

Supporting Information

Post-Polymerization Modification of
Polymethacrylates Enabled by Keto-Enol
Tautomerization

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Materials

Vinyl chloroacetate (>98%, TCI), 2,2'-azobis(2,4-dimethyl-4-methoxy valeronitrile) (V-70, Wako), 2,6-di-tert-butyl-4-methyl-phenol (BHT, \geq 99%, Sigma-Aldrich) sodium iodide (Amresco), sodium hydroxide (Fischer Scientific), Aliquat® 336 (Alfa Aesar), methacrylic acid (99%, Sigma-Aldrich), benzyl alcohol (99%, Alfa Aesar), benzylamine (Eastman-Kodak), furfuryl alcohol (98%, Alfa Aesar), cinnamyl alcohol (98%, Sigma-Aldrich) were all used as received. Methyl methacrylate (MMA, 99%, Acros Organics) was passed through basic alumina to remove inhibitors and acidic impurities prior to polymerization. Dichloromethane (DCM, ACS, Fischer Scientific) and tetrahydrofuran (THF, ACS, Fischer Scientific) were dried using a solvent purification system prior to use. 4-cyano-4-[(dodecylsulfanylthiocarbonyl)sulfanyl] pentanoic acid (CDTPA) and 4-(cyanopentanoic acid) dithiobenzoate (CPDB) were synthesized according to previous literature.¹

Instrumentation

Nuclear Magnetic Resonance (NMR) Spectroscopy. ¹H NMR spectra were recorded on a Varian Innova2 500 MHz NMR spectrometer using the residual solvent signal as a reference.

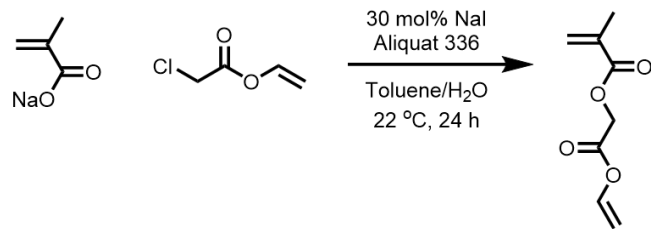
Gel Permeation Chromatography (GPC). Molecular weights and molecular weight distributions were determined *via* multi-angle laser light scattering size exclusion chromatography (MALS-SEC) in *N,N*-dimethylacetamide (DMAc) with 50 mM LiCl at 50 °C and a flow rate of 1.0 mL/min (Agilent isocratic pump, degasser, and autosampler; ViscoGel I-series 10 μ m guard column and two ViscoGel I-series G3078 mixed bed columns, with molecular weight ranges 0–20 \times 10³ and 0–10 \times 10⁶ g/mol, respectively). Detection consisted of a Wyatt Optilab T-rEX refractive index detector operating at 658 nm and a Wyatt miniDAWN Treos light scattering detector operating at 659 nm. Absolute molecular weights and polydispersities were calculated using Wyatt ASTRA software.

Procedures

Synthesis of sodium methacrylate

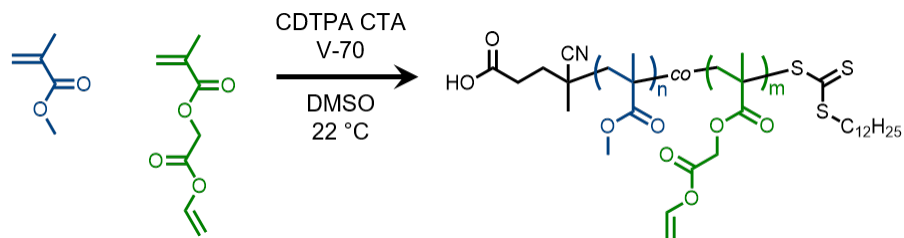
Sodium hydroxide (16.7 g, 419 mmol) was added to 175 mL of deionized water in a 250 mL round bottom flask prior to dropwise addition of methacrylic acid (30.0 g, 349 mmol). The reaction was carried out under constant stirring for 3 h at room temperature. The aqueous solution was then lyophilized to obtain the final product as a white solid (35.6 g, 94% yield).

Synthesis of vinyl methacryloxy acetate (VMAc)



Sodium methacrylate (10.0 g, 92.6 mmol) and sodium iodide (2.80 g, 18.5 mmol) were dissolved in 30 mL of deionized water and then transferred to a 250 mL round bottom flask. Vinyl chloroacetate (7.44 g, 61.6 mmol) and Aliquat 336 (2.50 g, 6.16 mmol) were then dissolved in 70 mL of toluene and transferred to the round bottom flask containing the aqueous solution of sodium methacrylate and sodium iodide. The flask was then covered with aluminum foil, and the reaction was allowed to proceed for 24 h under vigorous stirring. After 24 h, the reaction mixture was transferred to a 125 mL separatory funnel in order to isolate the organic layer. The organic layer was dried with anhydrous MgSO₄ prior to concentrating by rotary evaporation. Upon removal of toluene, a crude orange liquid was obtained. The product was isolated using column chromatography (Hexanes:EtOAc = 9:1) to afford the final product as an off-yellow clear liquid (5.64 g, 54% yield, R_f = 0.28). ¹H NMR (500 MHz, CDCl₃) δ 7.28 (dd, *J* = 13.9, 6.2 Hz, 1H), 6.25 (s, 1H), 5.69 (s, 1H), 4.97 (d, *J* = 13.9 Hz, 1H), 4.77 (s, 2H), 4.67 (d, *J* = 6.2 Hz, 1H), 2.00 (s, 3H). ¹³C NMR (125 MHz, CDCl₃): δ 166.6, 165.2, 140.6, 135.3, 127.2, 99.1, 60.5, and 18.3.

