Highly Isotactic Polylactide by Binary Organocatalyzed Polymerization of 1,3-Dioxolan-4-Ones

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Methods and Reagents

1,3-Dicyclohexylthiourea (TCI, >98.0%) and 1,3-bis[3,5-bis(trifluoromethyl)phenyl]thiourea (TCI, >98.0%) were purchased from commercial vendors. *N*′-[3,5-Bis(trifluoromethyl)phenyl]-*N*-cyclohexylthiourea was prepared as previously reported.[1] Benzyl alcohol (Aldrich, 99.8%) was distilled over calcium hydride (CaH_2). All solvents for polymerization were distilled over CaH_2 and stored over 3 Å molecular sieves (20% m/v) in a glovebox. Other materials used in this study were purchased from commercial chemical suppliers (Sigma-Aldrich, TCI Chemicals, Thermo Fisher Scientific, Acros Organics, and SAMCHUN Chemicals unless otherwise stated. Deuterated $CDCl_3$ was purchased from Cambridge Isotope Laboratory.

Characterizations

^{1}H NMR and homonuclear decoupled ^{1}H NMR spectra were recorded on a Bruker 400 MHz spectrometer at 25 °C. $CDCl_3$ (δH = 7.26 ppm) was used as the internal standard. The samples were obtained with the decoupling pulse based on the methyl region (δ = 1.5 ppm). When the methine region (δ = 5.15–5.22 ppm) was well-resolved, global spectral deconvolution was implemented to assign five *meso* dyads. P_m values were calculated as the *mmm* peak area relative to the total area. The number-averaged (M_n) and weight-averaged (M_w) molecular weights and the corresponding molecular weight distribution (M_w/M_n, $Đ$) were measured by gel permeation chromatography (GPC, Agilent 1200 series) using THF as an eluent at 25 °C at a flow rate of 1.00 mL min^{-1} with a refractive index (RI) detector. All calibrations were performed using polystyrene (PS) standards (Sigma-Aldrich, M_p 250–1,100,000). MALDI-ToF mass spectrometry measurements were performed using *trans*-2-[3-(4-*tert*-butylphenyl)-2-methyl-2-propenylidene] malononitrile as a matrix on a Bruker Autoflex Max instrument. Differential scanning calorimetry (DSC) (Q200 model, TA Instruments, Tzero Aluminum Pan) was performed under nitrogen from 0 to 220 °C with a heating rate of 10 °C min^{-1}.

(*S*)-Me$_3$DOX monomer synthesis

The parent α-hydroxy acid (7.53 mmol), and *p*-toluenesulfonic acid (0.75 mmol) were dissolved in a mixture of acetone and petroleum ether (1:1 v/v, 50 mL) and refluxed in a Dean–Stark apparatus, periodically removing water formed over 12 h. After cooling, the solvent was evaporated. The residue was dissolved in 50 mL of ethyl acetate and washed three times with 25 mL of aqueous sodium bicarbonate solution and brine. The organic layer was dried over sodium sulfate and the solvent evaporated in vacuo. The crude product was then stirred over CaH_2 for 16 h before vacuum distillation to obtain pure (*S*)-Me$_3$DOX (colorless oil, 41% yield). 2,2,5-trimethyl-1,3-dioxolan-4-one ((*S*)-Me$_3$DOX). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 4.47

(q 1H), 1.56 (s 3H), 1.49 (s 3H), 1.42 (d 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 173.38, 110.36, 70.43, 27.41, 25.58, 17.37.

Typical procedure for polymerization of (*S*)-Me$_3$DOX

TU-B (0.06 mmol), DBU (0.02 mmol), BnOH (0.02 mmol), and (*S*)-Me$_3$DOX (1.0 mmol) were added to an oven-dried ampoule with a stirring bar in an argon-filled glovebox. The ampoule was then sealed for 4 h. The reaction was then quenched with two drops of MeOH, and samples were taken for crude ^{1}H NMR analysis. The polymer was precipitated with cold MeOH to remove unreacted monomers and impurities. The precipitated polymer was dried under a vacuum at 60 °C.

Table S1. Ring-opening polymerization results of (*S*/*R*)-Me$_3$DOX.

Entry	Monomer	[M]:[I]:[C]	Time (h)	Conv.[a] (%)	$M_{n,theo}$[b] (g mol^{-1})	$M_{n,GPC}$[c] (g mol^{-1})	$Đ$	P_m[d]
1	(*S*)-Me$_3$DOX	50:1:1:1	6	73	2740	4000	1.44	n.d.
2	(*S*)-Me$_3$DOX	50:1:1:1	12	75	2810	4300	1.55	n.d.
3	(*S*)-Me$_3$DOX	50:1:1:1.5	4	74	2770	5000	1.41	0.77
4	(*S*)-Me$_3$DOX	50:1:1:1.5	6	77	2880	4000	1.44	n.d.
5	(*S*)-Me$_3$DOX	50:1:1:3	2	71	2660	5400	1.45	0.92
6[e]	(*S*)-Me$_3$DOX	50:1:1:3	2	79	2950	4660	1.52	n.d.
7	(*R*)-Me$_3$DOX	50:1:1:3	2	72	2700	5120	1.45	0.88
8	(*R*)-Me$_3$DOX	100:1:1:3	4	72	5290	7060	1.52	0.90
9	(*R*)-Me$_3$DOX	150:1:1:3	5	69	7560	7080	1.49	0.87

Conditions: Benzyl alcohol as an initiator, DBU/TU-B as catalysts, at 25 °C under bulk condition. [a]Monomer conversion determined by ^{1}H NMR in $CDCl_3$ using integrals of the characteristic signals. [b]Calculated using M_{Me3DOX} (72.08 g mol^{-1}) × ([M]$_0$ / [I]$_0$) × conversion + M_{BnOH} (108.14 g mol^{-1}). [c]Obtained from GPC analysis (THF, PS standards). [d]Possibility of formation of the *meso* diad from the homonuclear decoupled ^{1}H NMR spectrum calculated based on the CEC mechanism. [e]Condition: at 40 °C.

Table S2. Comparison of catalytic performance in ROP of DOXs.

