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Controlled organocatalyzed D,L-lactide ring-opening polymerizations: synthesis of low molecular weight oligomers

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Electronic Supplementary Information

Contents

Experimental

Reagents and equipment

All reagents were ≥98% pure and used as received. Propargyl alcohol (2-Propyn-1-ol), α-methyl propargyl alcohol ((±)-But-3-yn-2-ol), D,L-lactide (3,6-Dimethyl-1,4-dioxane-2,5-dione), 4-dimethylaminopyridine (DMAP), succinic anhydride (SA), trifluoroacetic acid (TFA), and 3-chloro-1-propanol were purchased from Alfa Aesar. Hydroquinone was purchased from Sigma Aldrich. Dichloromethane (DCM), hexanes, and acetonitrile, *N,N*-dimethylformamide (DMF), and diethyl ether were purchased from Fisher Scientific. Deionized distilled water (ddH_2O) with a resistivity of 18.2 MΩ/cm was obtained using a Barnstead ultrapure water filtration system. Alpha-Cyano-4-hydroxycinnamic acid (α-CHCA) was purchased from TCI America. Potassium chloride (KCl) was purchased from Macron. Sodium chloride (NaCl) was purchased from EMD. Sodium azide (NaN_3) was purchased from Amresco. All reactions were conducted in 8 mL Chemglass reaction vials with TFE lined silicone SURE-LINK septa caps. Reactions were evacuated with ultra-high purity nitrogen from Airgas using a Schlenk line connected to purging needles.

General Synthesis

4-dimethylaminopyridine (DMAP) and D,L-lactide (L) were weighed into 8 mL reaction vials. Propargyl alcohol (PA) or α-methyl propargyl alcohol (αMPA) was added volumetrically. Ratios of PA:L:DMAP or αMPA:L:DMAP that were investigated are listed in the text and in Table S1. A stir bar was added to the vial, and reactions were purged with nitrogen for 20 minutes. Vials were submerged in preheated 130 °C oil for times listed in the text and Table S1. After polymerizations, reaction vials were removed from oil, opened to atmosphere, and cooled before the slow addition of 1 mL of DCM. Reactions were recapped, vortexed until dissolved, and precipitated into 14 mL of hexanes in 15 mL conical tubes. Reactions were recapped, vortexed until dissolved, and precipitated into 14 mL of hexanes in 15 mL conical tubes. Tubes were shaken to aid precipitation, and supernatant was decanted. Fresh 15 mL of hexanes was added and shaken, and products were collected by decanting the supernatant and drying under an air stream. Samples were placed under vacuum to remove residual volatile solvents.

Hydroxyl end group modification

After lactide polymerization or Huisgen 1,3-dipolar cycloaddition, reaction vials were removed from oil and opened to atmosphere, and succinic anhydride (SA) was added in a ratio of 1:1 initiator:SA. Vials were recapped and stirred at 130 °C for 5 minutes. Products were dissolved in DCM and precipitated in hexanes as described above.

Huisgen 1,3-dipolar cycloaddition

A combination of 1.13 g 3-chloro-1-propanol and 1.17 g NaN_3 in 5 mL ddH_2O was stirred at 80 °C for 16 hours. The product, 3-azido-1-propanol, was extracted with diethyl ether 10x using 5 mL per extraction. Combined extractions were dried with anhydrous sodium sulfate and filtered. Solvent was removed via rotary evaporation. Successful substitution reaction was confirmed by peak shifts in ^{1}H-NMR spectra, and the yield was 93% (Fig. S20).

Azide-alkyne cycloaddition was conducted by dissolving ~200 mg of precipitated propargyl-functional oligo(lactide) in DMF and adding ~30 mg (2x excess) 3-azido-1-propanol. The mixture was stirred at 92 °C for 17 hours and precipitated in a mixture of 15 mL diethyl ether and 35 mL hexanes. Tubes were shaken to aid precipitation, and supernatant was decanted. Samples were placed under vacuum to remove residual volatile solvents.

^{1}H-NMR

Samples were dissolved in deuterated chloroform without TMS and analyzed by 1D ^{1}H-NMR (Brüker 400 MHz or 500 MHz, $CDCl_3$, 25 °C, 16 scans). Spectra for publication were prepared using Mestrelab Research MNova 11.

Matrix assisted laser desorption ionization time of flight (MALDI-TOF)

Samples and α-CHCA were prepared at 10 mg/mL using 1:1 acetonitrile:ddH_2O with 0.1% TFA. NaCl and KCl were prepared at 100 mg/mL in distilled, deionized water. Solutions were combined 10:10:1 (sample:α-CHCA:salt) and spotted on a Brüker MSP 96 target ground steel plate using 1 µL. Calibration was performed using aliquoted peptide calibration standards (Sigma-Aldrich). Linear mode suppressing ions below 200 Da exhibited the greatest signal/noise in spectra and was used for analysis. Data presented for publication were exported from Brüker Flex Analysis software, compiled using MATLAB R2016a, and graphed using GraphPad Prism 6.

Peak designation by MALDI-TOF analysis

Three samples (1:20:4 PA:L:DMAP, 1:20:4 αMPA:L:DMAP, and 20:4 L:DMAP) were analyzed with three sample preparations (no salt dopant, NaCl dopant, and KCl dopant) and compared (Figure S1). There were no differences between NaCl and KCl dopants, as well as no differences between salt dopant and no salt dopant. This suggested all species present were complexed with DMAP, as nitrogen-containing compounds are cationized by hydrogens in the solvent solution. Moreover, ^{1}H-NMR analysis identified four distinct CH and two distinct CH_3 proton shifts for DMAP, suggesting the presence of both DMAP catalyst and DMAP adducts in products. All peaks with MALDI spectra fell into one of two categories: (1) those numerically identical, and (2) those numerically separated by 14 Da, the mass difference between PA and αMPA (CH_2), between PA-initiated and αMPA-initiated reactions. Some peaks within category (1) were also numerically identical to those present in the DMAP-initiated/catalyzed reaction. Peak sets were designated by first identifying peaks separated by 72 Da, the mass of half a lactide unit, and then identifying the smallest identifiable peak in the series. These data were used to plot mass vs. lactide units, and the y-intercept of each plot was used to identify the base of each peak set (Figure S2).

Figures and Tables

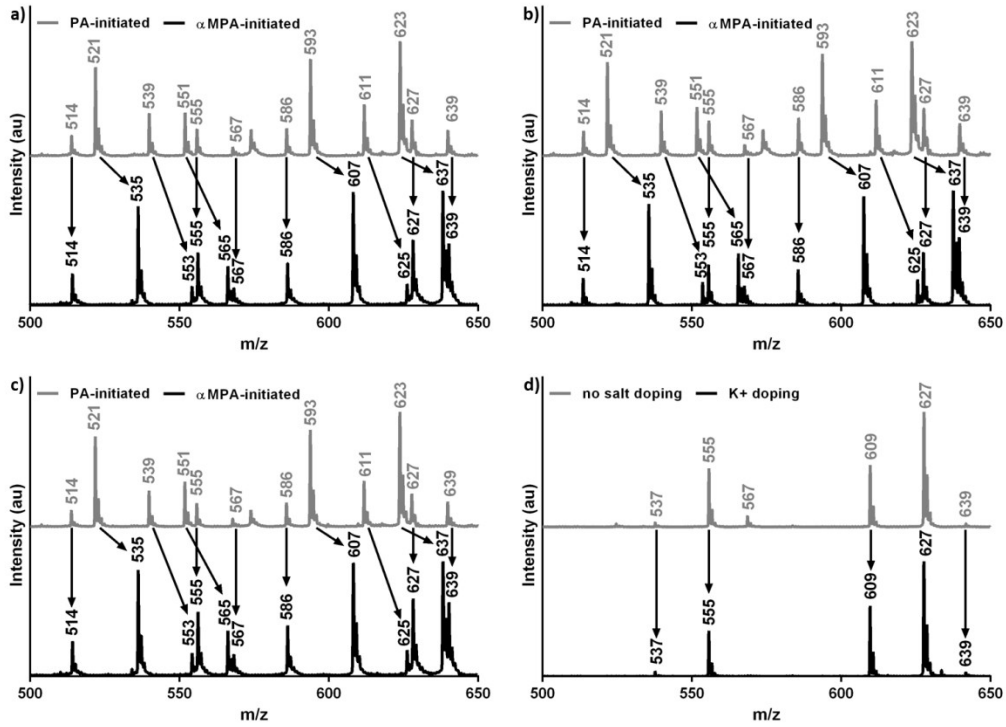


Figure S1.

(a-c) MALDI-TOF analysis of DMAP-catalyzed and propargyl alcohol-initiated (top, grey) or α-methyl propargyl alcohol-initiated (bottom, black) ROP of D,L-lactide prepared with (a) no salt doping, (b) NaCl salt doping, and (c) KCl salt doping. (d) DMAP-catalyzed/initiated ROP of D,L-lactide using either no salt doping (top, grey) or KCl salt doping (bottom, black).