RAFT copolymerization of MMA and VMAc



Methyl methacrylate (177 mg, 1.76 mmol), VMAc (300 mg, 1.76 mmol), and 4-cyano-4-[(dodecylsulfanylthiocarbonyl)sulfanyl] pentanoic acid (CDTPA, 14 mg, 3.53×10^{-2} mmol) were dissolved in 1.4 mL of DMSO and transferred to a 10 mL schlenk flask. The solution was allowed to purge under argon for 20 min prior to freezing at -78 °C in an acetone / dry ice mixture for 15 min. V-70 (5.4 mg, 1.76×10^{-2} mmol) was then added to the reaction flask, and the headspace was then purged with argon for an additional 20 min prior to thawing the reaction solution. Once thawed, the reaction was sonicated for 1 minute in order to further dissolve V-70. After sonication, the reaction proceeded at room temperature (22 °C) for 17 h. The polymerization was quenched by vitrifying the reaction at -78 °C in an acetone / dry ice mixture and then adding 2,6-di-tert-butyl-4-methyl-phenol (BHT, 3.9 mg, 1.76×10^{-2} mmol). After purging the frozen reaction mixture for 20 min, the solution was thawed and allowed to continue stirring for 6 h prior to opening the flask to air. The polymer was then purified by dialysis (Spectra/Por 3.5 kD MWCO) against acetone. NOTE: excessive dialysis (10×500 mL acetone) was needed to quantitatively remove BHT from the synthesized copolymers.

General procedure for organocatalyzed transesterification reactions

Previously synthesized PMMA-*co*-PVMAc (1.0 equiv enol esters), nucleophile (1.5 equiv), and triazabicyclodecene (10 mol%) were added to a 1 mL vial and dissolved at a polymer concentration of 50 mg/mL. The reaction solution was then placed on a shake plate at room temperature and allowed to react for 16 h unless otherwise noted. After the reaction, the solution was diluted with dichloromethane (50 mL). TBD was then removed by washing the organic layer with acidic brine (5 x 50 mL). The organic layer was then dried with anhydrous magnesium sulfate prior to removal of dichloromethane using rotary evaporation, followed by further drying under reduced pressure. The polymer was then purified by dialysis (Spectra/Por 3.5 kD MWCO) against acetone.

Supplemental Figures

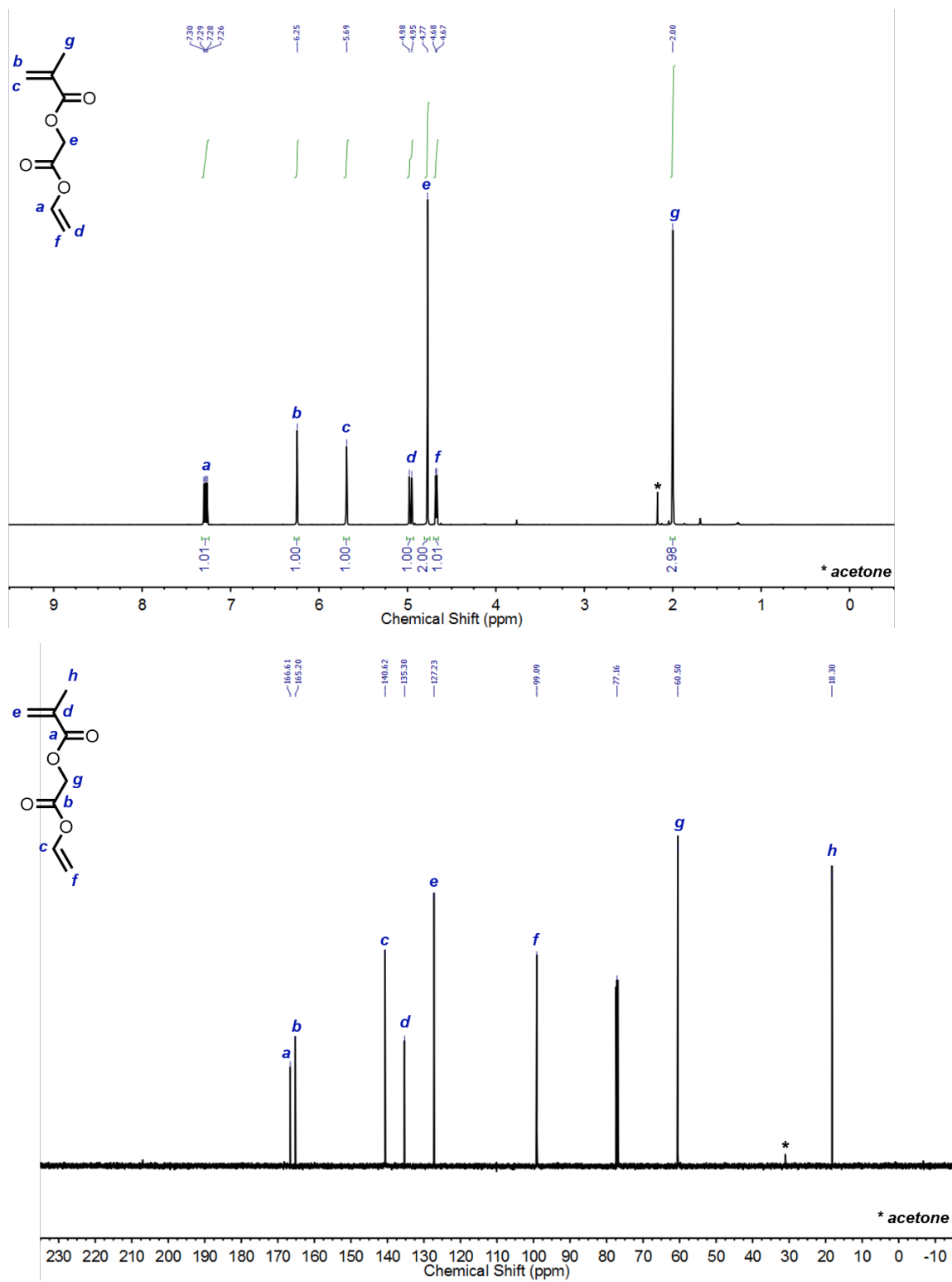


Figure S1. ¹H and ¹³C NMR spectra of vinyl methacryloxy acetate (VMAc) in CDCl₃ at 25 °C.