Entry	Monomer	Catalyst	Conditions	Polymer	Ref.
1	5-methyl-1,3-dioxolan-4-one (MeDOX) and derivates	Salen complexes, k_{obs} =3.0 × 10^{-5} s^{-1}	120 °C, 24 h, solution	poly(lactic acid)	15
2	5-phenyl-1,3-dioxolane-4-one (PhDOX)	Salen complexes	120 °C, 18 h, dynamic vacuum	poly(mandelic acid)	16
3	Me_3DOX	*p*-toluenesulfonic acid	120 °C, 6 h, bulk	poly(lactic acid)	17
4	Me_3DOX	Salen complexes	100 °C, 6 h, solution	poly(*rac*-lactic acid)	18
5	Me_3DOX	Binary organocatalyst $k_{p,app}$ =9.03 × 10^{-5} s^{-1}	ambient, 4 h bulk	poly(lactic acid), stereocomplex	This work

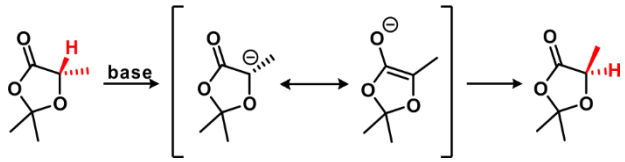


Figure S1. Epimerization of *α*-proton in (*S*)-Me_3DOX ROP.

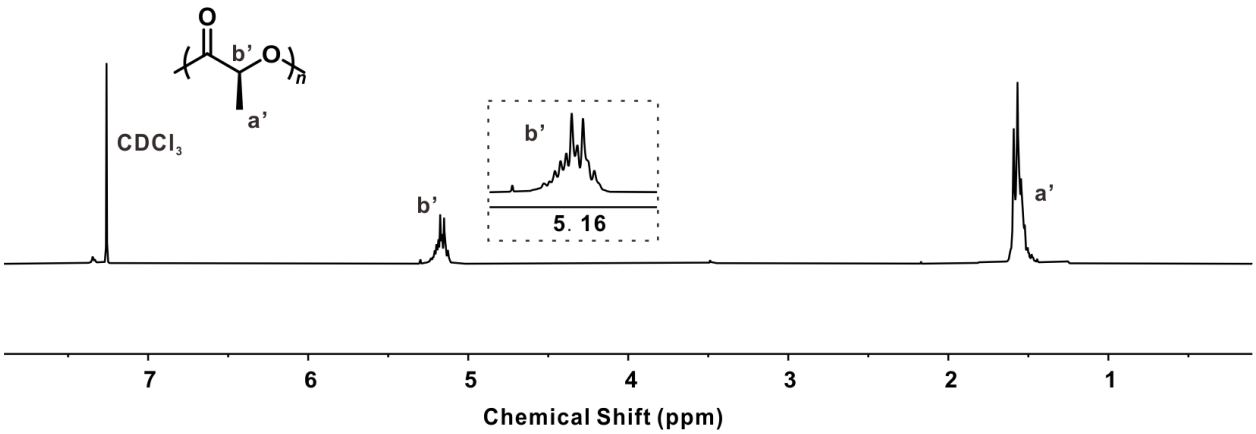


Figure S2. ^{1}H NMR spectrum of pure P(*S*-LA) (entry 3 in Table 1) (400 MHz, $CDCl_3$).

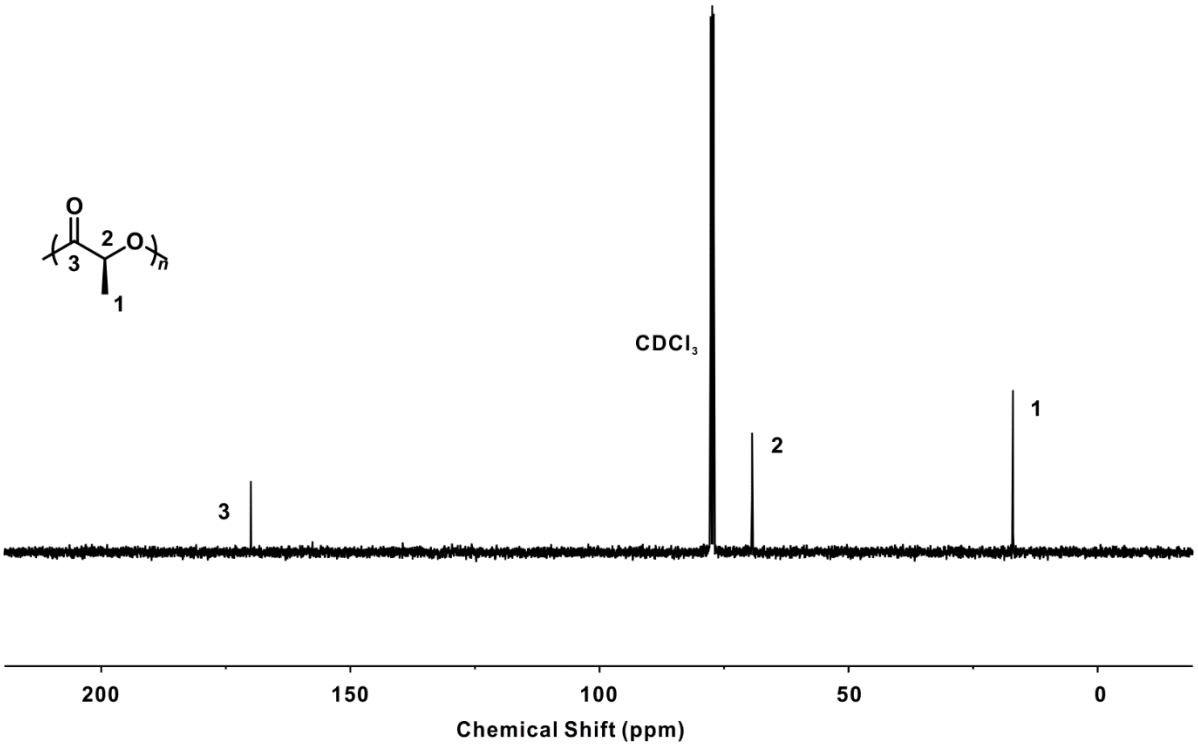


Figure S3. ^{13}C NMR spectrum of pure P(*S*-LA) (entry 6 in Table 1) (101 MHz, $CDCl_3$).

