Supplementary Information

Fully Biobased Triblock Copolymers Generated Using an Unconventional Oscillatory Plug Flow Reactor

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Materials

Benzoic acid (>99%, TCI Chemicals), polyethylene glycol (PEG, Sigma), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, ACROS Organics, 98%), 1,5,7-Triazabicyclo[4.4.0]dec-5-ene (TBD, ACROS Organics, 98%), benzyl alcohol (Sigma Aldrich, 99%), Telechelic poly(β-farnesene)-diol (PFD) (KRASOL^{TM} F 3000) (Cray Valley), dichloromethane (anhydrous, Honeywell, >99%) were used as received. D,L-lactide (Corbion) was purified via recrystallization and subsequent filtration. The purified D,L-lactide was then stored in a glove box under nitrogen gas until further use.

Methods

^{1}H-NMR spectra were recorded on a JEOL instrument operating at 400 MHz for 64 scans. Samples were dissolved in $CDCl_3$ at a concentration of 10 mg/ml. Analysis of the ^{1}H-NMR spectra was performed using iNMR reader software.

SEC measurements were performed on a TOSOH EcoSEC instrument using $CHCl_3$ eluent running at 1 ml/min. Samples were dissolved at C = 5 mg/ml in $CHCl_3$ with 100 ppm of toluene internal standard and passed through a 0.2 µm Teflon filter prior to measurement. Eluograms were converted to molar mass (MW) distributions using calibration data from polystyrene standards. Polystyrene standards (Polymer Standards Service; PSS) with a molar mass ranging from 400 – 1 000 000 g/mol were used. Raw SEC data was processed and subsequently analyzed using Igor analysis software.

DSC was performed on a TA Instruments Q20 instrument under N_2 atmosphere using hermetic pans and lids. The instrument was calibrated with an indium standard. Specimen mass ranged from ~3–5 mg. The thermal history of the samples was erased using an initial isothermal treatment at 150 °C for 5 min. The cooling and heating ramps were conducted at a rate of 10 °C/min. The DSC was equipped with a refrigerated cooling system, and thus the lower reliable temperature limit was –50 °C. Data were analyzed with the TA Universal Analysis suite, which was used to generate T_g.

Visualization of the flow profile was performed by dissolving 50 mg of an organic dye in acetone 20 mL acetone or PEG solution. Prior to loading the colored solution into the injection syringes, a 0.2 μm Teflon filter was used to remove any particulate matter in the solution and the HANU flow reactor was flushed with acetone (twice the equivalent reactor volume). A standard flowrate of 1 mL/min was used to investigate the effect of the pulsator frequency and -amplitude.

Synthesis

Preparation of lactide solution (1 M) in anhydrous DCM: A 2-neck round bottom flask (50 mL) was washed with $CHCl_3$ and flame dried 3 times whilst flushing with argon gas. In a glove box, 4.49 g of purified lactide was weighed into the flask. Anhydrous DCM (27.14 mL) was added using a syringe and left to stir for 45 minutes under argon. For reactions that require the benzyl alcohol to be in the same injector syringe as lactide, 32.2 μL of benzyl alcohol was added using a reusable syringe to make a 100:1 concentration ratio of lactide to benzyl alcohol. All procedures were carried out under inert conditions using a vacuum pump and Schlenk line. This process is the same for following polymerization reactions described.

Preparation of DBU solution (0.3M) in anhydrous DCM: 186 μL DBU was added to a 10 mL glass vial followed by 7.4 mL of anhydrous DCM. To avoid water contamination as much as possible, anhydrous DCM was added just before loading the solution into the injector syringe. For reactions that require DBU and benzyl alcohol to be in the same injector syringe, benzyl alcohol was added to the glass vial to obtain a 6:1 concentration ratio of DBU to benzyl alcohol.

Poly(lactide) synthesis using constant monomer to initiator ratio: Using a dual injector syringe system, the lactide/benzyl alcohol solution (100:1 concentration ratio) and the DBU solution

(0.3 M) were pumped through the HANU flow reactor (pre-filled with DCM) at precalculated flowrates so that the total plug volume would equate to 5 mL with a lactide to DBU concentration ratio of 50:1. Using an HPLC pump (Knauer BlueShadow) the reagent plug was pumped through the HANU flow reactor at various predetermined flow rates. The degree of mixing and plug flow behavior was controlled using a pulsator (Creaflow) integrated into the flow reactor setup. The product was collected using two separate glass vials each holding 2.5 mL of the total 5 mL plug. In order to quench the reaction, 5 mg of propanoic acid was added to the vials prior to sample collections. Samples were then left to dry overnight in the fume hood followed by an overnight drying period under vacuum conditions. All reactions were carried out at room temperature and atmospheric pressure. The HANU flow reactor was placed at a 3° degree tilt to aid in the expulsion of air bubbles from the system.