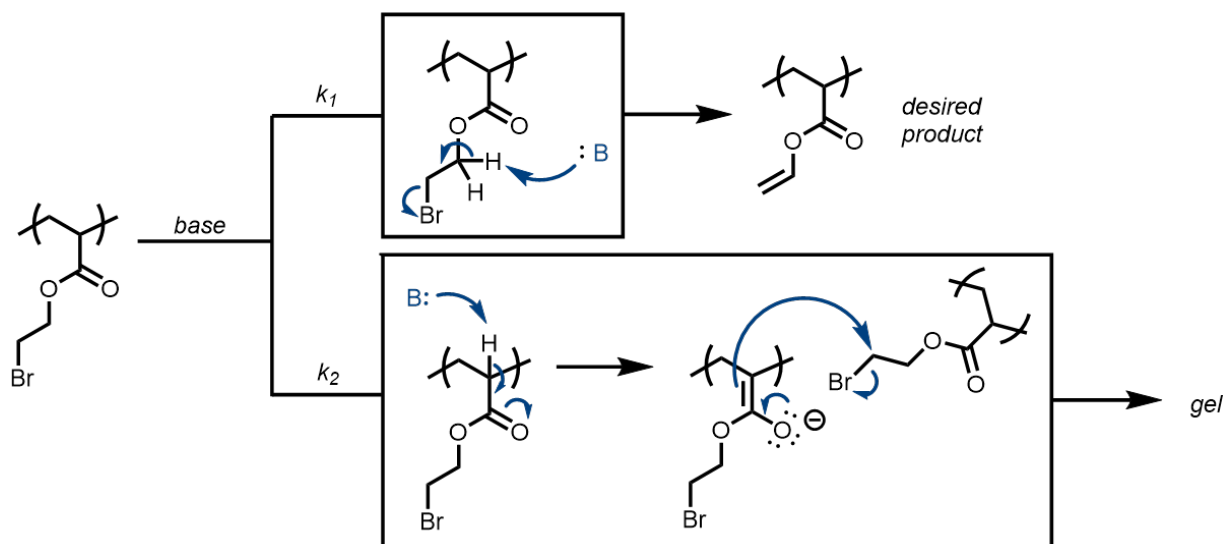


Figure S2. Proposed mechanism of PBEA gelation.

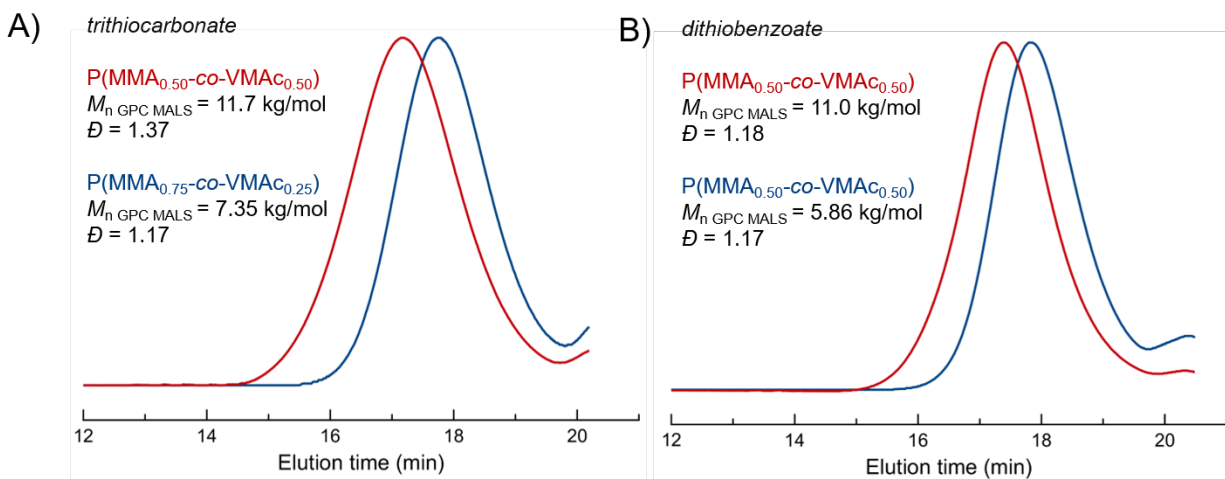
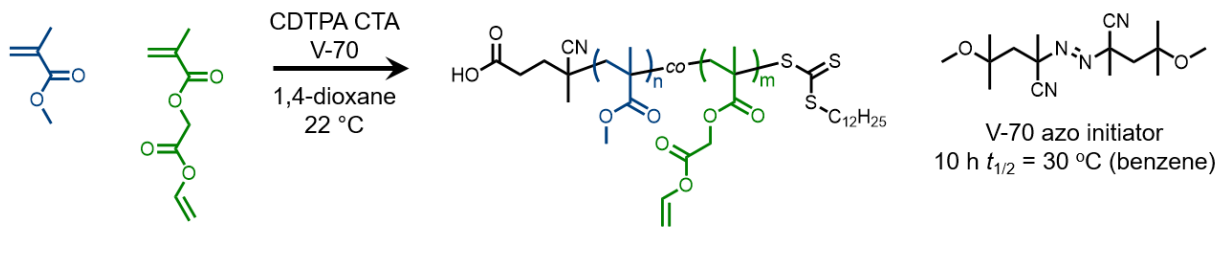


Figure S3. GPC chromatograms of copolymers using (A) trithiocarbonate and (B) dithiobenzoate chain transfer agent.



Conditions:

[MMA]:[VMAc]:[CTA]:[V-70] = 50:50:1:0.20

[MMA+VMAc]₀ = 2.5 M

blue trace – t_f : 16 h, 25% conv.

red trace – quenched : 1 h

open to air diluted with acetone (15 mL)
 chilled on ice

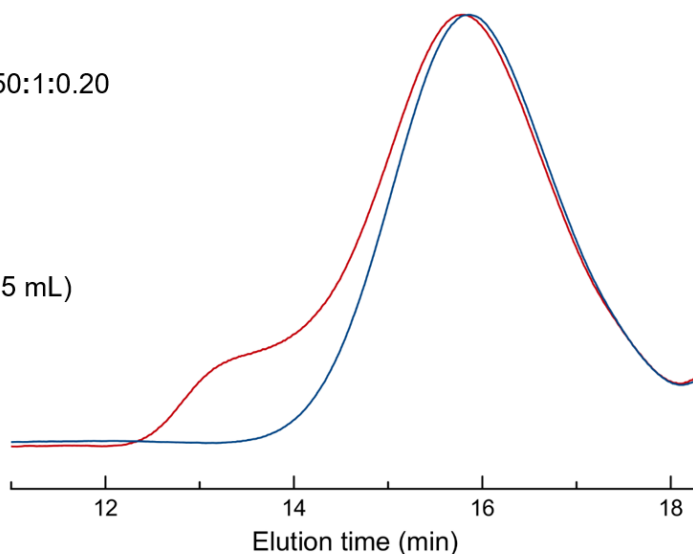


Figure S4. GPC chromatogram of RAFT copolymerization of MMA and VMAc quenched upon exposure to atmospheric oxygen.