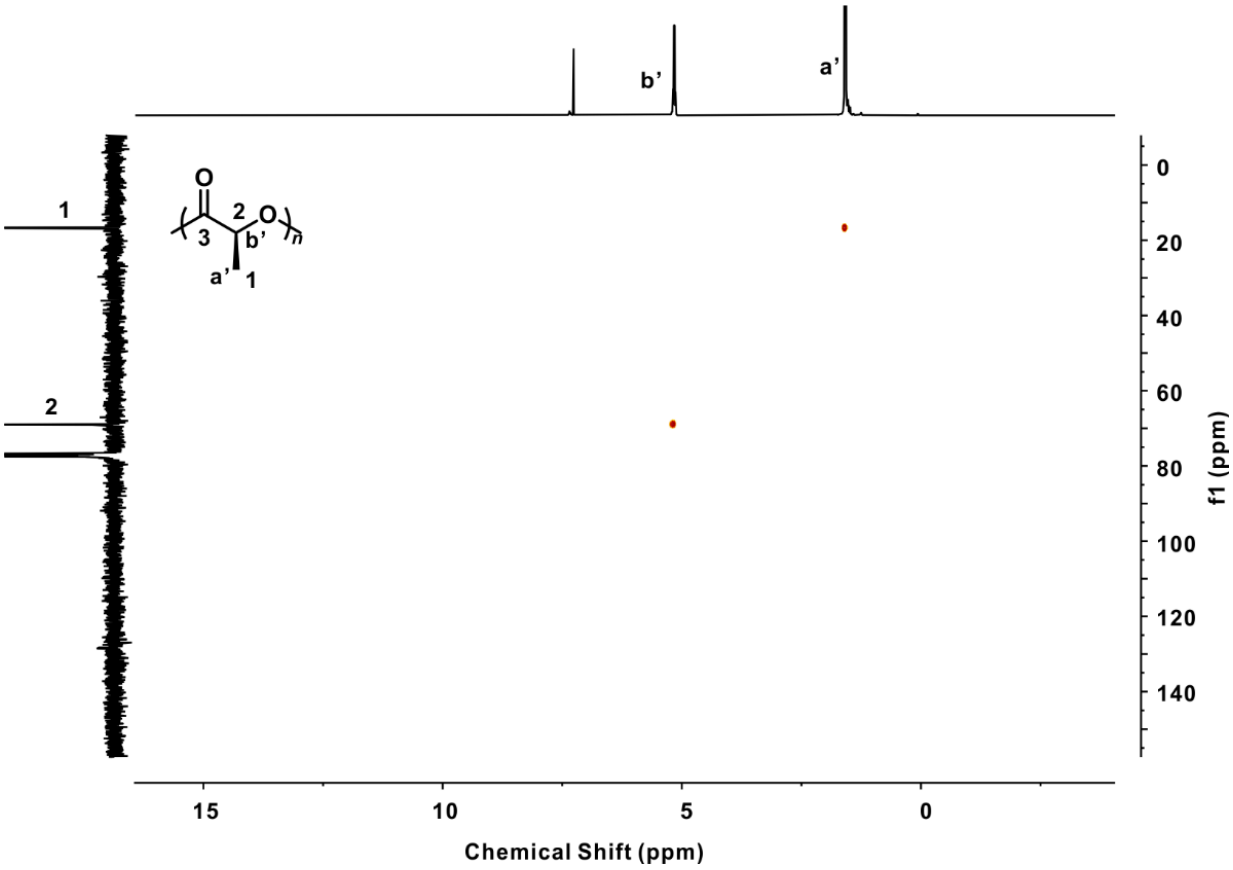


Figure S4. HSQC NMR spectrum of pure P(*S*-LA) (entry 6 in Table 1) ($CDCl_3$).

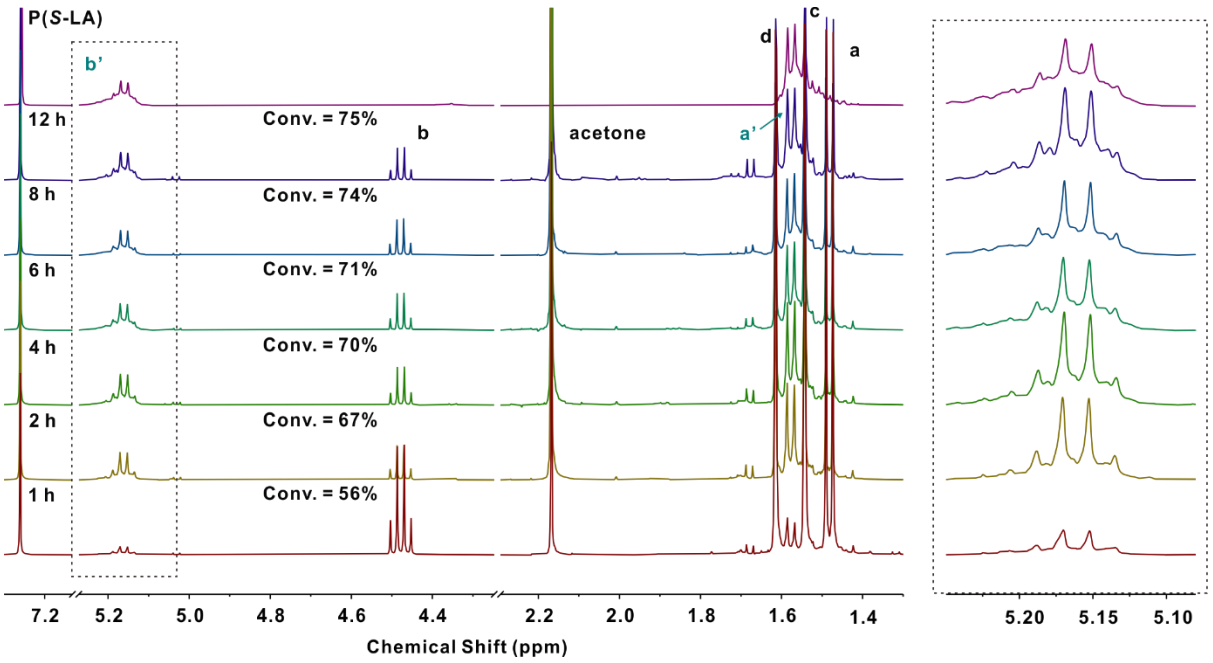


Figure S5. Stacked ^{1}H NMR spectra of samples taken from the (*S*)-Me$_3$DOX polymerization reaction (Table S1, entry 2) (400 MHz, $CDCl_3$).