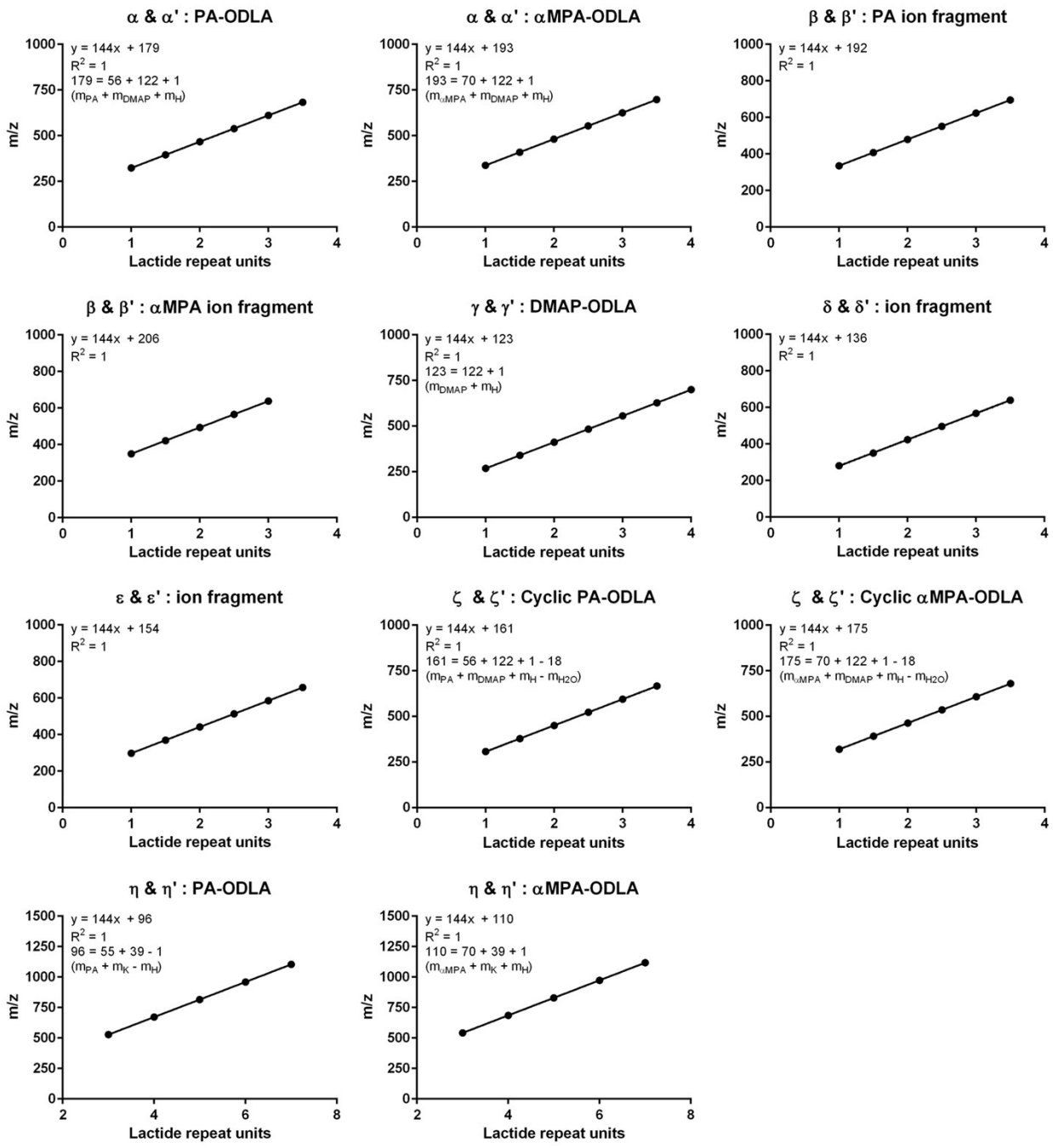


Figure S2.

Linear regression of peak sets to identify end groups of oligo(lactide) formed during polymerizations of propargyl alcohol (PA), 4-dimethylaminopyridine (DMAP), and D,L-lactide or α-methyl propargyl alcohol (αMPA), DMAP, and D,L-lactide.

Table S1.

Reagent ratios and polymerization times for all reactions described in the text.

Initiator	*Ratio*[a]	*Time*	*% conv.*[b]	M_n *by* ^{1}*H-NMR*[c]	M_n/M_w, *PDI by MALDI-TOF*[d]	*Notes*
PA	1:20:4	5 min	99%	2825 Da	752/847 Da, 1.12	
PA	1:20:4	10 min	97%	2124 Da	833/955 Da, 1.15	
PA	1:20:4	15 min	98%	2606 Da	817/930 Da, 1.14	
PA	1:20:4	30 min	97%	2367 Da	847/964 Da, 1.14	
PA	1:20:4	60 min	98%	2985 Da	823/963 Da, 1.17	
PA	1:5:0.06	5 min	72%	759 Da	660/732 Da, 1.11	10 wt% HQ
DMAP	0:20:4	5 min	80%	3720 Da	794/895 Da, 1.13	DMAP-initiated
PA	1:20:0	5 min	0%	N/A	N/A	No reaction
αMPA	1:20:0	5 min	0%	N/A	N/A	No reaction
αMPA	1:20:4	5 min	96%	2041 Da	721/840 Da, 1.16	
αMPA	1:20:4	10 min	96%	1922 Da	779/890 Da, 1.14	
αMPA	1:20:4	15 min	97%	2036 Da	822/919 Da, 1.12	
αMPA	1:20:4	30 min	97%	2127 Da	856/956 Da, 1.12	
αMPA	1:20:4	60 min	97%	2104 Da	850/947 Da, 1.11	
αMPA	1:20:2	5 min	87%	3620 Da	782/938 Da, 1.20	
αMPA	1:20:1	5 min	88%	3150 Da	826/1017 Da, 1.23	
αMPA	1:20:0.5	5 min	65%	3120 Da	881/1087 Da, 1.23	
αMPA	1:10:1	5 min	92%	2200 Da	759/947 Da, 1.25	
αMPA	1:5:1	5 min	97%	1470 Da	763/883 Da, 1.16	
αMPA	1:2:1	5 min	97%	1160 Da	656/719 Da, 1.10	
αMPA	1:10:5	5 min	96%	2050 Da	772/858 Da, 1.11	
αMPA	1:5:2.5	5 min	97%	1550 Da	725/809 Da, 1.12	
αMPA	1:2:0.03	5 min	82%	480 Da	619/701 Da, 1.13	
αMPA	1:2:0.03	10 min	99%	690 Da	685/764 Da, 1.11	
αMPA	1:2:0.03	15 min	99%	760 Da	661/734 Da, 1.11	
αMPA	1:5:0.06	5 min	73%	720 Da	753/873 Da, 1.16	
αMPA	1:5:0.06	10 min	89%	880 Da	727/829 Da, 1.14	
αMPA	1:5:0.06	15 min	94%	1020 Da	758/870 Da, 1.15	
αMPA	1:10:0.11	5 min	32%	1010 Da	772/953 Da, 1.23	
αMPA	1:10:0.11	10 min	71%	1280 Da	736/857 Da, 1.16	
αMPA	1:10:0.11	15 min	83%	1460 Da	747/896 Da, 1.20	
αMPA	1:2:0.03	1 min	0%	N/A	N/A	No reaction
αMPA	1:2:0.03	2 min	68%	942 Da	631/711 Da, 1.12	
αMPA	1:2:0.03	3 min	91%	991 Da	647/725 Da, 1.12	
αMPA	1:2:0.03	4 min	90%	1617 Da	686/765 Da, 1.12	
αMPA	1:2:0.03	90 sec	62%	489 Da	668/756 Da, 1.13	

[a]Ratios are PA:L:DMAP or αMPA:L:DMAP. [b]Percent conversion (X) calculated by ^{1}H-NMR via peak integrals indicated in Fig. 1a. X = 100*area(peak C)/[area(peak C)+area(peak D)]. [c]M_n = [area(peak C)+area(peak F)]*144+56 for PA-initiated; [area(peak C)+area(peak F)]*72+70 for αMPA. [d]$M_n = \Sigma N_i M_i / \Sigma N_i$ and $M_w = \Sigma N_i M_i^2 / \Sigma N_i M_i$, where N_i is the intensity of the "i^{th}" peak, and M_i is the mass of the "i^{th}" peak. PDI = M_w/M_n.

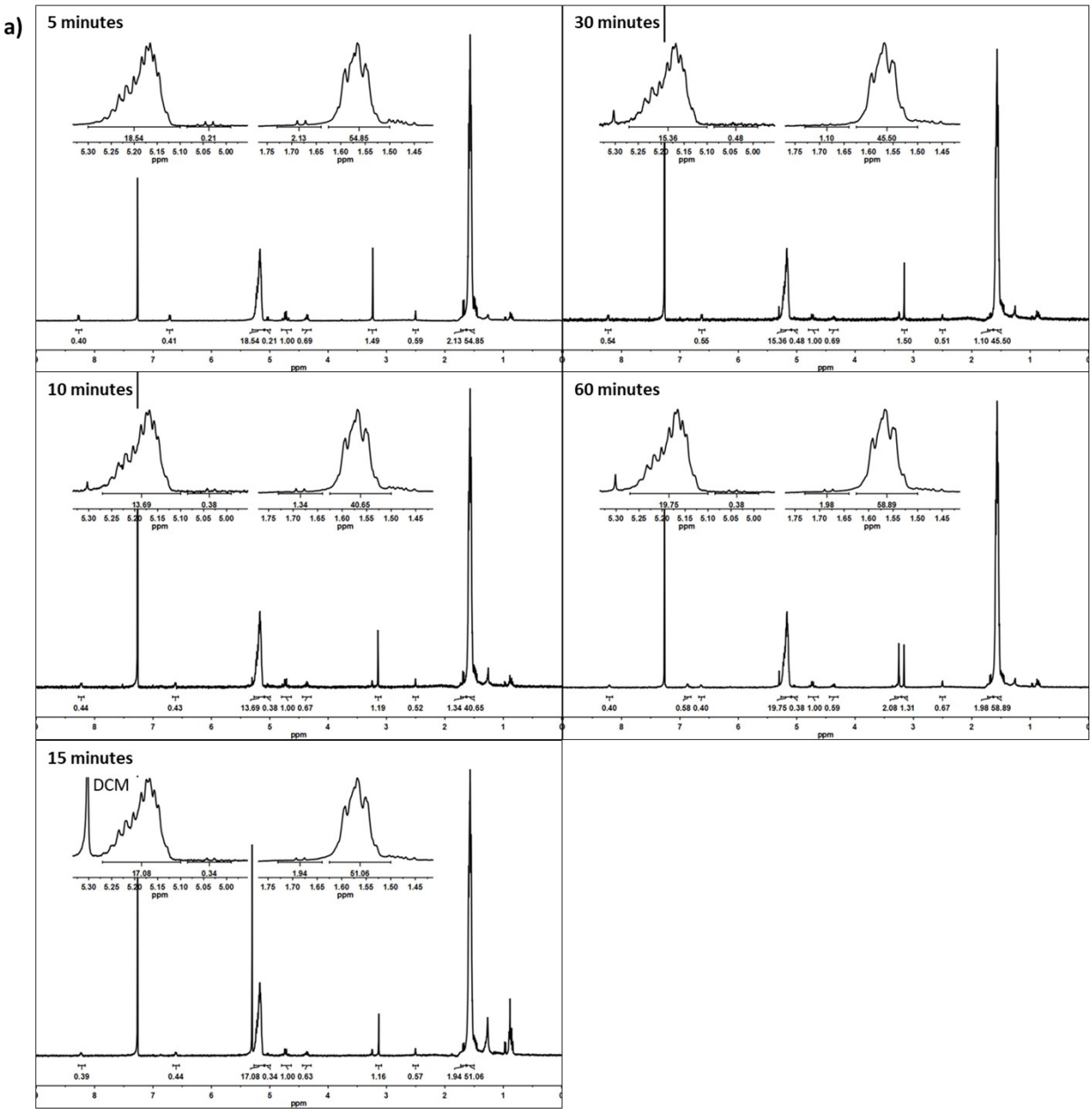


Figure S3a.

^{1}H-NMR for polymerizations of 1:20:4 propargyl alcohol:lactide:4-dimethylaminopyridine (PA:L:DMAP) reacted for 5-60 minutes. DCM, dichloromethane.