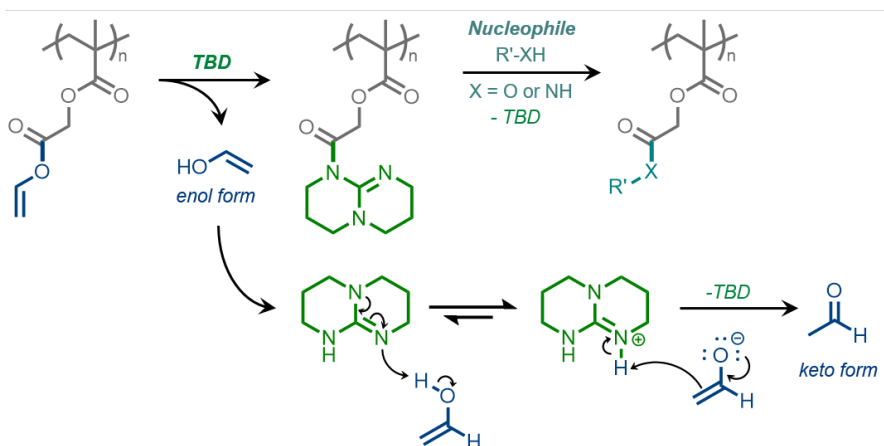


Figure S5. General mechanism of TBD-catalyzed acyl substitution of enol ester side chains.

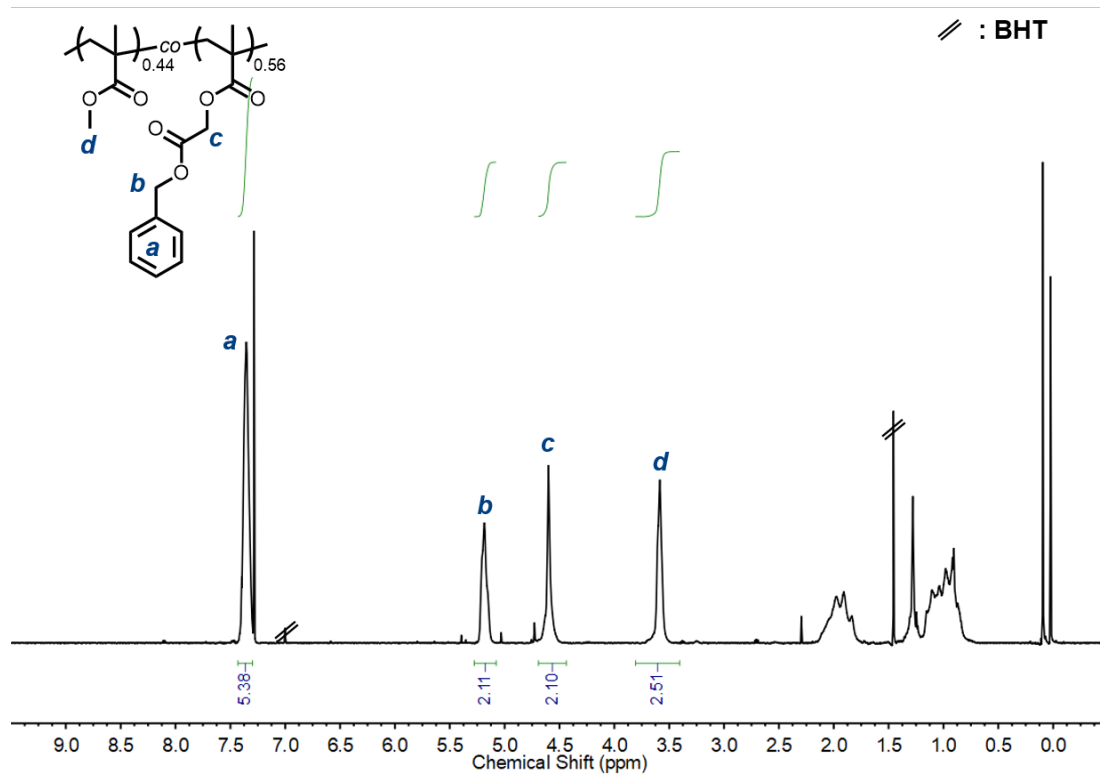
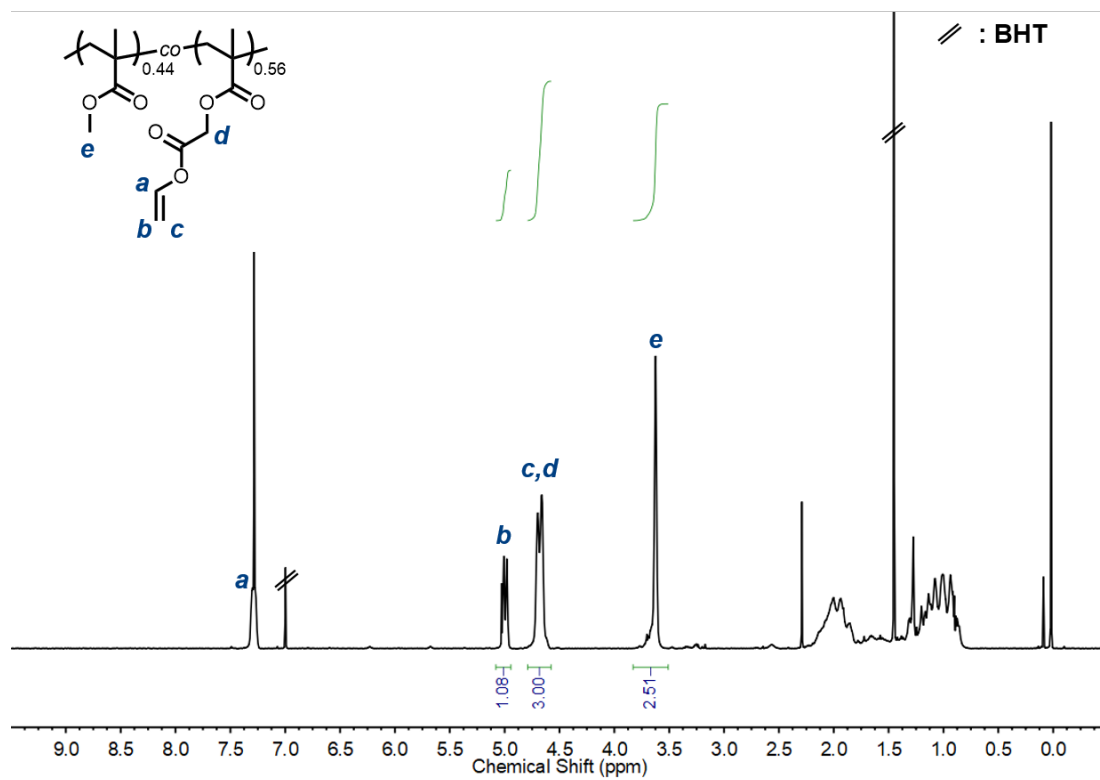