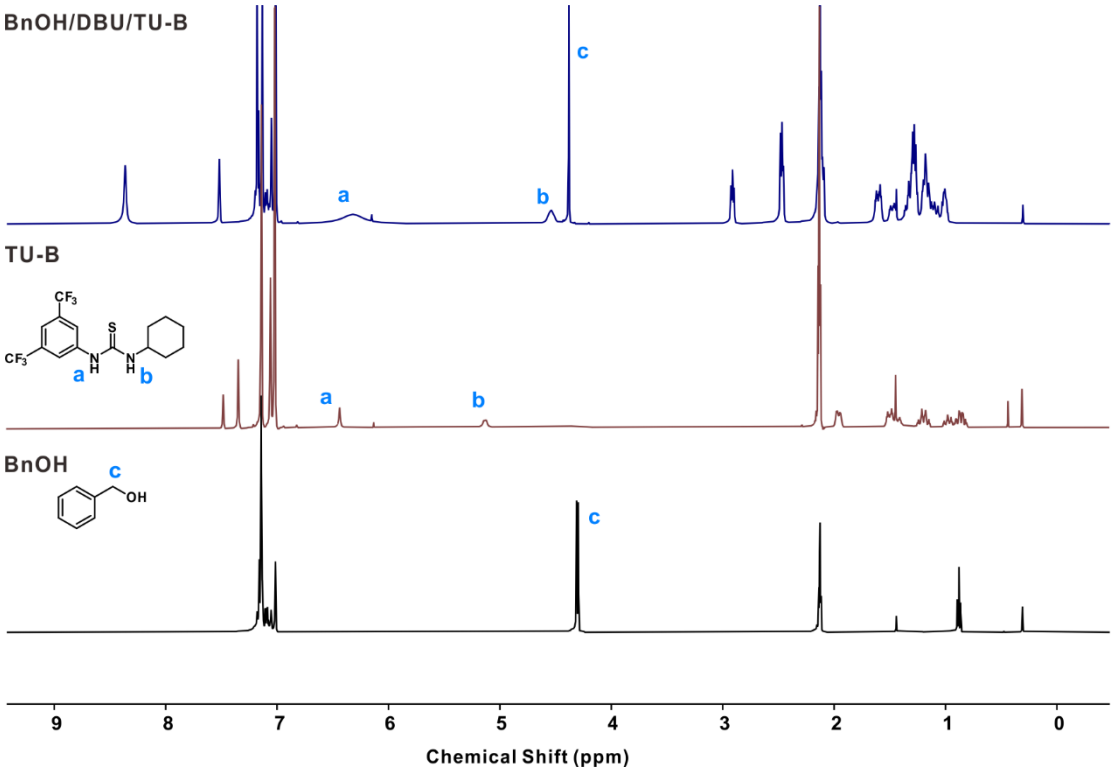


Figure S6. ^{1}H NMR spectra of BnOH/DBU/TU-B (1:1:3), TU-B and BnOH (400 MHz, toluene-d_8).

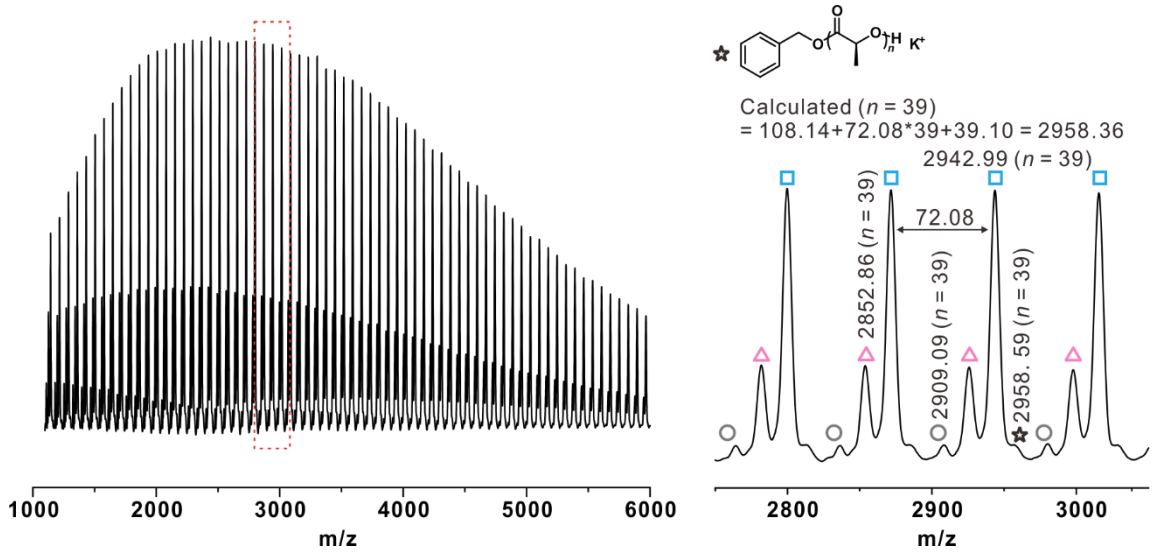


Figure S7. Representative MALDI-ToF full spectrum of P(*S*-LA) (entry 7 in Table 1). (Experimental condition: linear positive mode, sodium trifluoroacetate (NaTFA) as anionization agent, 2,5-Dihydroxybenzoic acid (DHB) as a matrix, laser intensity 75%).