Poly(lactide) synthesis using variable monomer to initiator ratio: Similar to the methodology described above, a dual injector syringe system was used to pump the lactide solution (1 M) and the DBU/benzyl alcohol solution (6:1) into the flow reactor. The flow rates of the injector syringes were set accordingly to obtain a 5 mL plug with varying ratios of lactide to benzyl alcohol. The total time taken for the reaction to reach 95% monomer conversion was calculated according to a rate constant obtained using various DBU concentrations.

Purification of crude poly(lactide): Collected samples were left to dry overnight in a fume hood. The dried samples were then dissolved in a minimal volume of tetrahydrofuran (THF, 99.5%) (~2.5 mL) followed by precipitation in cooled methanol. A Buchner funnel and (filter paper) were used to filter the purified polymer which was collected into a glass vial and dried overnight using a vacuum pump. This method of purification was performed on all polymers synthesized throughout this article.

ABA poly(lactide-*b*-farnesene-*b*-lactide) synthesis in flow (using constant monomer to initiator ratio: A dual injector syringe system was used to pump a solution of poly(farnesene)-diol and lactide monomer (1:1 weight ratio) and a 0.3 M solution of either DBU or TBD through the HANU reactor (prefilled with DCM). Note that for the TBD solution, chloroform was used to dissolve the organocatalyst completely. A plug flow volume of 5 mL was achieved using predetermined flowrates and -times. Using an HPLC pump (Knauer BlueShadow) the reagent plug was pumped through the HANU flow reactor at various predetermined flow rates. The degree of mixing and plug flow behavior was controlled using a pulsator (Creaflow) integrated into the flow reactor setup. The product was collected using two separate glass vials each holding 2.5 mL of the total 5 mL plug. In order to quench the reaction, 5 mg of propanoic acid was added to the vials prior to sample collections. Samples were then left to dry overnight in the fume hood followed by an overnight drying period under vacuum conditions. All reactions were carried out at room temperature and atmospheric pressure. The HANU flow reactor was placed at a 3° degree angle tilt to aid in the expulsion of air bubbles from the system.

ABA poly(lactide-*b*-farnesene-*b*-lactide) synthesis in flow (using variable monomer to initiator ratio: A solution of poly(farnesene)-diol (0.1 M) and TBD (0.2 M) was loaded in a syringe pump. In a second syringe pump a lactide solution (1 M) was loaded. To load the reagent plug into the system, the flowrate of the lactide solution was set to 1 mL/min while the poly(farnesene)-diol and TBD flowrate was set so as to achieve a predetermined monomer to initiator ratio (wt:wt), based on precalculated flowrates. Once the plug was loaded into the reactor system, the plug was pumped through the HANU reactor at a constant flowrate of 1 mL/min. Samples were collected in glass vials and subsequently quenched using 5 mg of propanoic acid. Samples were then left to dry overnight in the fume hood followed by an overnight drying period under vacuum conditions. All reactions were carried out at room temperature and atmospheric pressure. The HANU flow reactor was placed at a 3° degree angle tilt to aid in the expulsion of air bubbles from the system.

