] The yield of re-precipitated polymer. [b] SEC data, DMF as an eluent, 40 °C. [c] The polymer is partially soluble in DMF, the data are given for soluble fraction.

S4. DSC of polymers

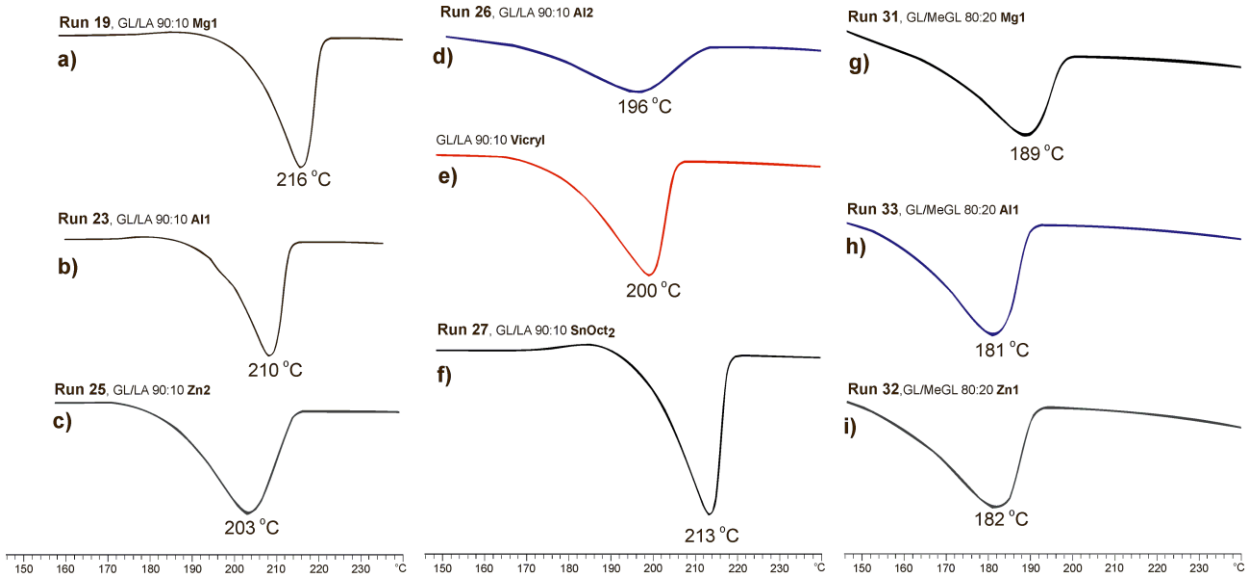

Figure S14 DSC of the products obtained by copolymerization of (*a–f*) glycolide with lactide (GL: LA = 90 : 10) and (*g–i*) glycolide with methyl glycolide (GL: MeGL = 80 : 20).