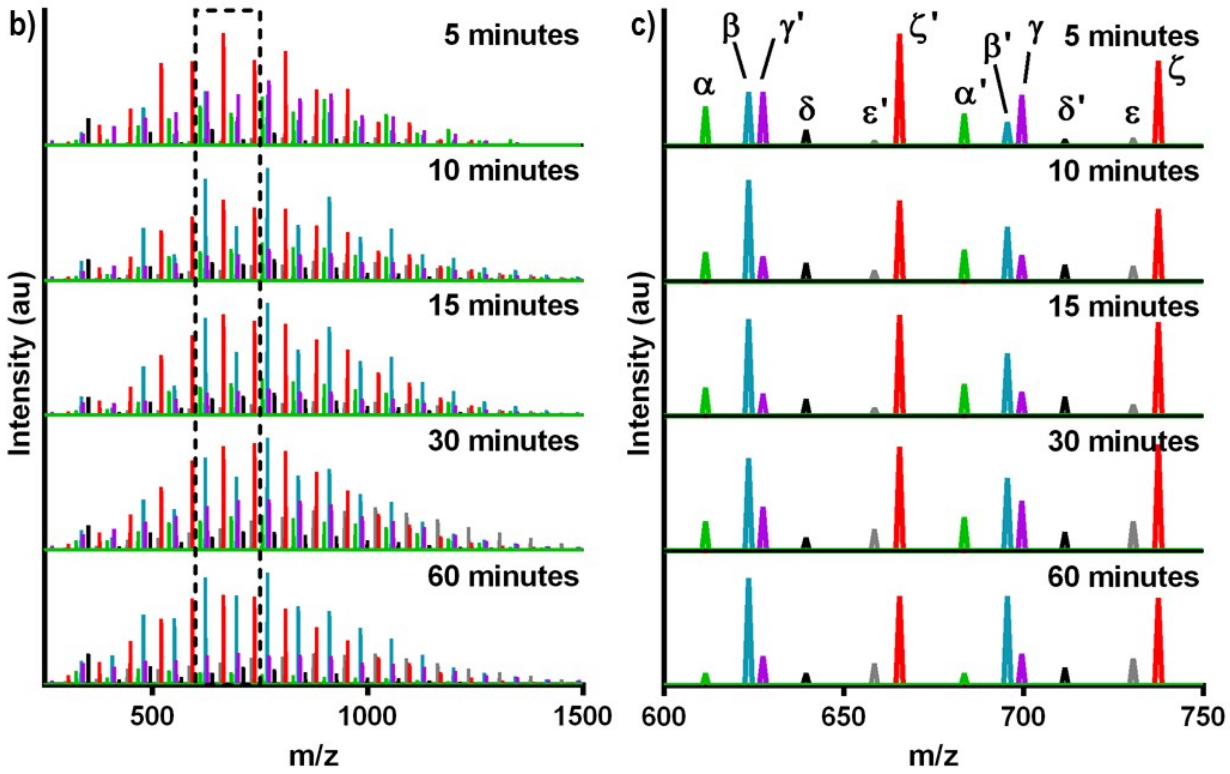


Figure S3b-c.

MALDI-TOF for polymerizations of 1:20:4 propargyl alcohol:lactide:4-dimethylaminopyridine (PA:L:DMAP) reacted for 5-60 minutes, where (c) is one 144 Da peak set of (b).

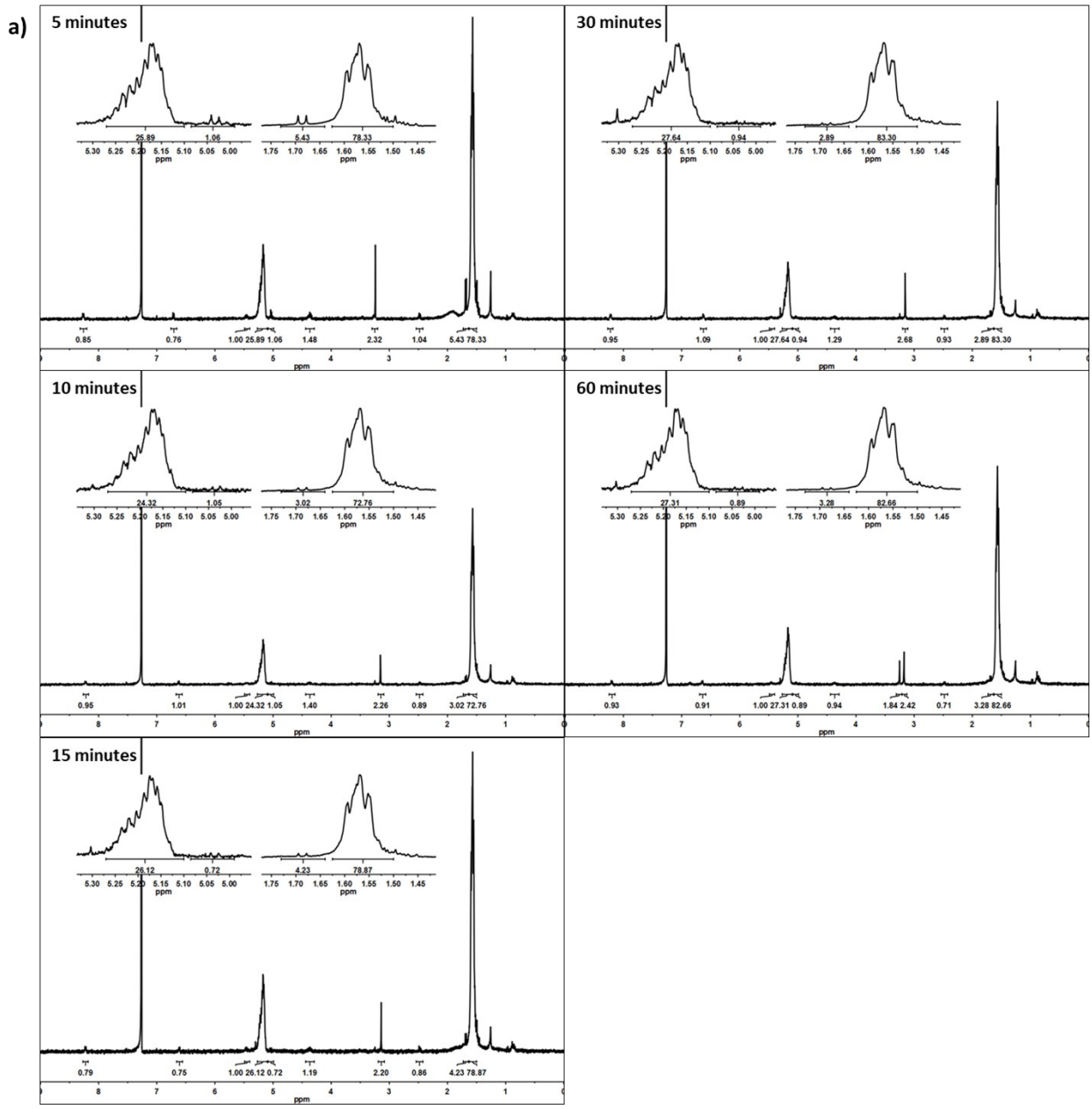


Figure S4a.

^{1}H-NMR for polymerizations of 1:20:4 α-methyl propargyl alcohol:lactide:4-dimethylaminopyridine (αMPA:L:DMAP) reacted for 5-60 minutes**.**

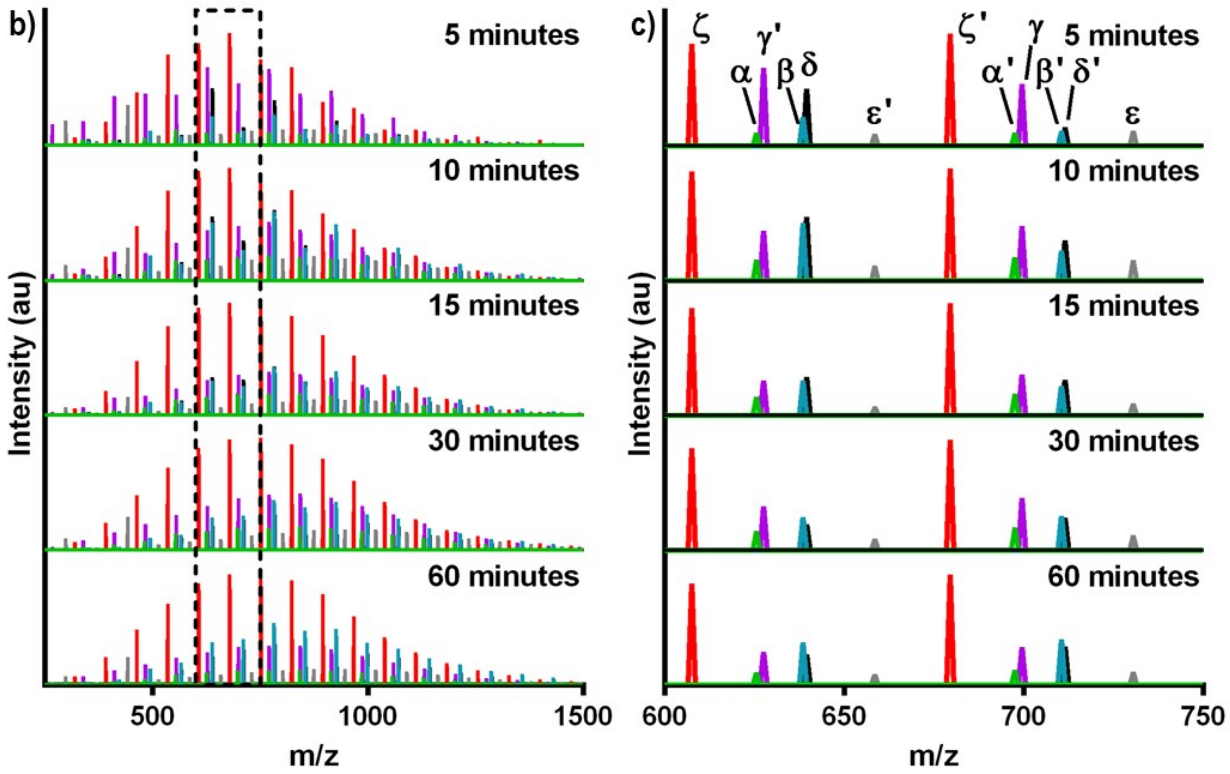
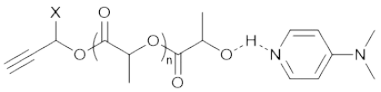
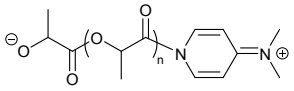
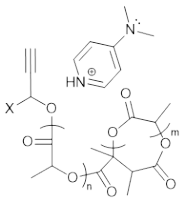
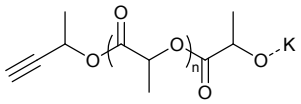
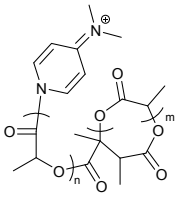


Figure S4b-c.

MALDI-TOF for polymerizations of 1:20:4 α-methyl propargyl alcohol:lactide:4-dimethylaminopyridine (αMPA:L:DMAP) reacted for 5-60 minutes, where (c) is one 144 Da peak set of (b).

Table S2.