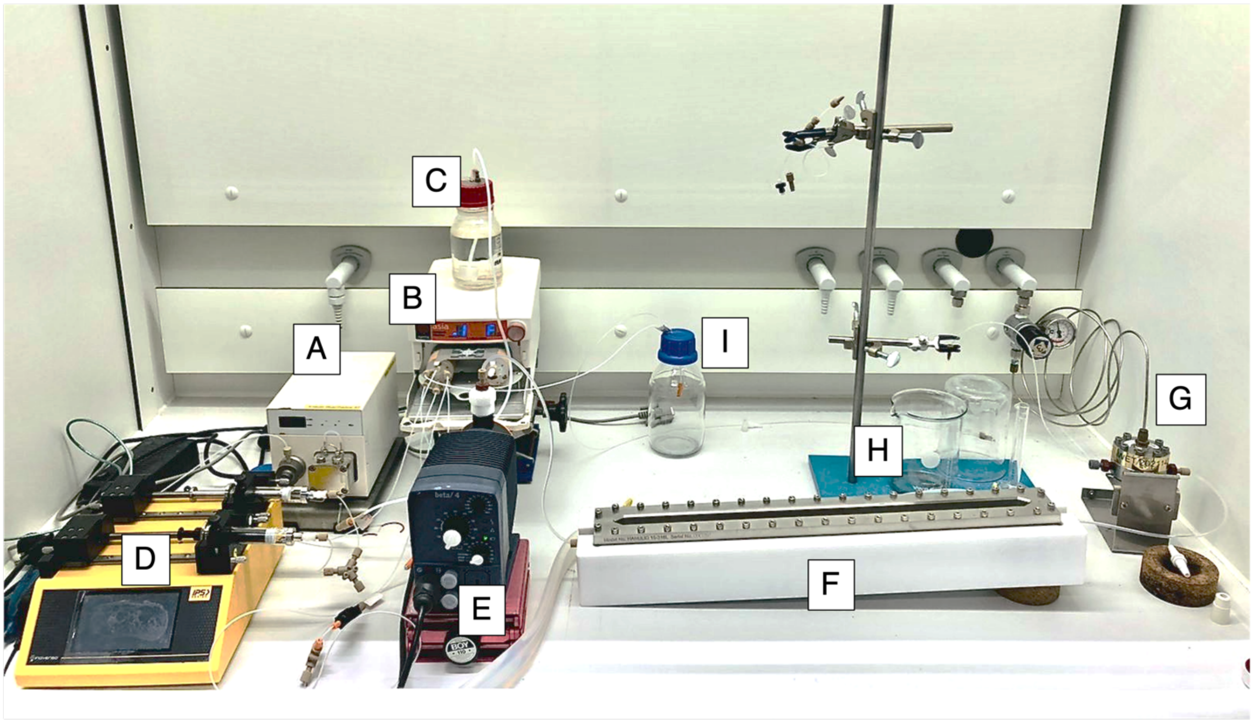

Figure S1. Photograph of the reactor set-up used to synthesize the polymers described in the main body of the article. **A)** HPLC pump, **B)** flow modulator, **C)** solvent beaker, **D)** dual syringe pump injector, **E)** beta/4 pulsator unit (Creaflow B.V.), **F)** HANU™ HX 15 flow reactor (stainless steel 316L, v1.0, Creaflow B.V.), **G)** back pressure regulator, **H)** beaker for sample collection.

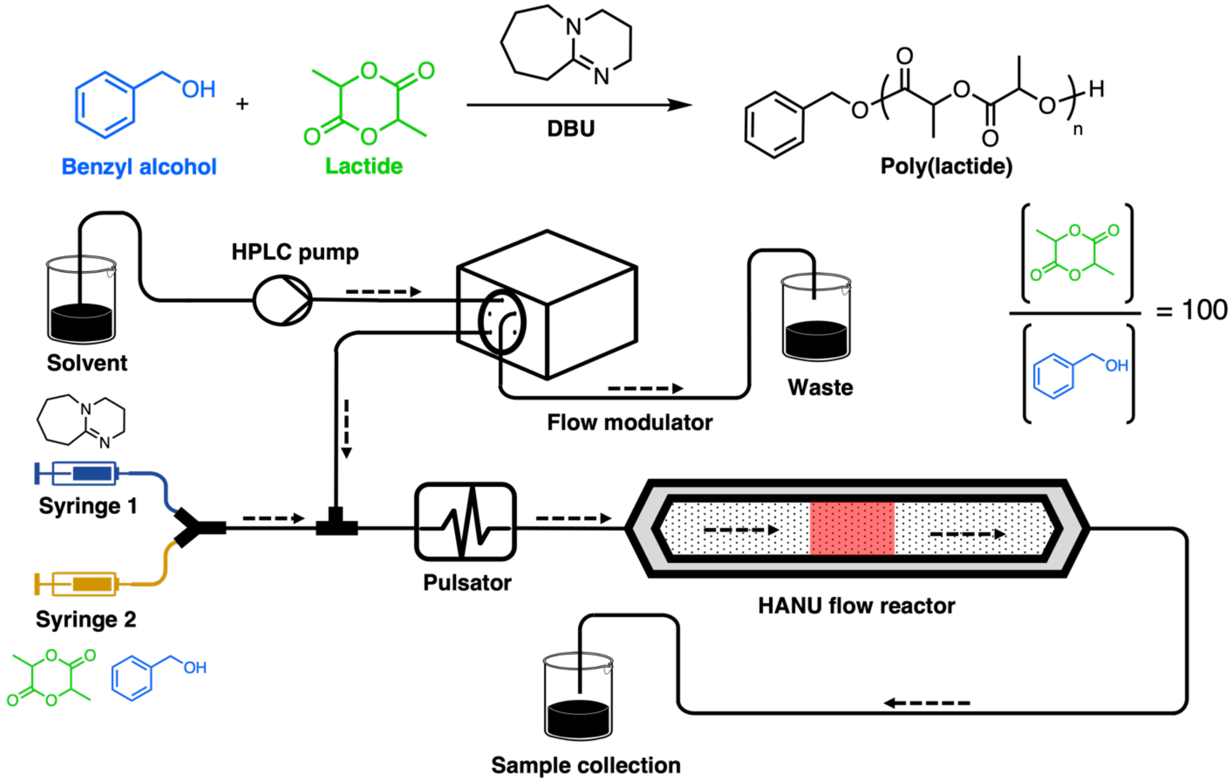

Figure S2. Schematic overview of the HANU flow reactor setup, along with the reaction scheme for the synthesis of poly(lactide) homopolymer for the determination of the effect of the reactor parameters on the molecular characteristics.