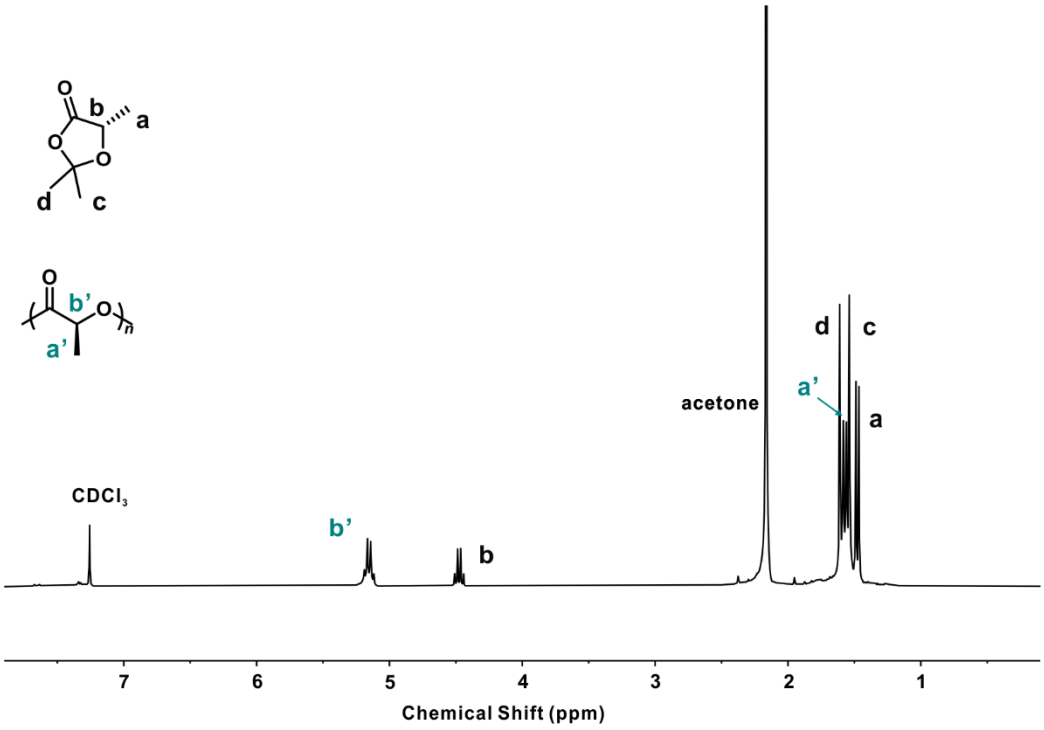


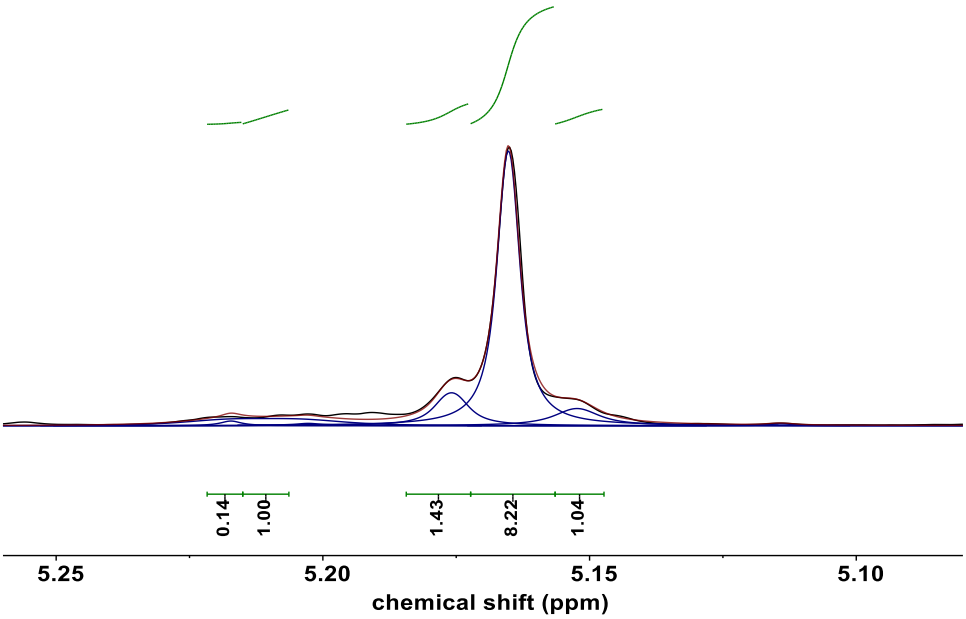
Figure S8. ^{1}H NMR spectrum of crude P(*S*-LA) (entry 7 in Table 1) (400 MHz, $CDCl_3$).

Calculation of P_m value

The homonuclear decoupled ^{1}H NMR spectra were measured to determine the stereoregularity of obtained PLAs, and the P_m values were calculated according to the chain-end control (CEC) mechanisms.[2, 3] In the methine region corresponding to five tetrad *meso* dyads, we applied Bernoullian statistics based on the CEC (Table S3).

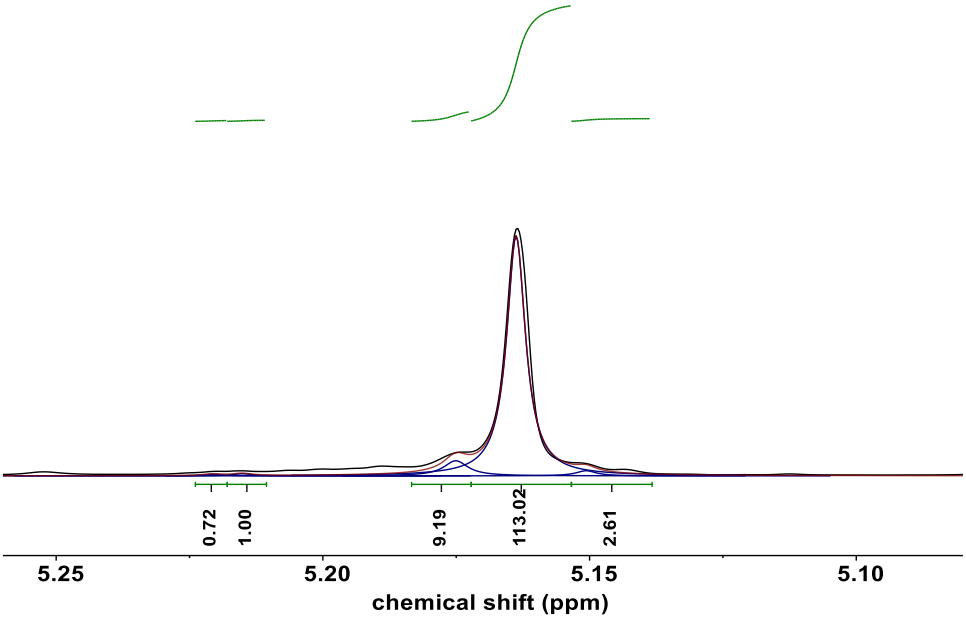
Table S3. Tetrad probabilities of CEC based on Bernouillan statistics.