Peak identities for oligo(D,L-lactide) (ODLA) presented in Fig. 1, Fig. S3, and Fig. S4.

Peak	*Identity*	*Structure*
α	PA-ODLA-DMAP-H^+, n odd αMPA-ODLA-DMAP-H^+, n odd	 X = H, propargyl alcohol; CH_3, α-methyl propargyl alcohol.
α'	PA-ODLA-DMAP-H^+, n even αMPA-ODLA-DMAP-H^+, n even	
γ	DMAP-ODLA-H^+, n odd	
γ'	DMAP-ODLA-H^+, n even	
ζ	Cyclic PA-ODLA, n+m odd Cyclic αMPA-ODLA, n+m odd	 X = H, propargyl alcohol; CH_3, α-methyl propargyl alcohol.
ζ'	Cyclic PA-ODLA, n+m even Cyclic αMPA-ODLA, n+m even	
η	αMPA-ODLA-K^+, n odd	
Fig. S8	HQ-DMAP-ODLA-H^+	Undefined
Fig. S10	Cyclic DMAP-ODLA, n+m odd	
	Cyclic DMAP-ODLA, n+m even	

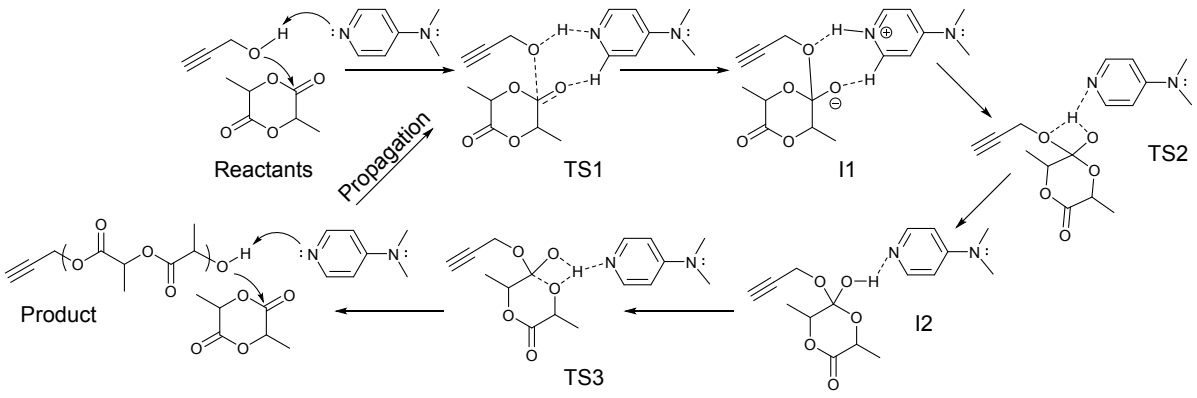


Figure S5.

Base activation of propargyl alcohol by 4-dimethylaminopyridine to initiate ring-opening polymerization of D,L-lactide.

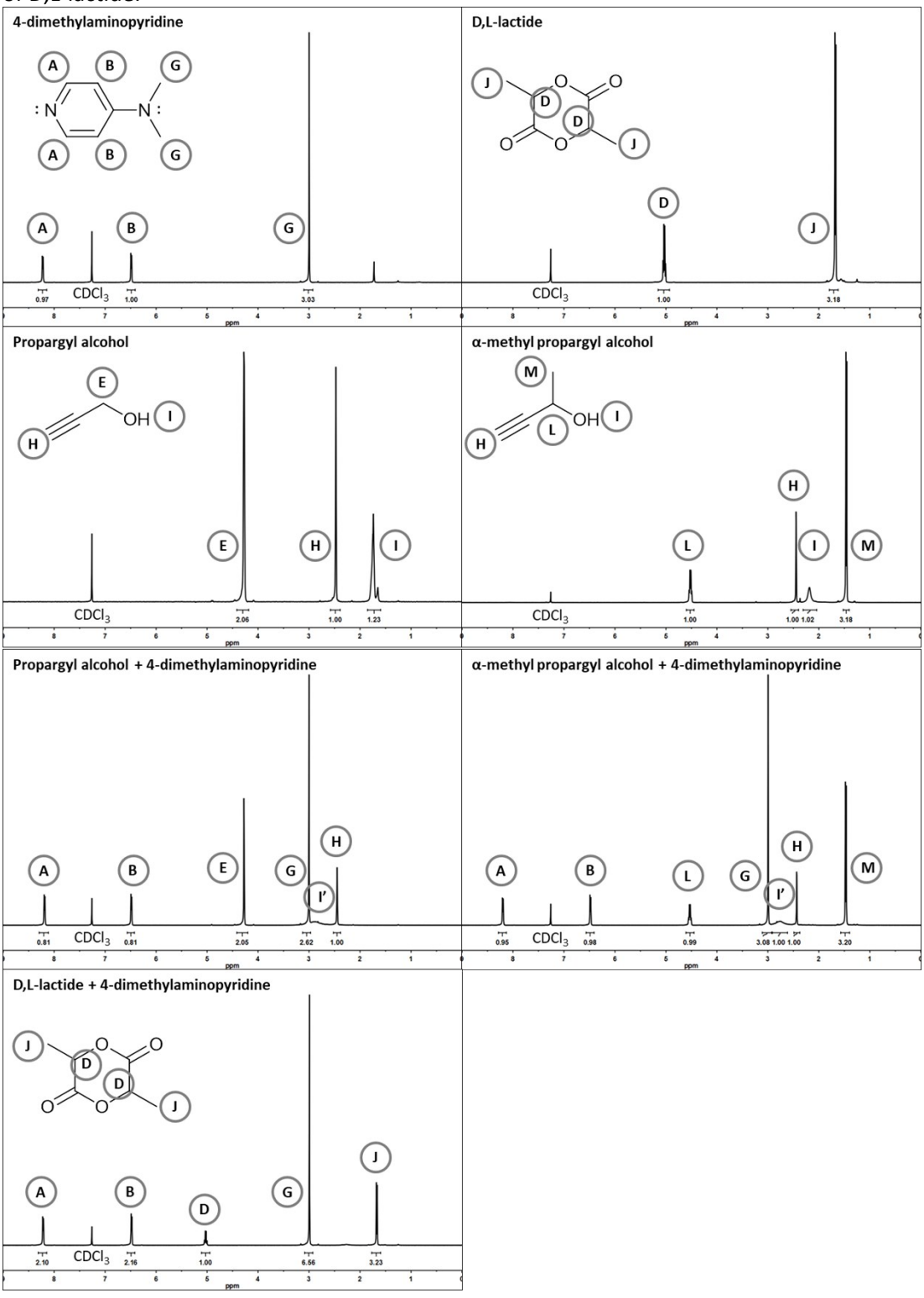


Figure S6.

^{1}H-NMR of 4-dimethylaminopyridine (DMAP), D,L-lactide, propargyl alcohol (PA), and α-methyl propargyl alcohol (αMPA), and combinations of DMAP and PA, DMAP and αMPA, and DMAP and lactide demonstrating that DMAP interacts with either alcohol but not lactide to initiate polymerization.

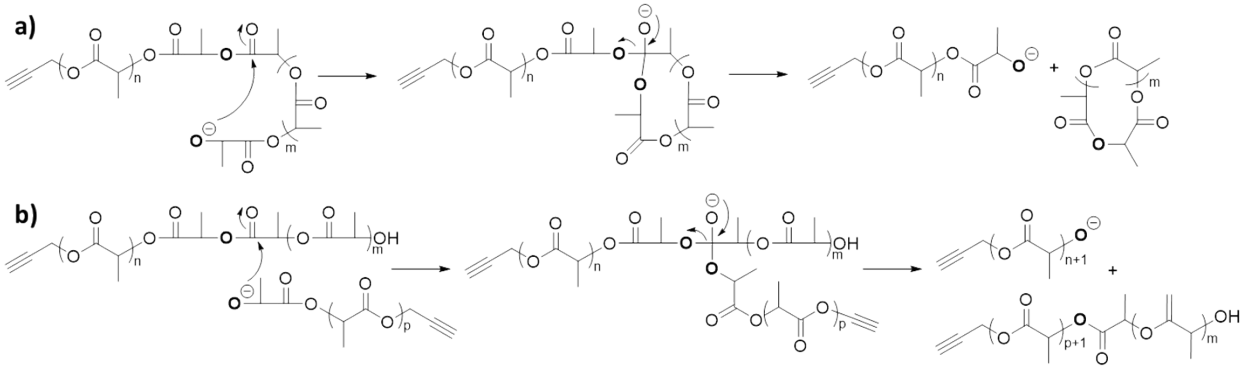


Figure S7.

Reaction mechanisms for (a) intramolecular and (b) intermolecular transesterification.

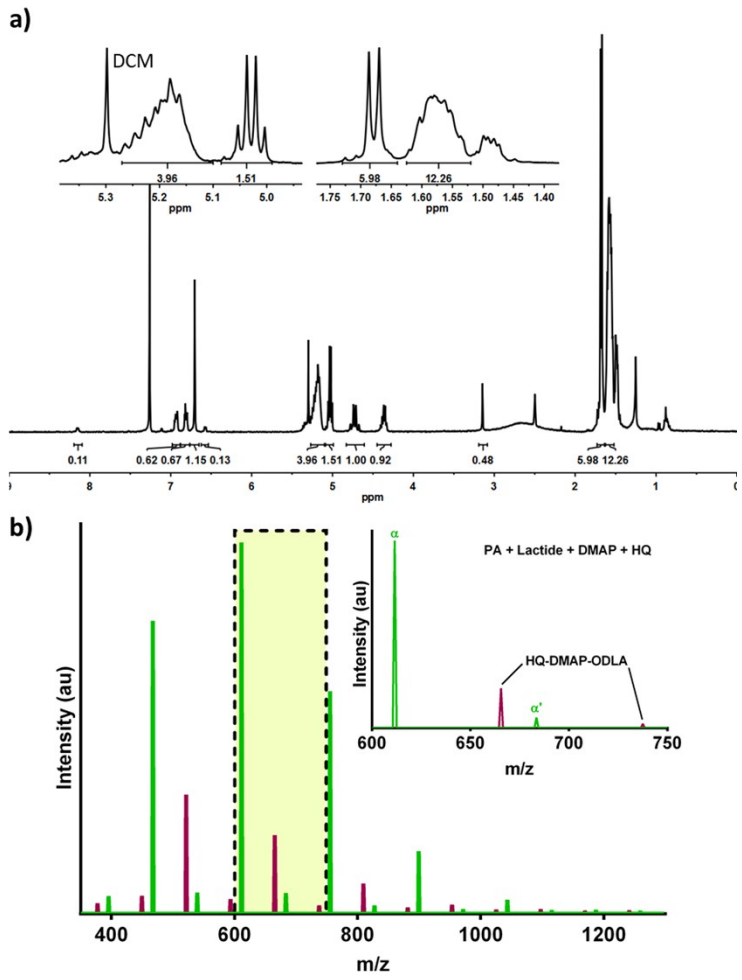


Figure S8.