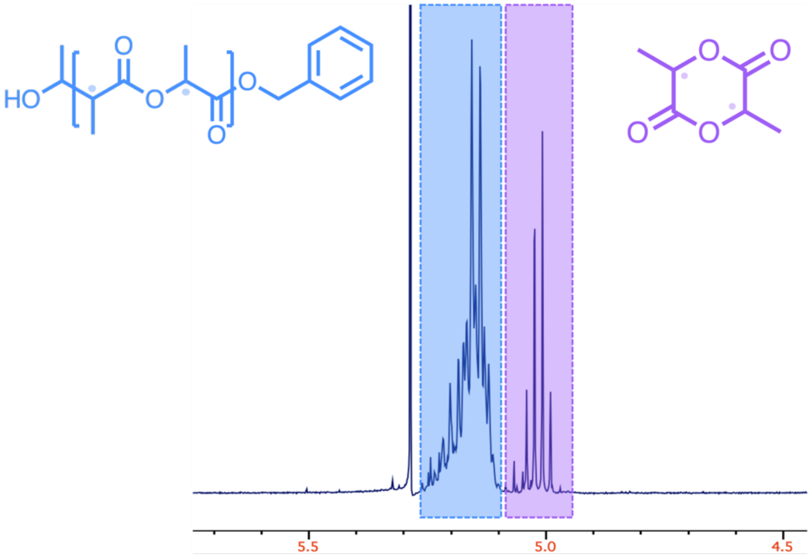

Figure S3. ^{1}H NMR analysis of crude PLA homopolymer. Characteristic peaks corresponding to the monomer and polymer repeating units. These data were used to calculate the conversion for every polymer product.

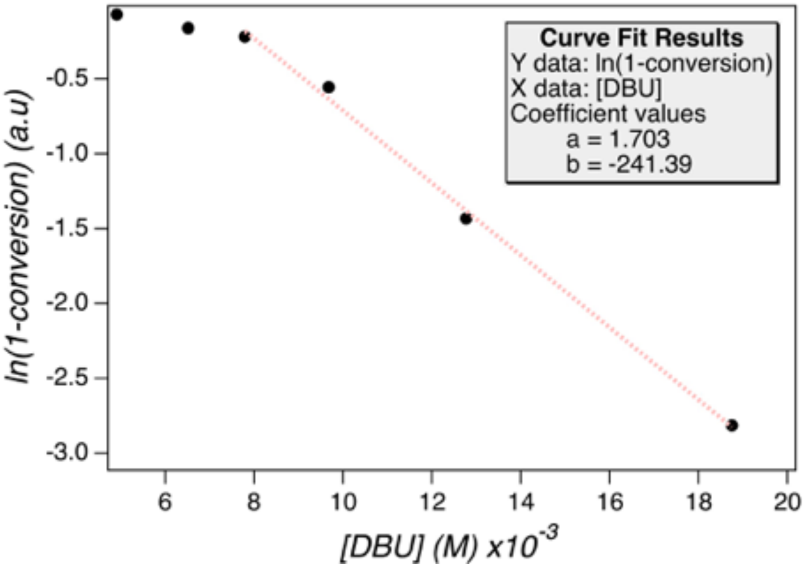

Figure S4. Conversion kinetics with respect to a change in DBU catalyst concentration. From these data, the rate constant was calculated and used to compensate for the additional time needed for the reaction to reach 90% conversion.