Tetrad	Probability of CEC (Bernouillan)
rmr	$0.5P_r^2$
rmm/*mmr*	$0.5P_mP_r$
mmr/*rmm*	$0.5P_mP_r$
mmm	$P_m^2+0.5P_mP_r$
mrm	$0.5(P_m^2+P_mP_r)$



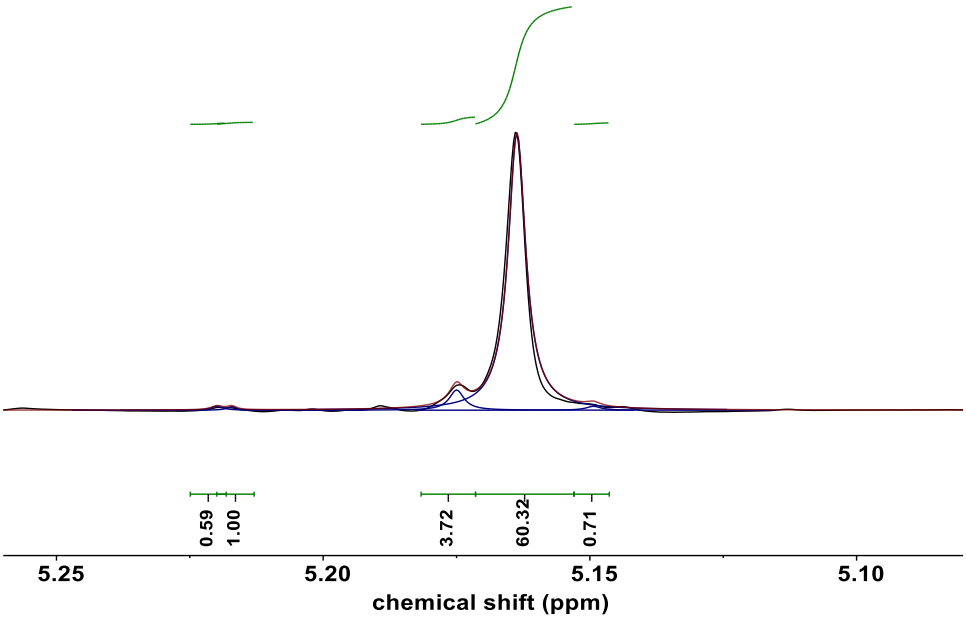
ppm	Tetrad	Ratio	$P_{m,CEC}$
5.22	*rmr*	0.012	0.85
5.21	*rmm*/*mmr*	0.085	0.78
5.18	*mmr*/*rmm*	0.121	0.59
5.17	*mmm*	0.695	0.78
5.15	*mrm*	0.088	0.82
Average		0.77	

Figure S9. Homonuclear decoupled ^{1}H NMR spectrum of the methine region of P(*S*-LA) from (*S*)-Me$_3$DOX (entry 5 in Table 1) (400 MHz, CDCl$_3$).



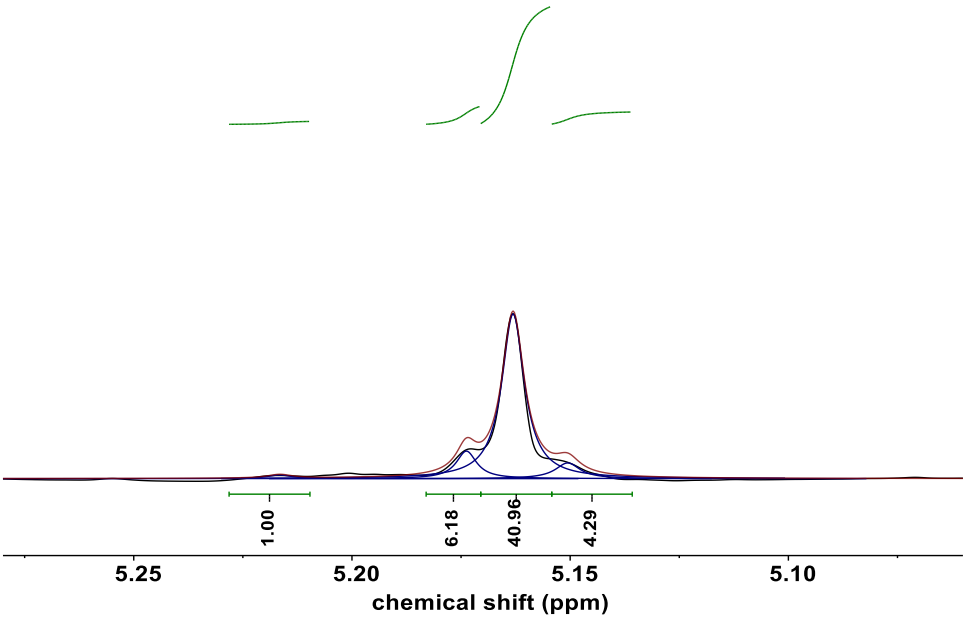
ppm	Tetrad	Ratio	$P_{m,CEC}$
5.22	*rmr*	0.006	0.89
5.22	*rmm/mmr*	0.008	0.98
5.18	*mmr/rmm*	0.073	0.82
5.16	*mmm*	0.893	0.93
5.15	*mrm*	0.021	0.96
Average		0.92	

Figure S10. Homonuclear decoupled ^{1}H NMR spectrum of the methine region of P(*S*-LA) from (*S*)-Me$_3$DOX (entry 6 in Table 1) (400 MHz, $CDCl_3$).