Figure S6. ^1H NMR spectra of P(MMA-co-VMAc) and transesterification products with benzyl alcohol.

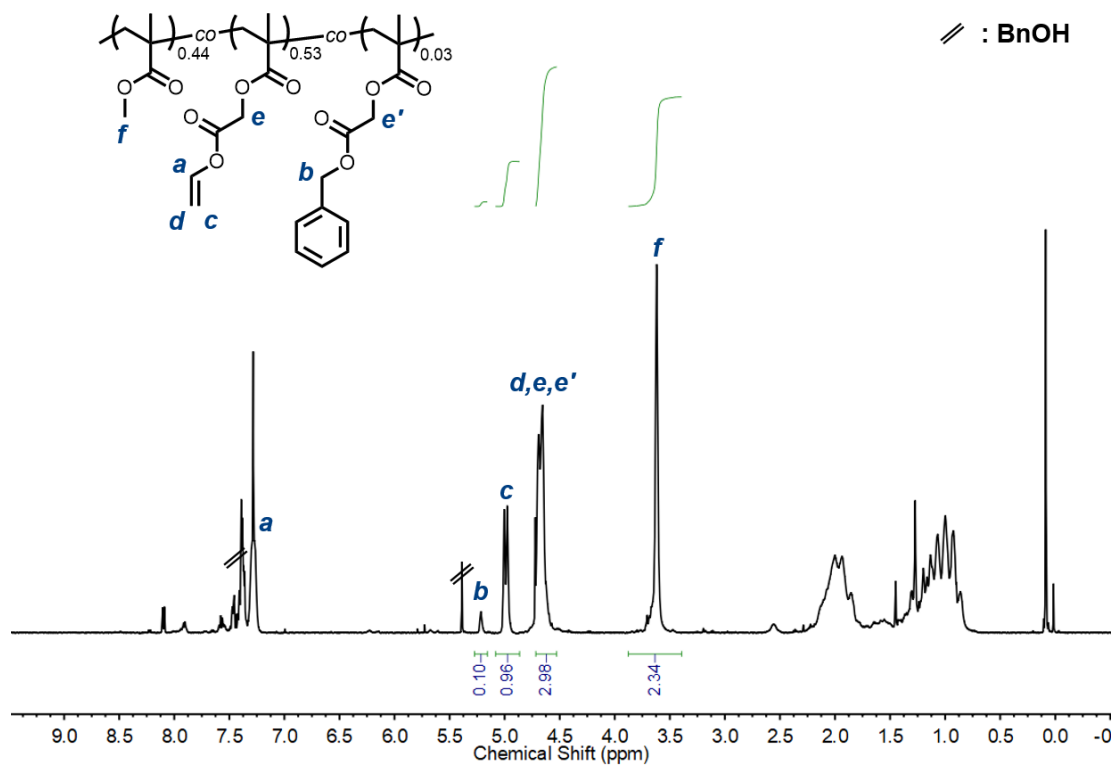
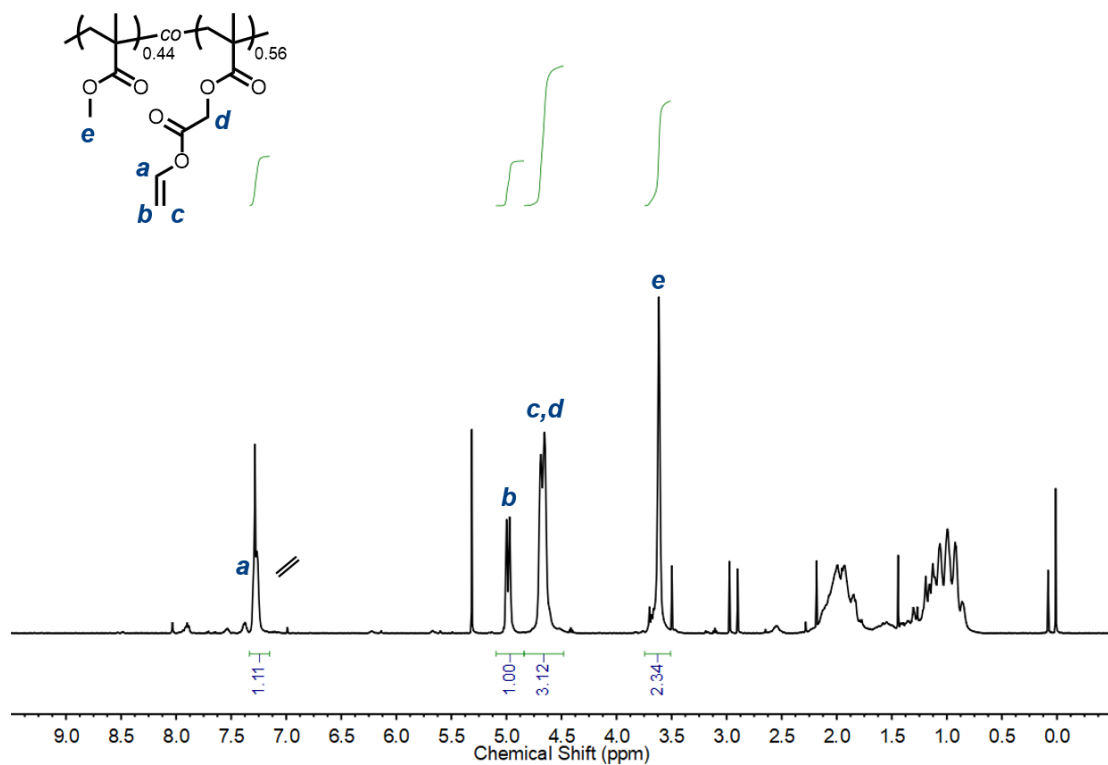