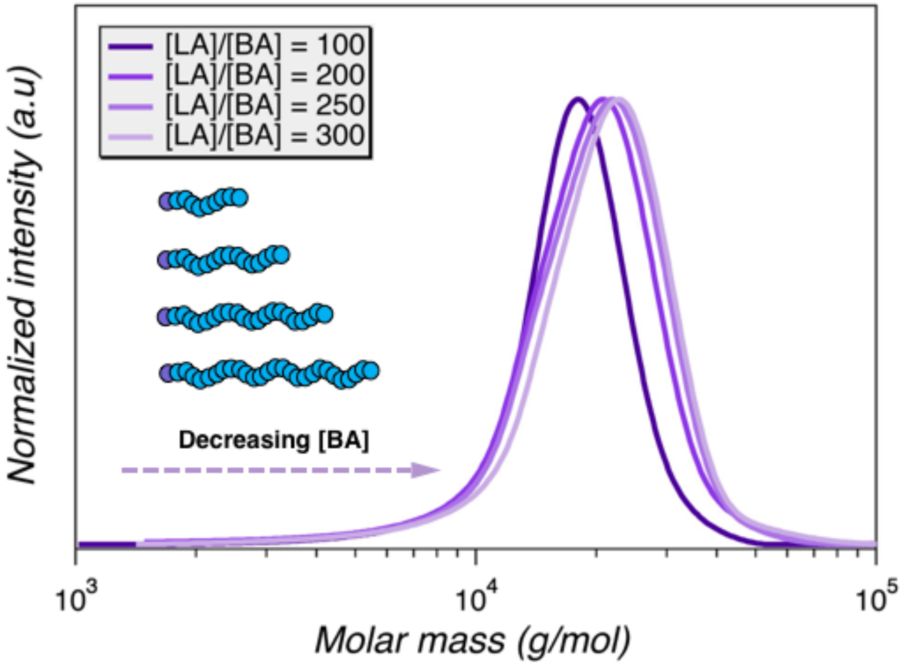

Figure S5. Size exclusion chromatography (SEC) analysis and data of poly(lactide) synthesis using various concentrations of initiator (benzyl alcohol) in order to vary the ratio of monomer to initiator and tune the target molecular weight. The SEC data suggests that there is a slight increase in molecular weight as the monomer to initiator ratio increases, albeit relatively far from the target molecular weight.

Table S1. Data corresponding to the synthesis of poly(lactide) targeting different molecular weights via *in situ* modulation of the monomer to initiator ratios. Ideal reactor settings were used for all experiments (1 mL/min / 0.6 Hz / 0.04 mL/stroke).

[LA]/[BA]	Conversion (%)	Target Mw (g/mol)	Mn (g/mol) (^{1}HNMR)	Mn (g/mol) (SEC)	Dispersity
100	0.925	13320	15.7K	15.9K	1.14
200	0.954	27475	22.3K	16.6K	1.24
250	0.909	32724	23.3K	17.5K	1.21
300	0.875	37800	23.8K	18.4K	1.22

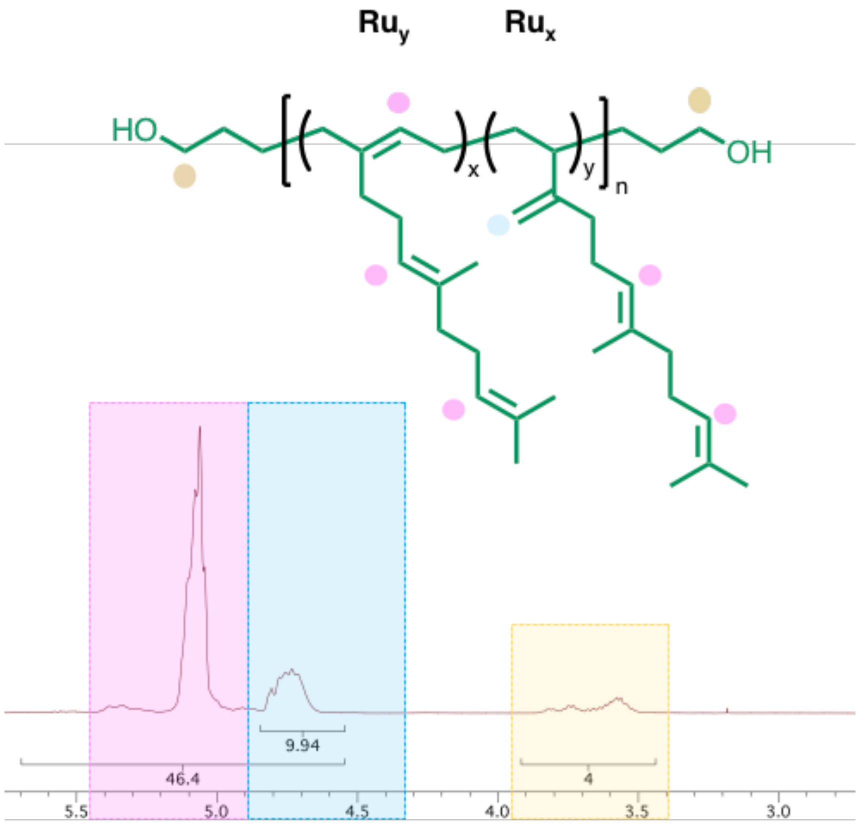

Figure S6. ^{1}H NMR analysis of commercial telechelic_poly(β-farnesene)-diol (PFD) in order to verify the molecular weight.