Hydroquinone (HQ) was added to a polymerization of lactide with propargyl alcohol (PA) and 4-dimethylaminopyridine (DMAP) to investigate the effect on PA-ODLA cyclicization. (a) ^{1}H-NMR demonstrates polymerization to ~72% conversion after 5 minutes. (b) MALDI-TOF shows the appearance of HQ-lactide-DMAP peaks (spectrum collected in reflector mode).

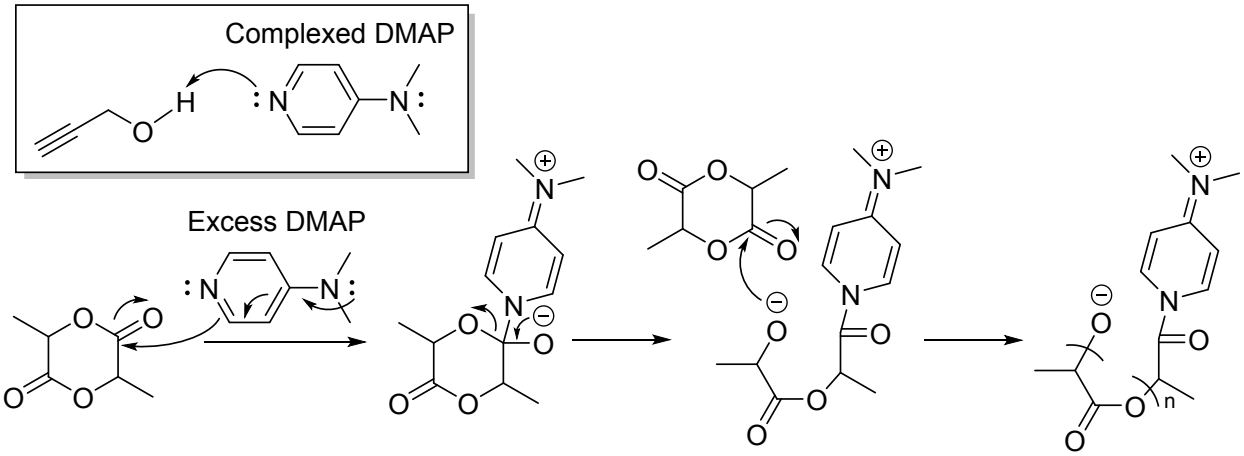


Figure S9.

Nucleophilic attack of 4-dimethylaminopyridine (DMAP) on lactide to initiate ring-opening polymerization when DMAP is available in excess relative to propargyl alcohol.

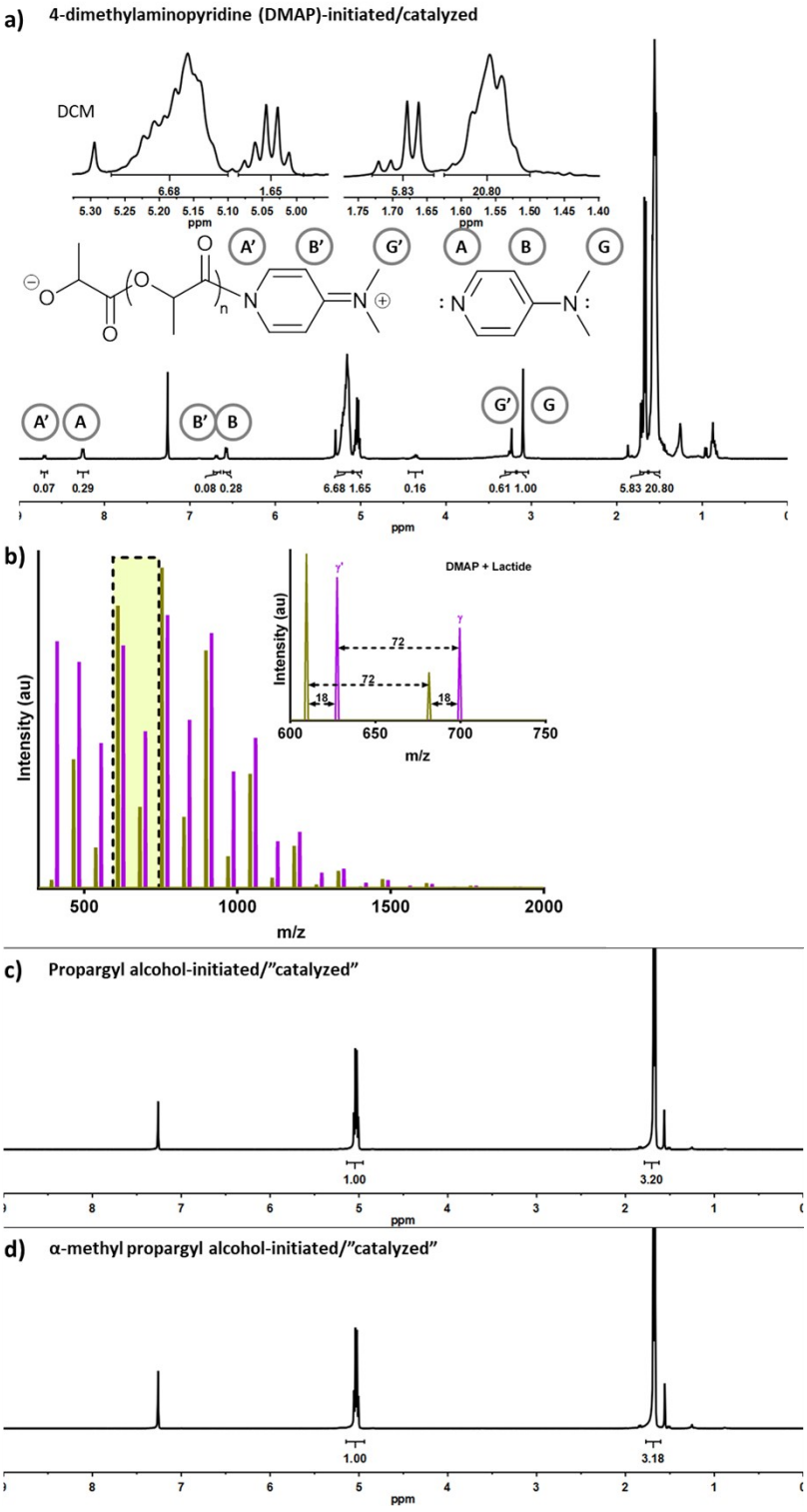


Figure S10.

(a) ^{1}H-NMR and (b) MALDI-TOF demonstrate 4-dimethylaminopyridine (DMAP) can initiate and catalyze lactide polymerization (spectrum collected in reflector mode). (c) Propargyl alcohol and (d) α-methyl propargyl alcohol cannot self-initiate and catalyze, as only pure lactide monomer precipitates after "polymerization."

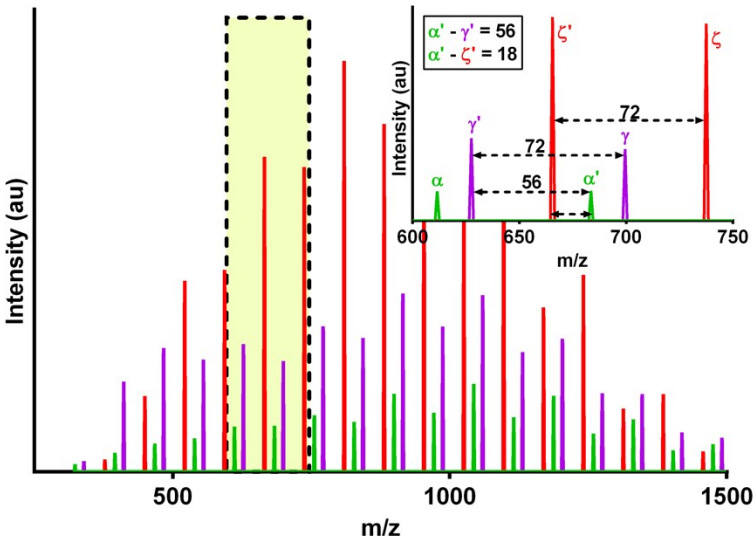


Figure S11.

MALDI-TOF of 5-minute 1:20:4 propargyl alcohol:lactide:4-dimethylaminopyridine (PA:L:DMAP) using reflector mode suggests that peaks sets “β,” “δ,” and “ε” are temporary ion fragments created during analysis and are not formed during polymerization (compare to Fig. 1b and Fig. S3b-c).

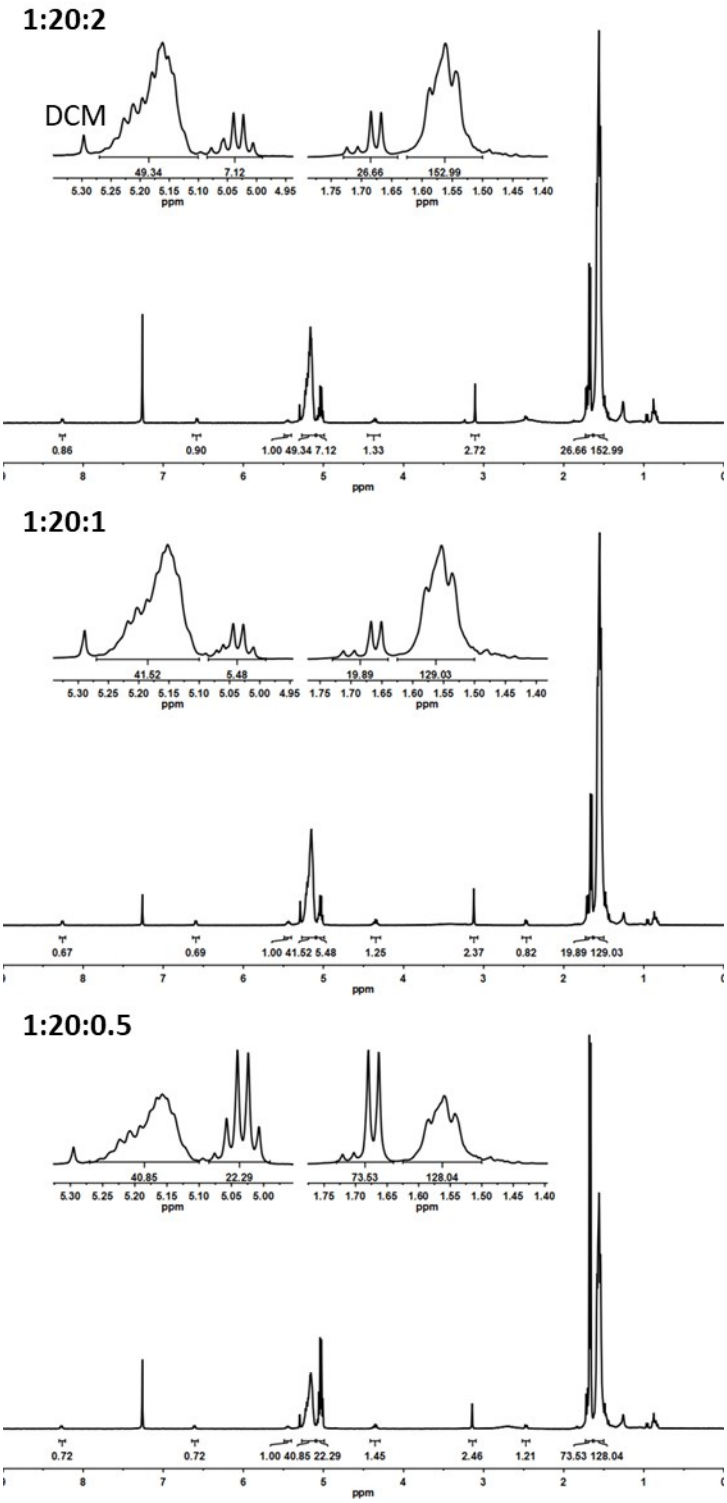


Figure S12.