Figure S7. ¹H NMR spectra of P(MMA-co-VMAC) and transesterification products with benzyl alcohol in the absence of TBD.

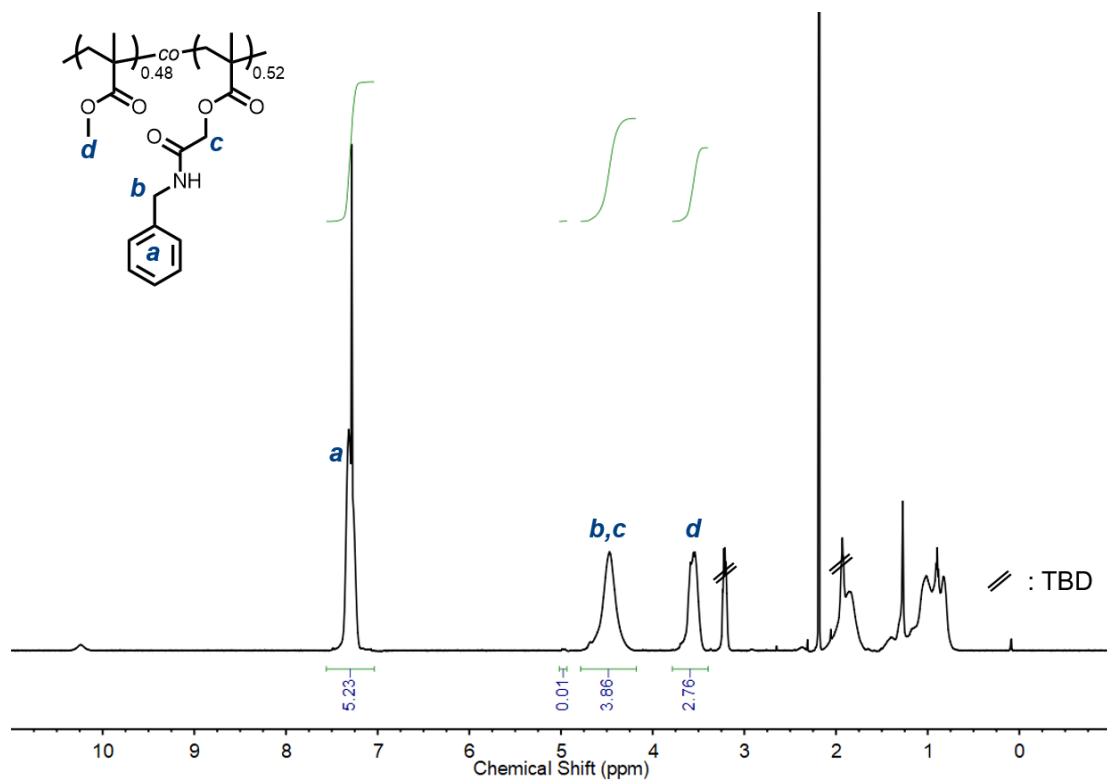
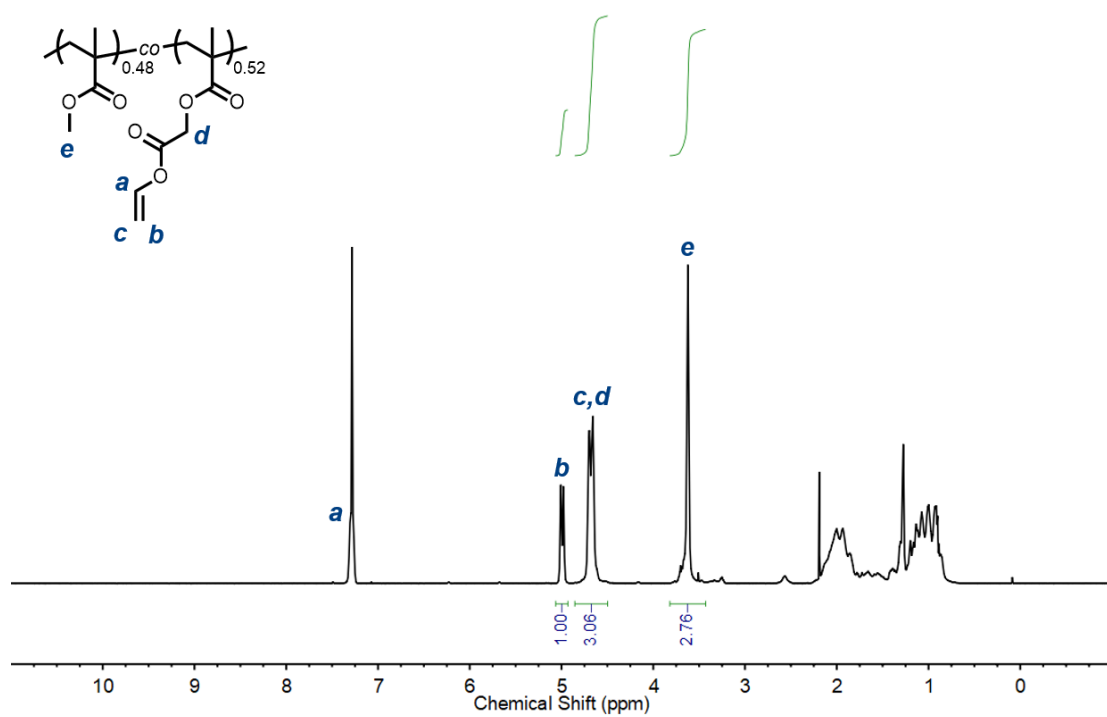


Figure S8. ¹H NMR spectra of P(MMA-co-VMAc) and amidation products with benzylamine.