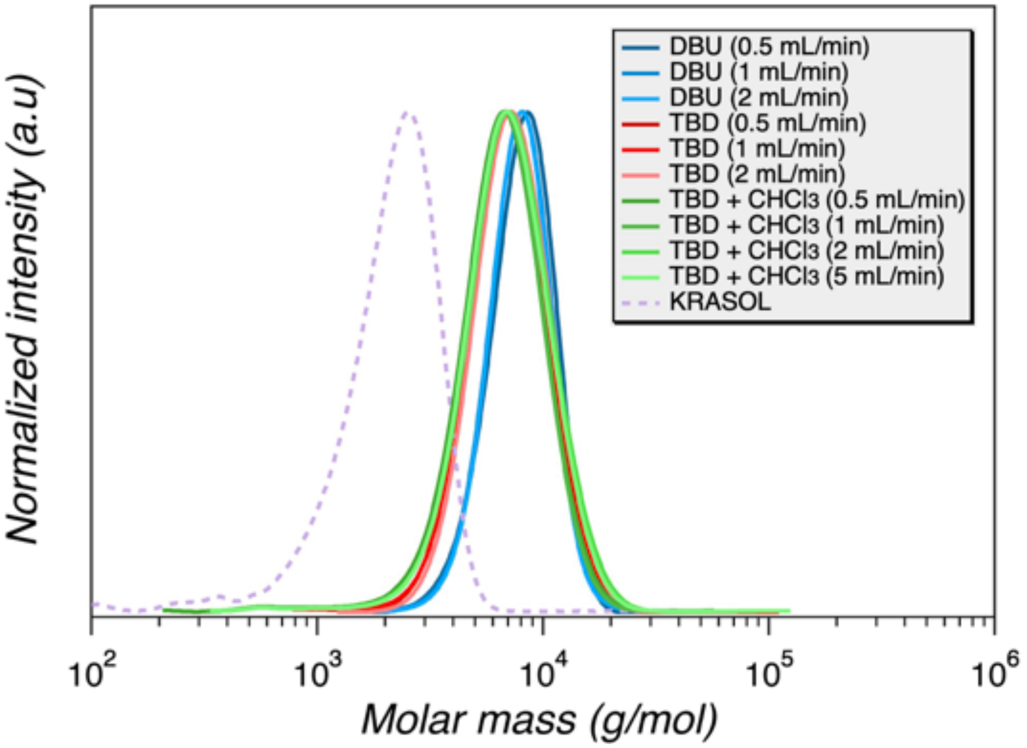

Figure S7. Size exclusion chromatography (SEC) analysis and data of ABA-poly(lactide-*b*-farnesene-*b*-lactide) synthesis comparing the effect of DBU and TBD organocatalyst on various molecular characteristics. From these data can be concluded that, overall, using TBD as a catalyst leads to higher conversions irrespective of the flowrate. Furthermore, using $CHCl_3$ to dissolve TBD increases the polymerization kinetics slightly and provide a high reproducibility with respect to the polydispersity index. KRASOL refers to the commercial poly(farnesene)-diol. All samples had a target molecular weight of 5.7 kg/mol with a 1:1 weight ratio of lactide to poly(farnesene)-diol.

Table S2. Data corresponding to the synthesis of ABA-poly(lactide-*b*-farnesene-*b*-lactide) comparing TBD and DBU as an organocatalyst. For all experiments pulsation was set at 0.6 Hz; 0.04 mL/stroke.

Flow rate (mL/min)	**Conv.**	**Mn (kg/mol)**	**Đ**
	DBU		
0.5	0.86	5.7	1.15
1.0	0.77	4.6	1.17
2.0	0.66	3.7	1.14
5.0	0.54	-	-
	TBD		
0.5	0.88	5.2	1.19
1.0	0.91	5.1	1.20
2.0	0.93	5.9	1.18
5.0	0.85	3.6	1.22
	TBD (in CHCl3)		
0.5	0.91	5.2	1.24
1.0	0.93	4.5	1.23
2.0	0.96	5.0	1.24
5.0	0.90	5.4	1.23