^{1}H-NMR for polymerizations of 1:20:2, 1:20:1, and 1:20:0.5 α-methyl propargyl alcohol:lactide:4-dimethylaminopyridine (αMPA:L:DMAP) reacted for 5 minutes**.**

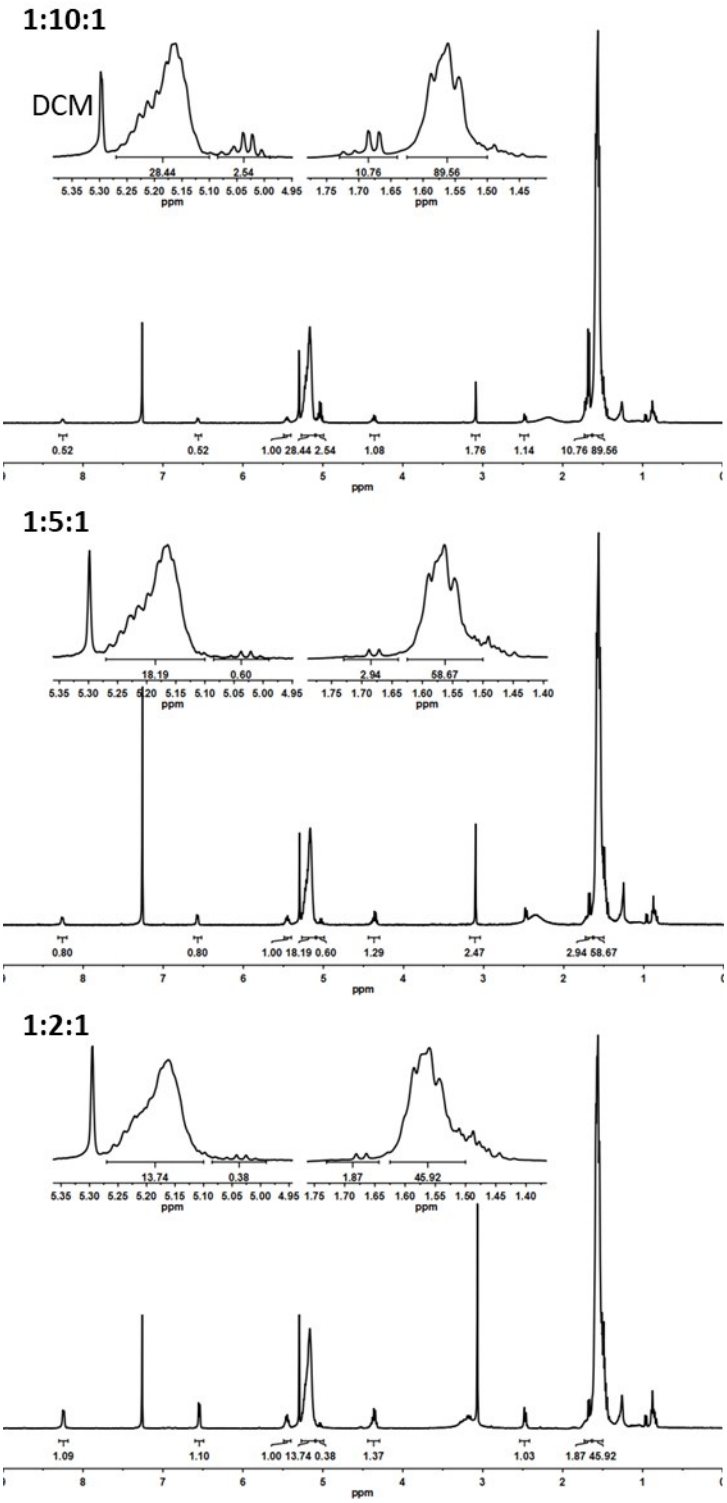


Figure S13.

^{1}H-NMR for polymerizations of 1:10:1, 1:5:1, and 1:2:1 α-methyl propargyl alcohol:lactide:4-dimethylaminopyridine (αMPA:L:DMAP) reacted for 5 minutes**.**

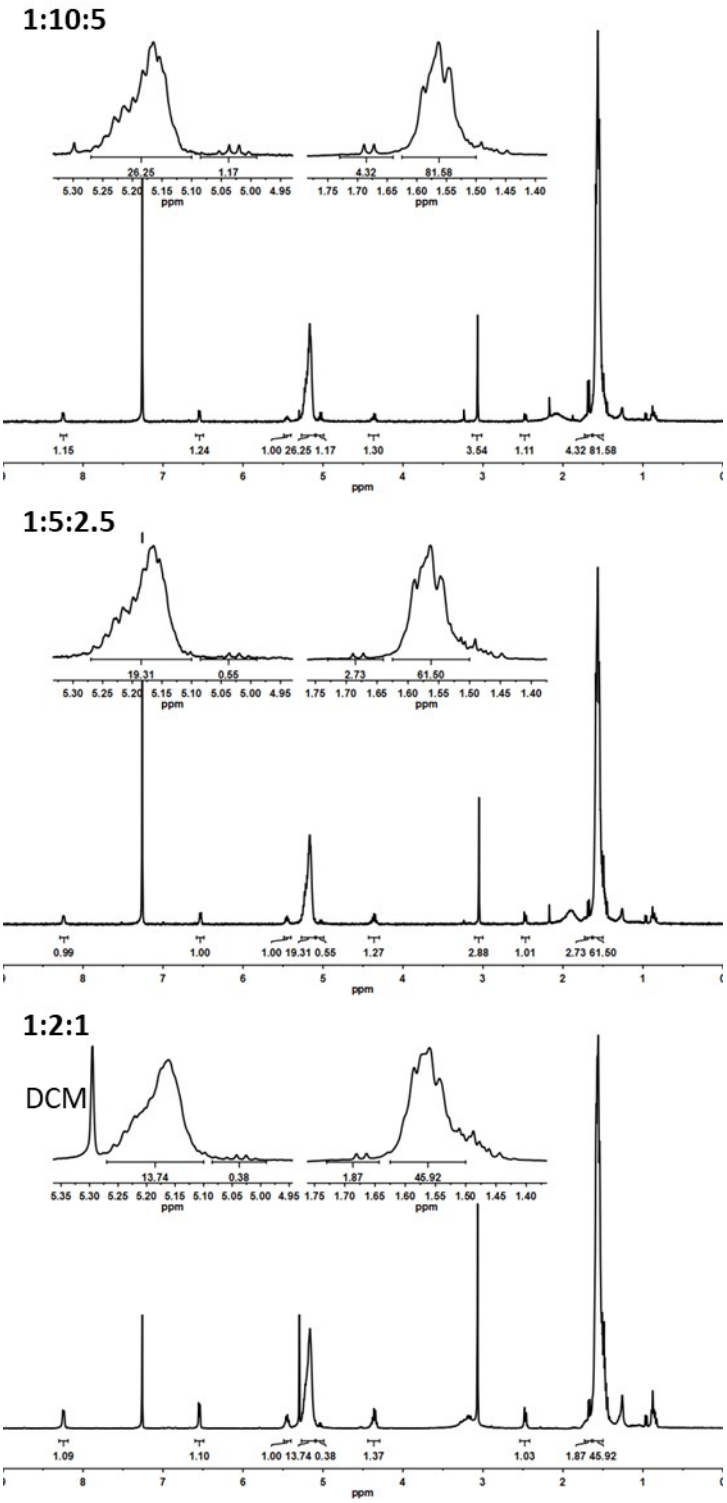


Figure S14.

^{1}H-NMR for polymerizations of 1:10:5, 1:5:2.5, and 1:2:1 α-methyl propargyl alcohol:lactide:4-dimethylaminopyridine (αMPA:L:DMAP) reacted for 5 minutes**.**

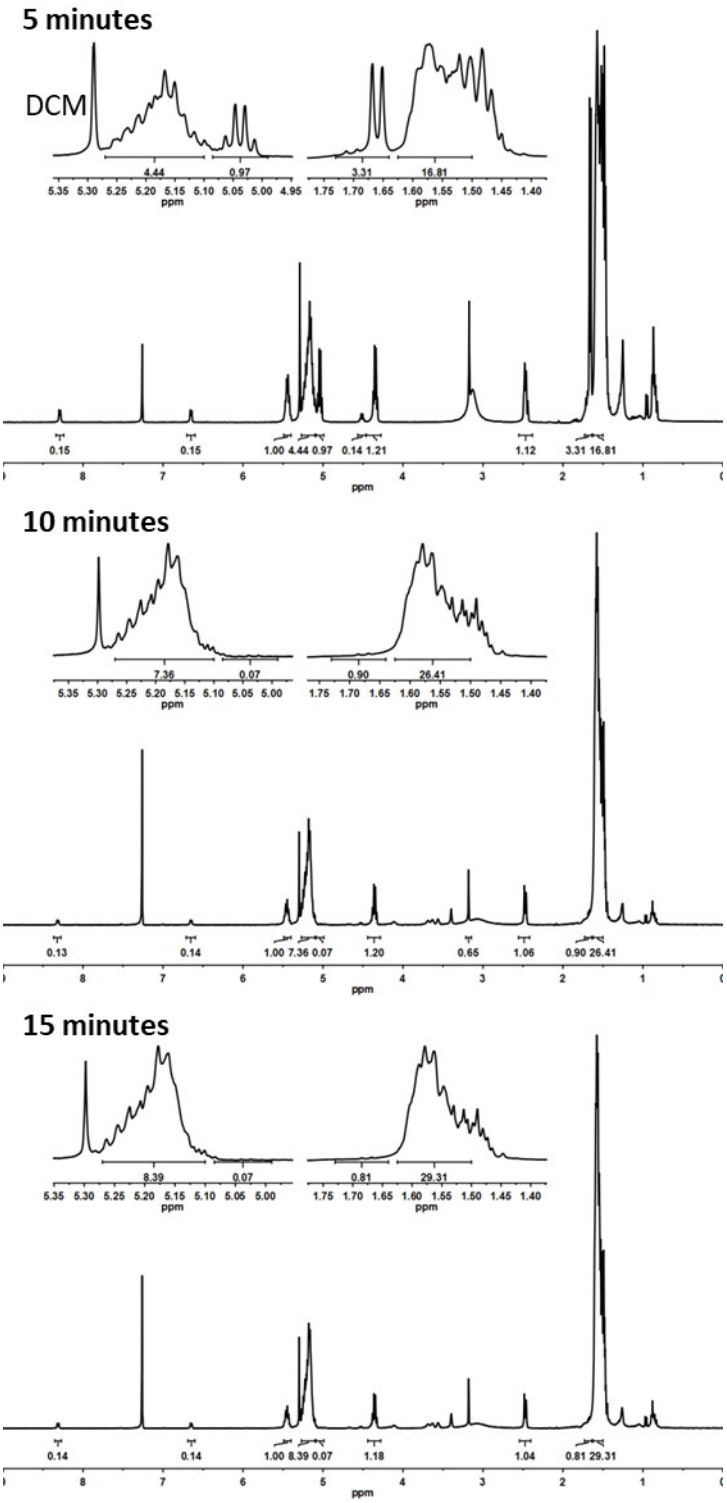


Figure S15.