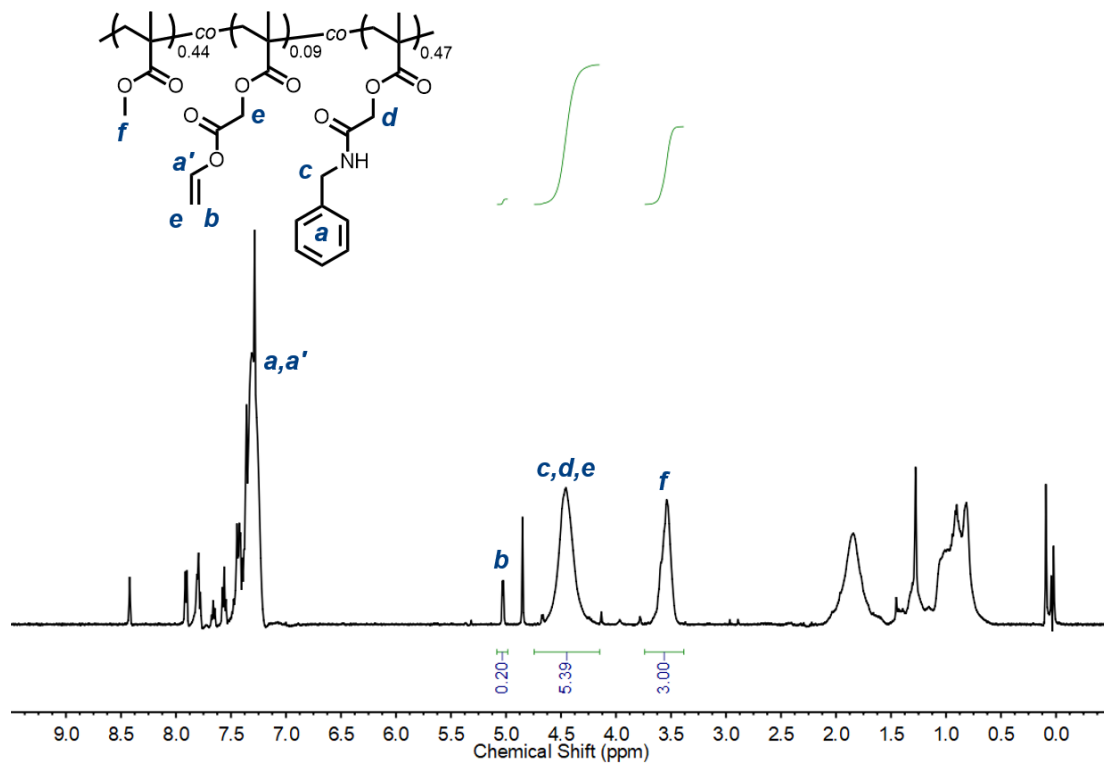
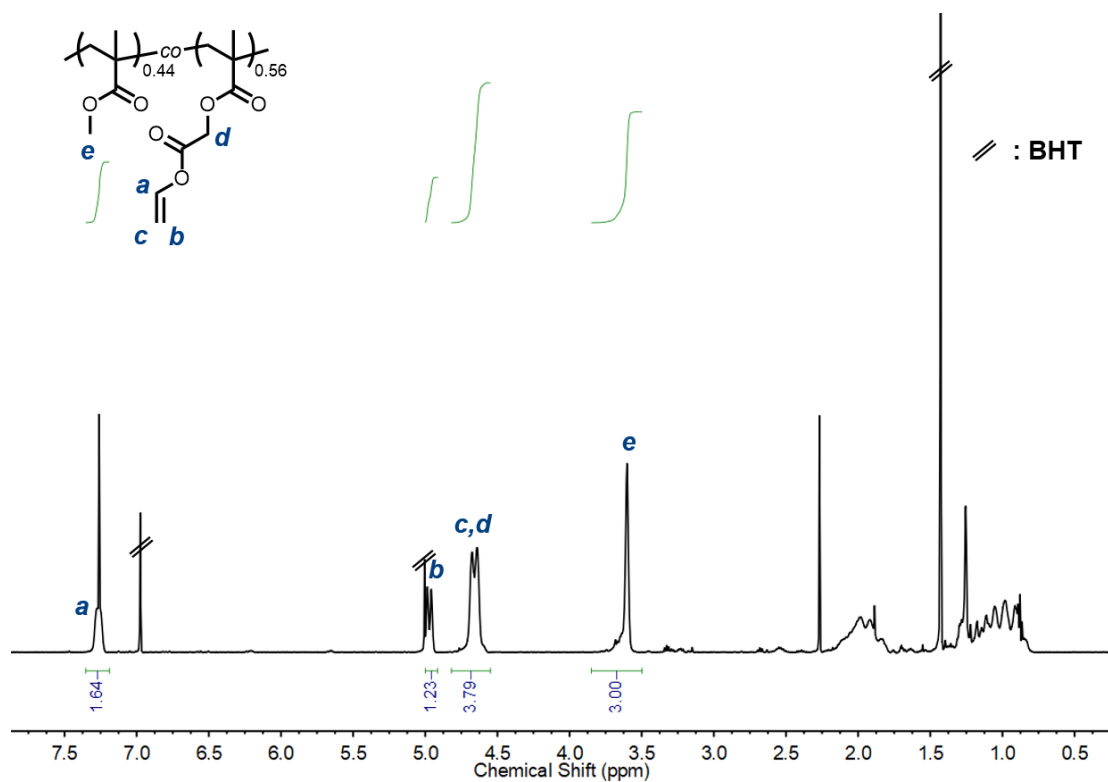


Figure S9. ¹H NMR spectra of P(MMA-co-VMAc) and amidation products with benzylamine in the absence of TBD.