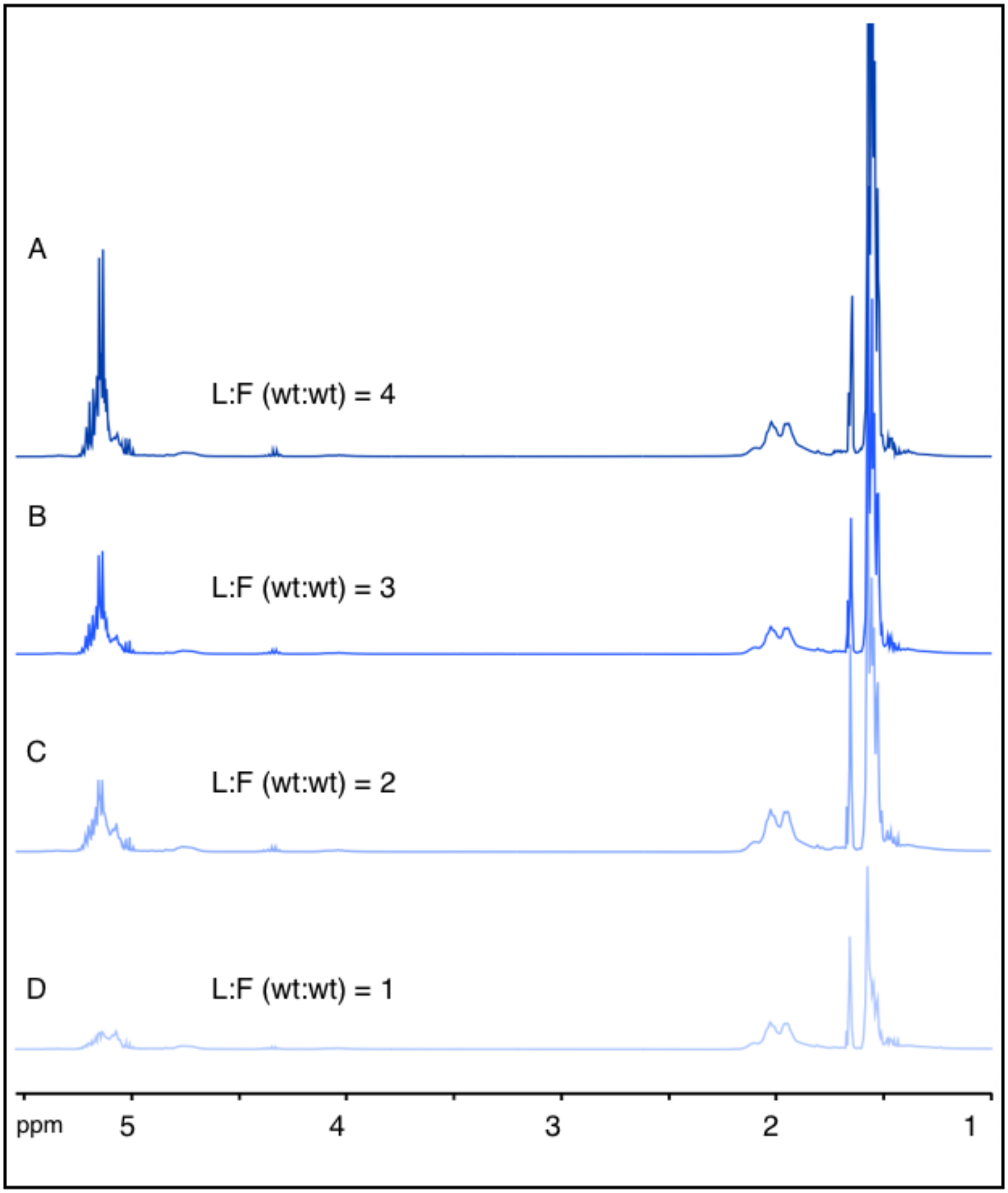

Figure S8. ^{1}H NMR analysis of consecutively increasing chain lengths of the PLA components in the LFL triblock copolymer.