^{1}H-NMR for polymerizations of 1:2:0.03 α-methyl propargyl alcohol:lactide:4-dimethylaminopyridine (αMPA:L:DMAP) reacted for 5, 10, and 15 minutes**.**

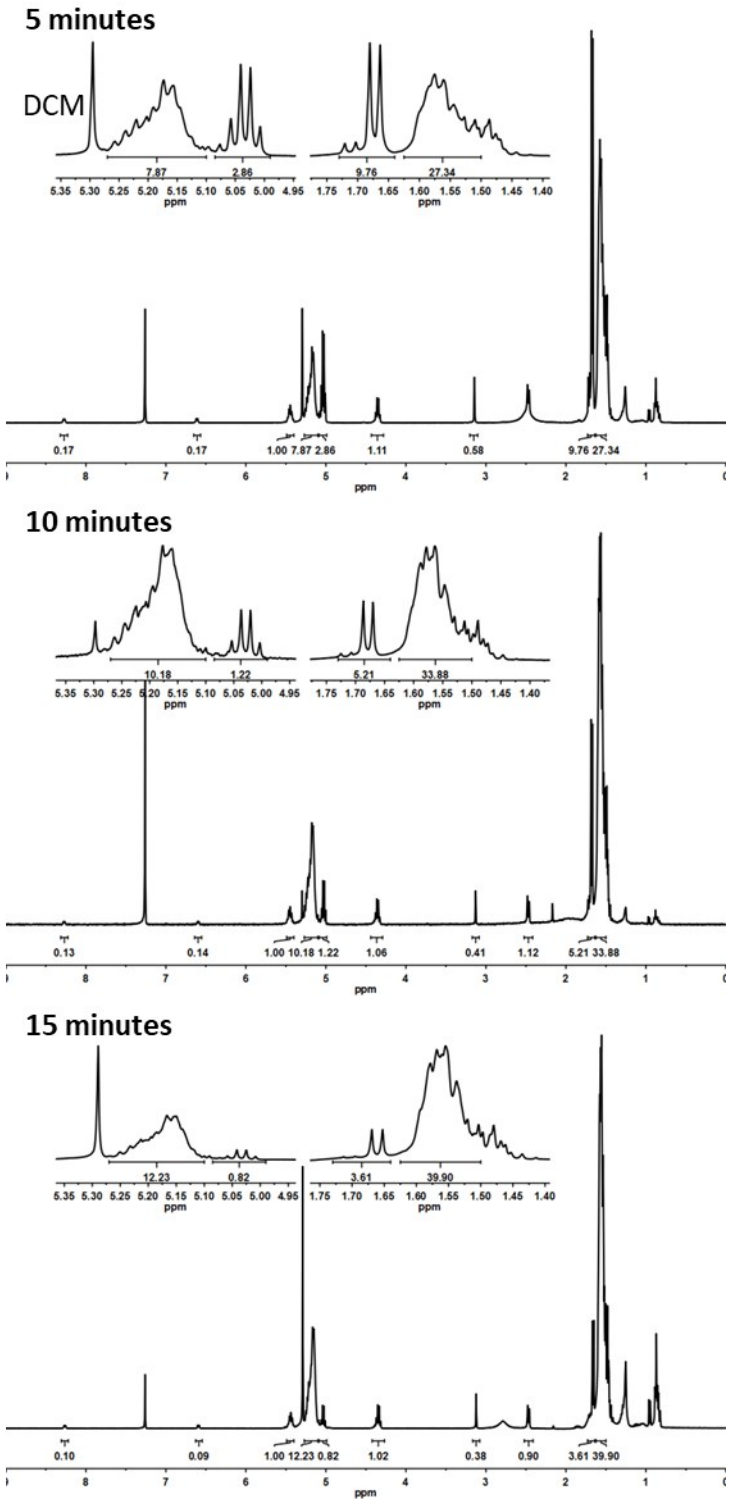


Figure S16.

^{1}H-NMR for polymerizations of 1:5:0.06 α-methyl propargyl alcohol:lactide:4-dimethylaminopyridine (αMPA:L:DMAP) reacted for 5, 10, and 15 minutes**.**

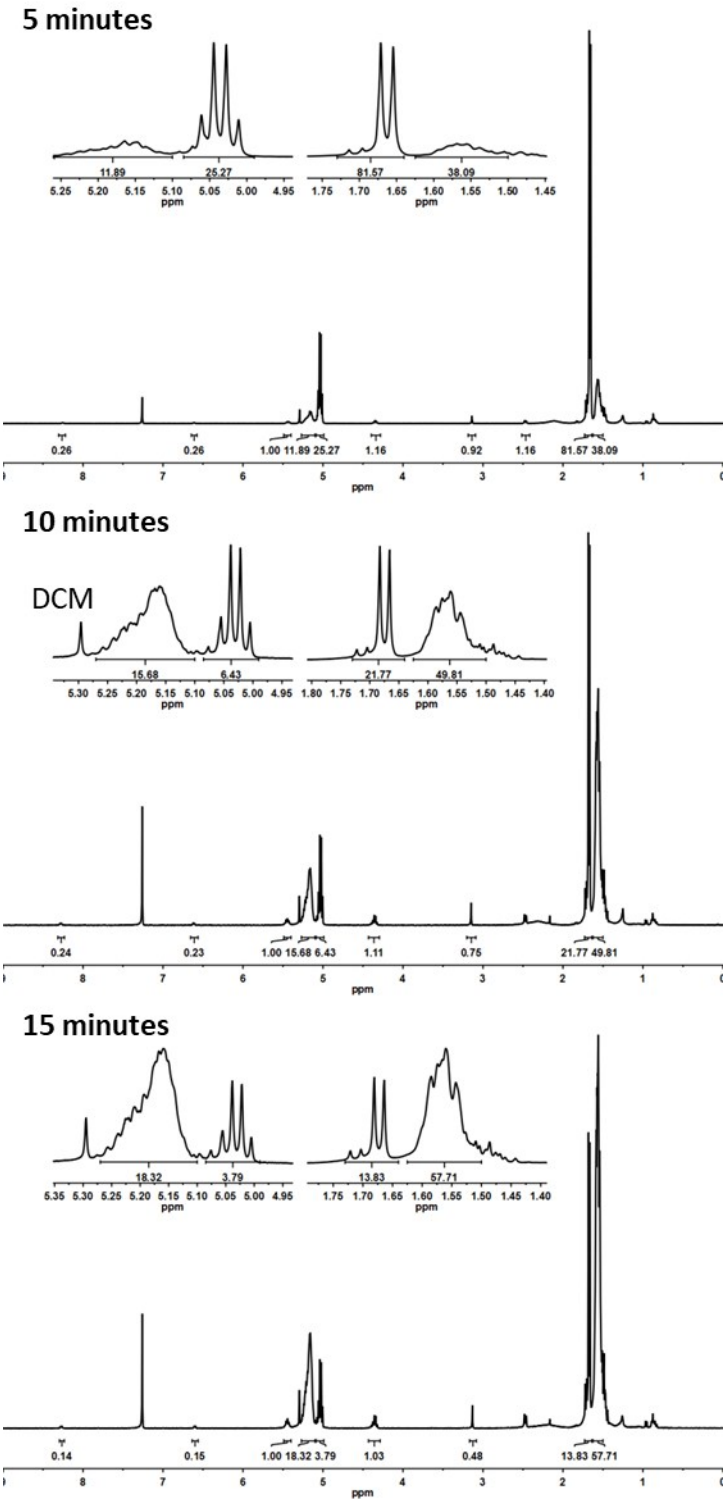


Figure S17.

^{1}H-NMR for polymerizations of 1:10:0.11 α-methyl propargyl alcohol:lactide:4-dimethylaminopyridine (αMPA:L:DMAP) reacted for 5, 10, and 15 minutes**.**