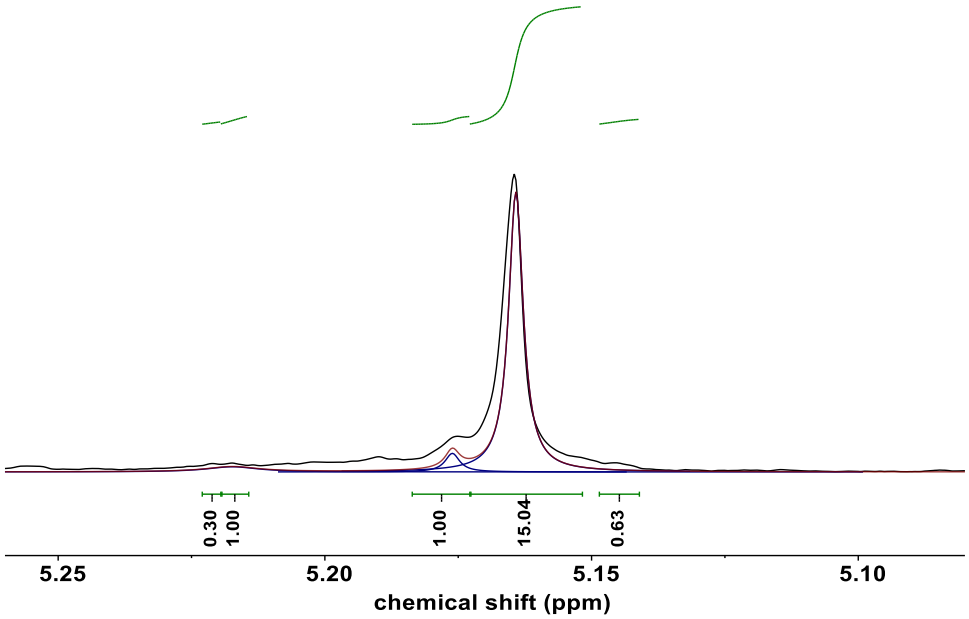
ppm	Tetrad	Ratio	$P_{m,CEC}$
5.23	*rmr*	0.009	0.87
5.22	*rmm/mmr*	0.015	0.97
5.18	*mmr/rmm*	0.050	0.89
5.16	*mmm*	0.915	0.94
5.15	*mrm*	0.011	0.98
Average		0.93	

Figure S11. Homonuclear decoupled ^{1}H NMR spectrum of the methine region of P(*S*-LA) from (*S*)-Me$_3$DOX (entry 7 in Table 1) (400 MHz, $CDCl_3$).



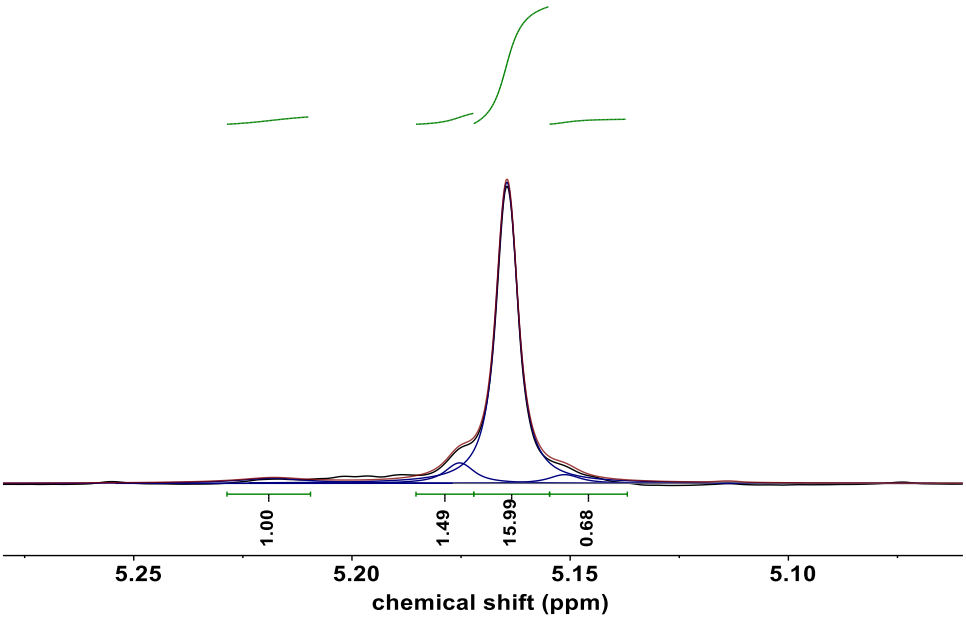
ppm	Tetrad	Ratio	$P_{m,CEC}$
-	*rmr*	0.000	1.00
5.22	*rmm/mmr*	0.019	0.96
5.17	*mmr/rmm*	0.118	0.62
5.16	*mmm*	0.781	0.85
5.15	*mrm*	0.082	0.84
Average		0.85	

Figure S12. Homonuclear decoupled ^{1}H NMR spectrum of the methine region of P(*S*-LA) from (*S*)-Me$_3$DOX (entry 8 in Table 1) (400 MHz, $CDCl_3$).