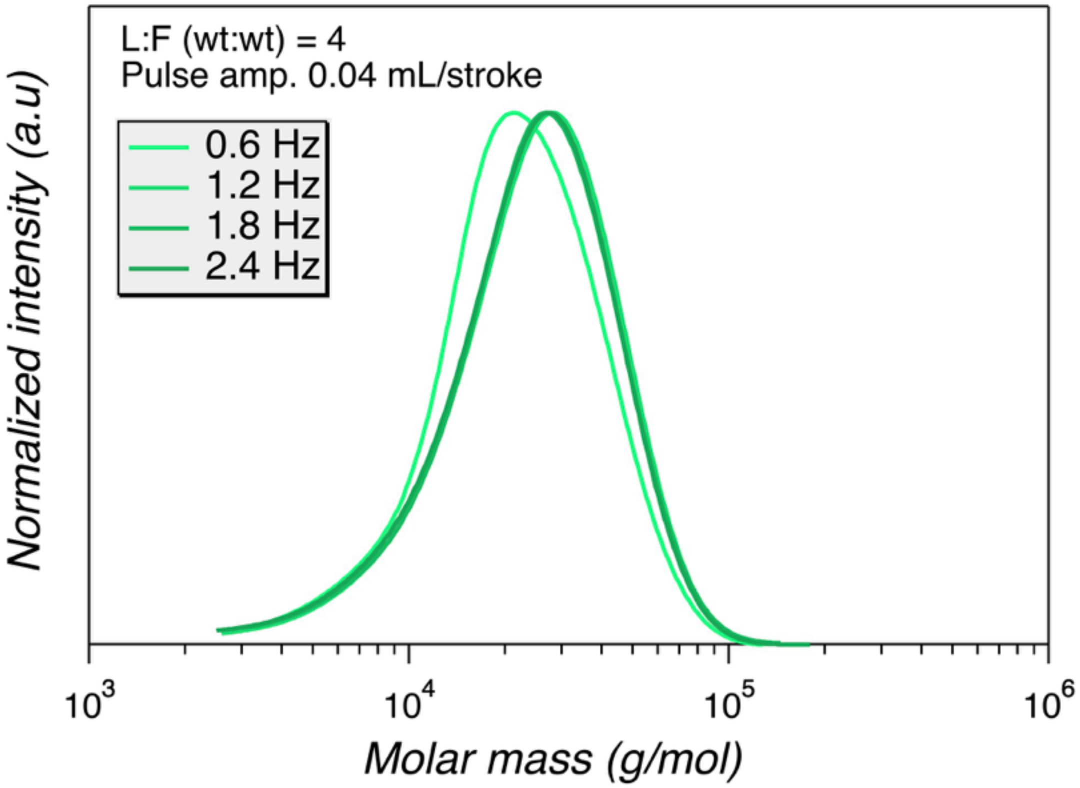

Figure S9. Size exclusion chromatography (SEC) of LFL triblock copolymers synthesized at different pulsation frequencies.

Table S3. Data corresponding to the synthesis of ABA-poly(lactide-*b*-farnesene-*b*-lactide) comparing different pulsation frequencies. All pulsations were performed at 5% amplitude.

Pulsation frequency	**M_n(theo) (kg/mol)**	**Conv. (%)**	**M_n(NMR) (kg/mol)**	**M_n(SEC) (kg/mol)**	**ϕ_L**	**Đ**
0.6	14.4	94	13.1	17.7	0.79	1.43
1.2	14.4	95	11.3	19.4	0.75	1.47
1.8	14.4	98	11.6	19.4	0.76	1.46
2.4	14.4	96	10.1	18.6	0.72	1.48

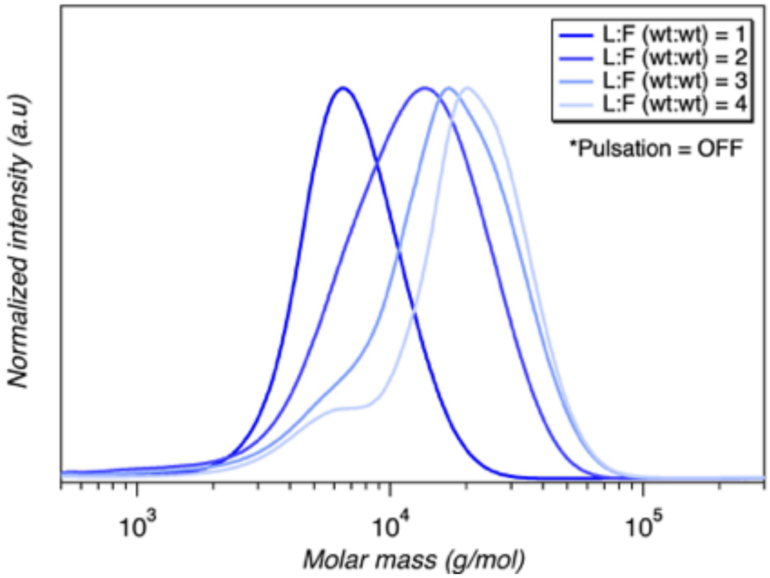

Figure S10. Size exclusion chromatography (SEC) of LFL triblock copolymers of different molecular weights synthesized without pulsation.

Table S4. Data corresponding to the synthesis of varying molecular weight ABA-poly(lactide-*b*-farnesene-*b*-lactide) samples without pulsation.

[LA]:[PFD] (wt:wt)	**[LA]:[TBD] (mol:mol)**	**M_n(theo) (kg/mol)**	**Conv. (%)**	**M_n(NMR) (kg/mol)**	**M_n(SEC) (kg/mol)**	**ϕ_L**	**Đ**
1:1	57	5.6	94	5.8	5.9	0.52	1.40
2:1	114	8.6	96	9.3	8.3	0.70	1.75
3:1	170	11.5	96	12.1	10.8	0.77	1.81
4:1	225	14.4	88	13.9	13.3	0.80	1.72