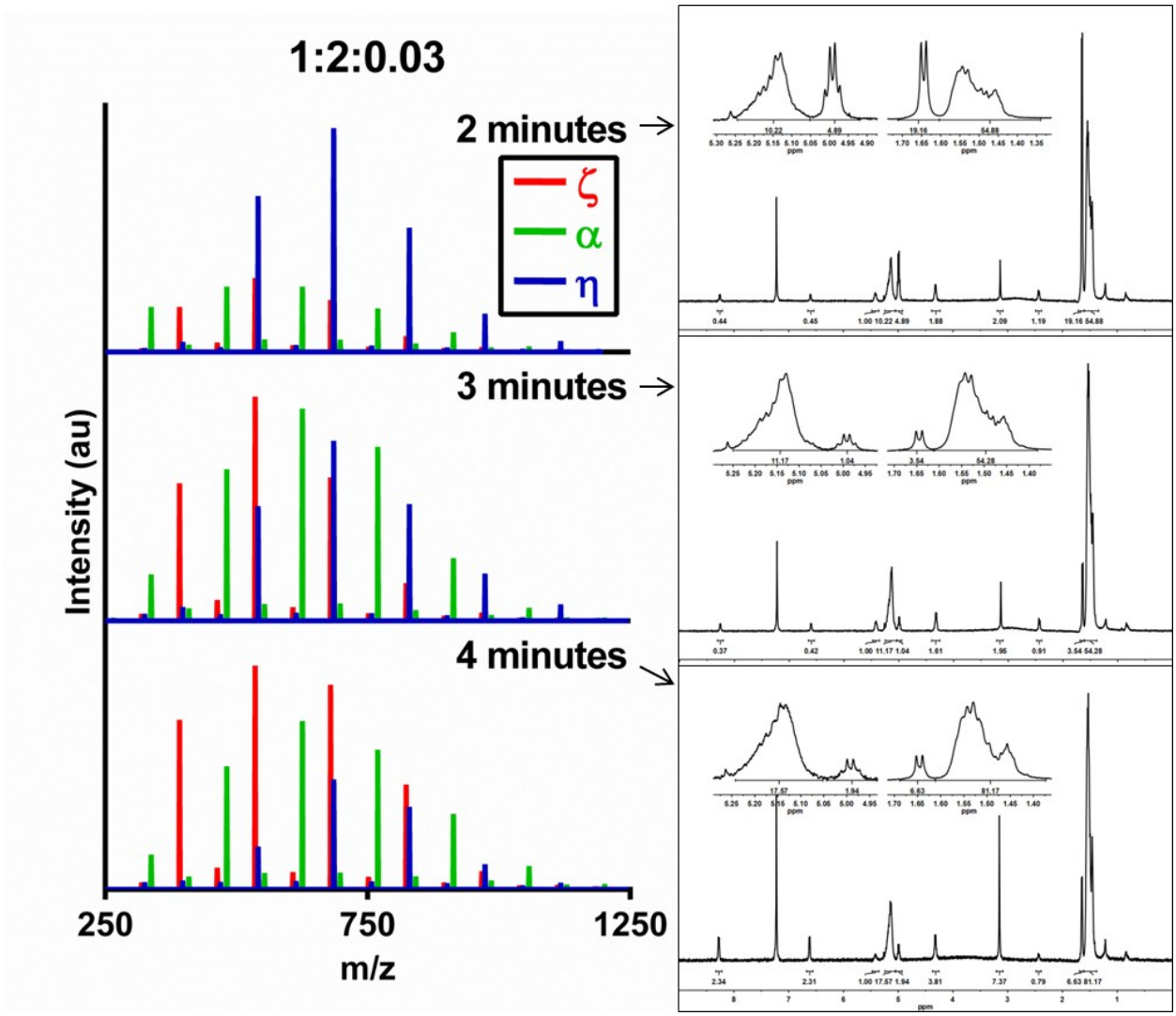


Figure S18.

MALDI-TOF and ^{1}H-NMR for polymerizations of 1:2:0.03 α-methyl propargyl alcohol:lactide:4-dimethylaminopyridine (αMPA:L:DMAP) reacted for 2, 3, and 4 minutes**.**

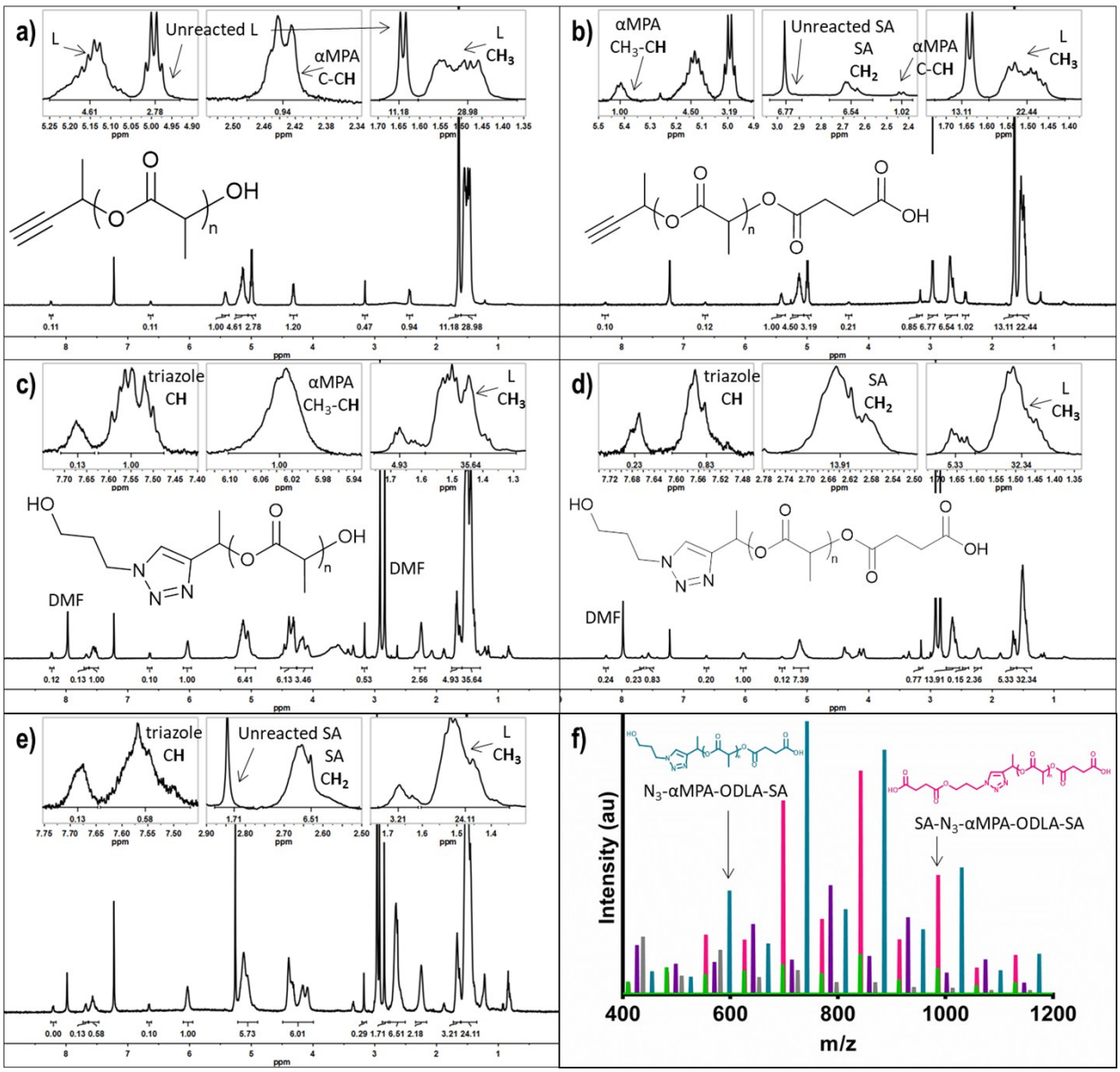


Figure S19.

^{1}H-NMR of proof of concept conjugations presented in Fig. 3 using (a) α-methyl propargyl alcohol-initiated oligo(D,L-lactide) (αMPA-ODLA) as a heterobifunctional linker. (b) αMPA-ODLA reacted with succinic anhydride (SA) to form αMPA-ODLA-SA. (c) 3-azido-1-propanol reacted with αMPA-ODLA to form N_3-αMPA-ODLA. (d) 3-azido-1-propanol reacted with αMPA-ODLA-SA to form N_3-αMPA-ODLA-SA. Note that SA-N_3-αMPA-ODLA-SA also forms. (e) SA reacted with N_3-αMPA-ODLA to form N_3-αMPA-ODLA-SA. Note that SA-N_3-αMPA-ODLA-SA also forms. (f) MALDI-TOF of (e).

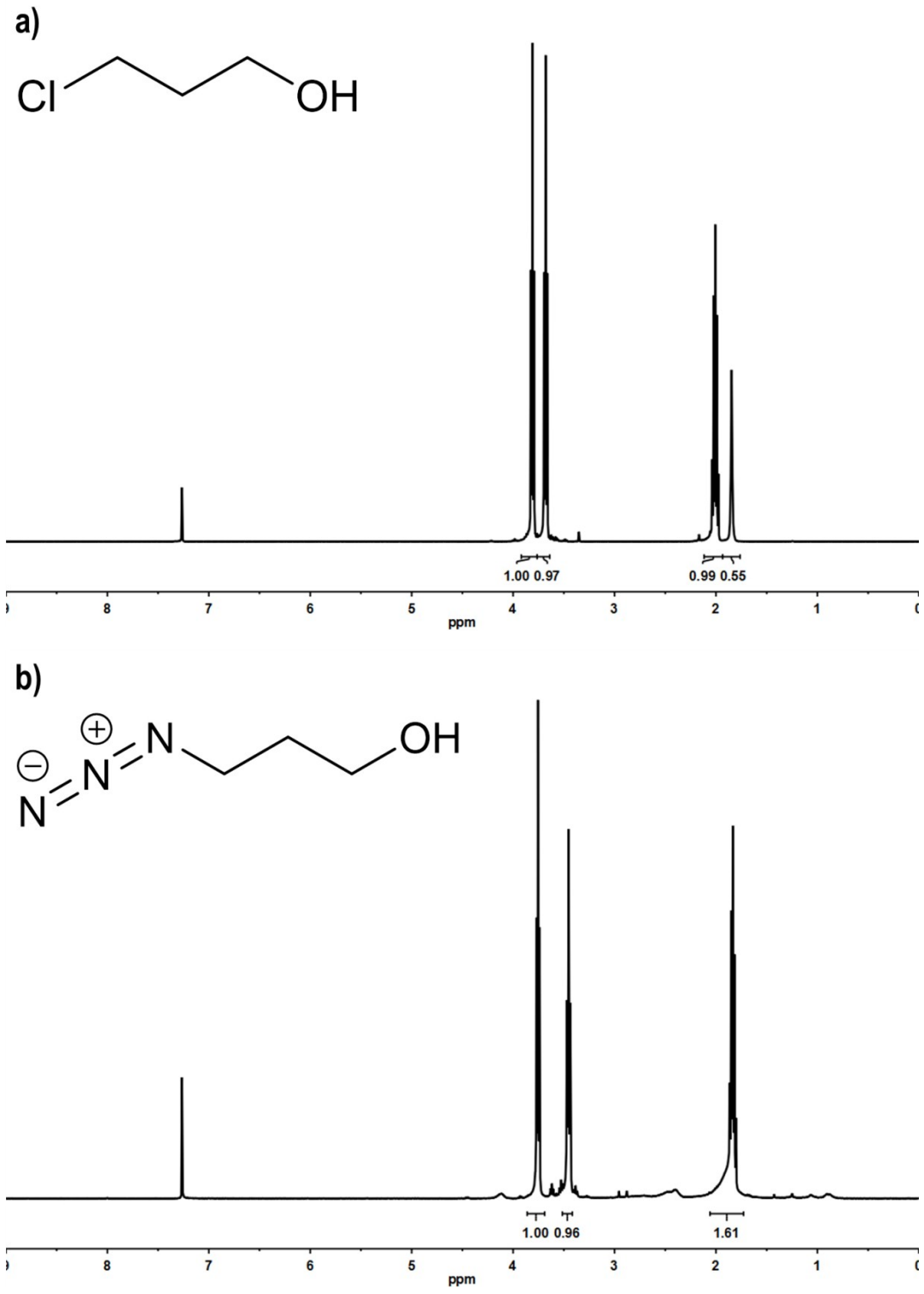


Figure S20.

^{1}H-NMR of 3-chloro-1-propanol precursor (a) and 3-azido-1-propanol product (b). Notice the ppm shifts of CH_2 peaks.