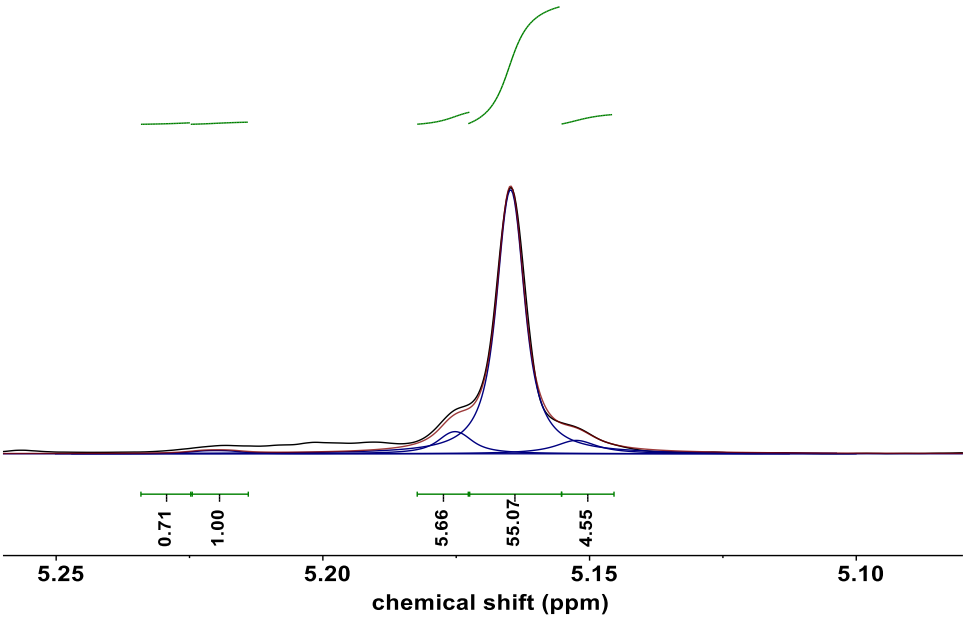
ppm	Tetrad	Ratio	$P_{m,CEC}$
5.22	*rmr*	0.017	0.82
5.22	*rmm/mmr*	0.056	0.87
5.18	*mmr/rmm*	0.056	0.87
5.16	*mmm*	0.837	0.89
5.15	*mrm*	0.035	0.93
Average		0.88	

Figure S13. Homonuclear decoupled ^{1}H NMR spectrum of the methine region of P(*R*-LA) from (*R*)-Me$_3$DOX (entry 1 in Table S1) (400 MHz, $CDCl_3$).



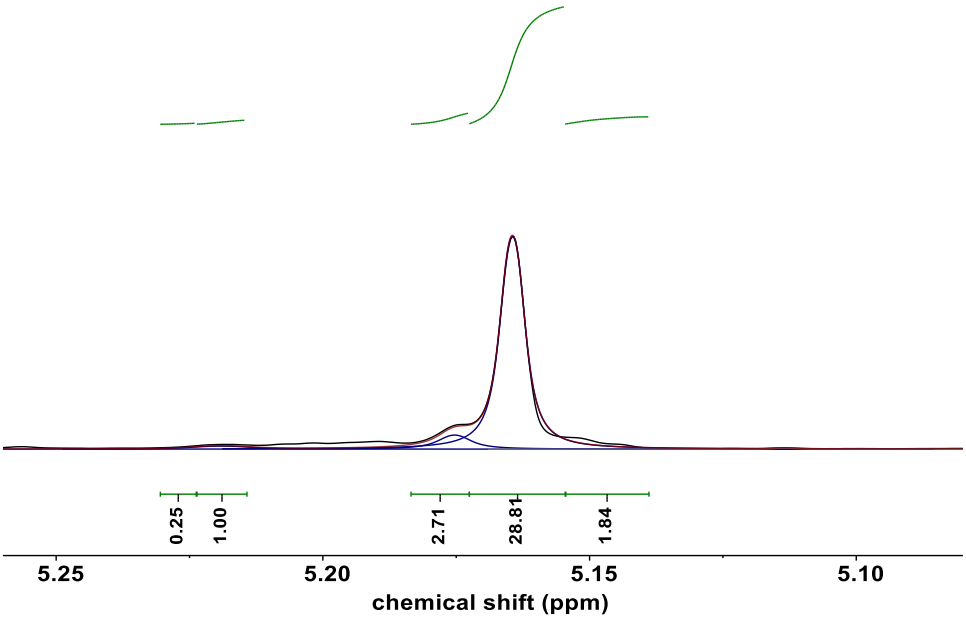
ppm	Tetrad	Ratio	$P_{m,CEC}$
-	*rmr*	0.000	1.00
5.22	*rmm/mmr*	0.052	0.88
5.18	*mmr/rmm*	0.078	0.81
5.16	*mmm*	0.835	0.89
5.15	*mrm*	0.035	0.93
Average		0.90	

Figure S14. Homonuclear decoupled ^{1}H NMR spectrum of the methine region of P(*R*-LA) from (*R*)-Me$_3$DOX (entry 2 in Table S1) (400 MHz, $CDCl_3$).



ppm	Tetrad	Ratio	$P_{m,CEC}$
5.23	*rmr*	0.011	0.85
5.22	*rmm/mmr*	0.015	0.97
5.18	*mmr/rmm*	0.084	0.78
5.16	*mmm*	0.822	0.88
5.15	*mrm*	0.068	0.86
Average		0.87	

Figure S15. Homonuclear decoupled ^{1}H NMR spectrum of the methine region of P(*R*-LA) from (*R*)-Me$_3$DOX (entry 3 in Table S1) (400 MHz, $CDCl_3$).



ppm	Tetrad	Ratio	$P_{m,CEC}$
5.23	*rmr*	0.007	0.88
5.22	*rmm/mmr*	0.029	0.94
5.18	*mmr/rmm*	0.078	0.81
5.16	*mmm*	0.832	0.88
5.15	*mrm*	0.053	0.89
Average		0.88	

Figure S16. Homonuclear decoupled ^{1}H NMR spectrum of the methine region of *sc*-PLA (400 MHz, $CDCl_3$).

References

S1. O. Coulembier, D. P. Sanders, A. Nelson, A. N. Hollenbeck, H. W. Horn, J. E. Rice, M. Fujiwara, P. Dubois and J. L. Hedrick, *Angew. Chem. Int. Ed.*, 2009, ***48***, 5170–5173.

S2. B. Orhan, M. J.-L. Tschan, A.-L. Wirotius, A. P. Dove, O. Coulembier and D. Taton, *ACS Macro Lett.*, 2018, ***7***, 1413–1419.

S3. X. Jiang, N. Zhao and Z. Li, *Chin. J. Chem.*, 2021, ***39***, 2403–2409.