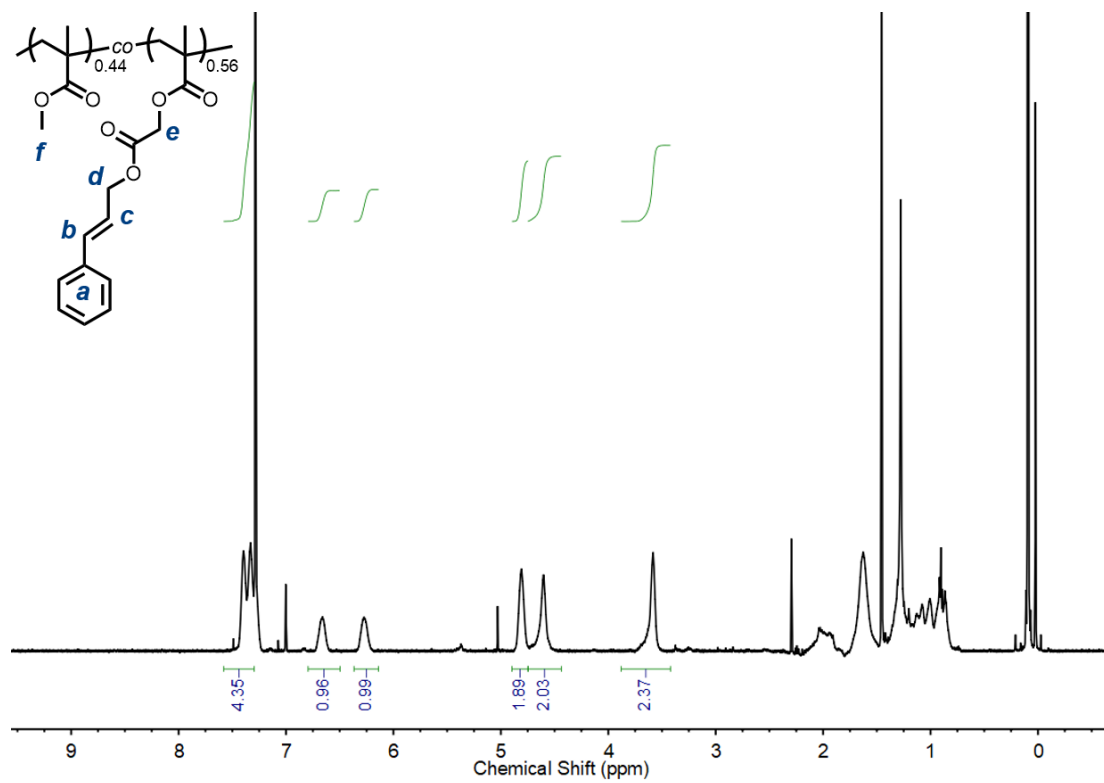
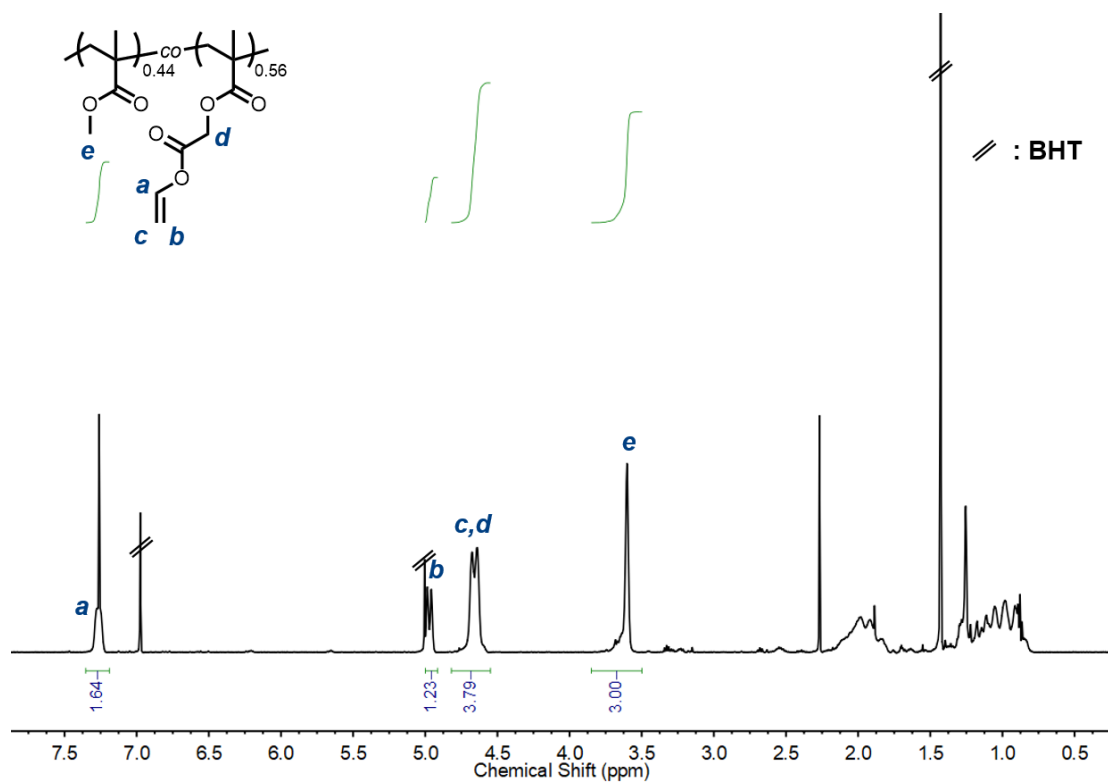


Figure S10. ^1H NMR spectra of P(MMA-co-VMAc) and transesterification products with cinnamyl alcohol.

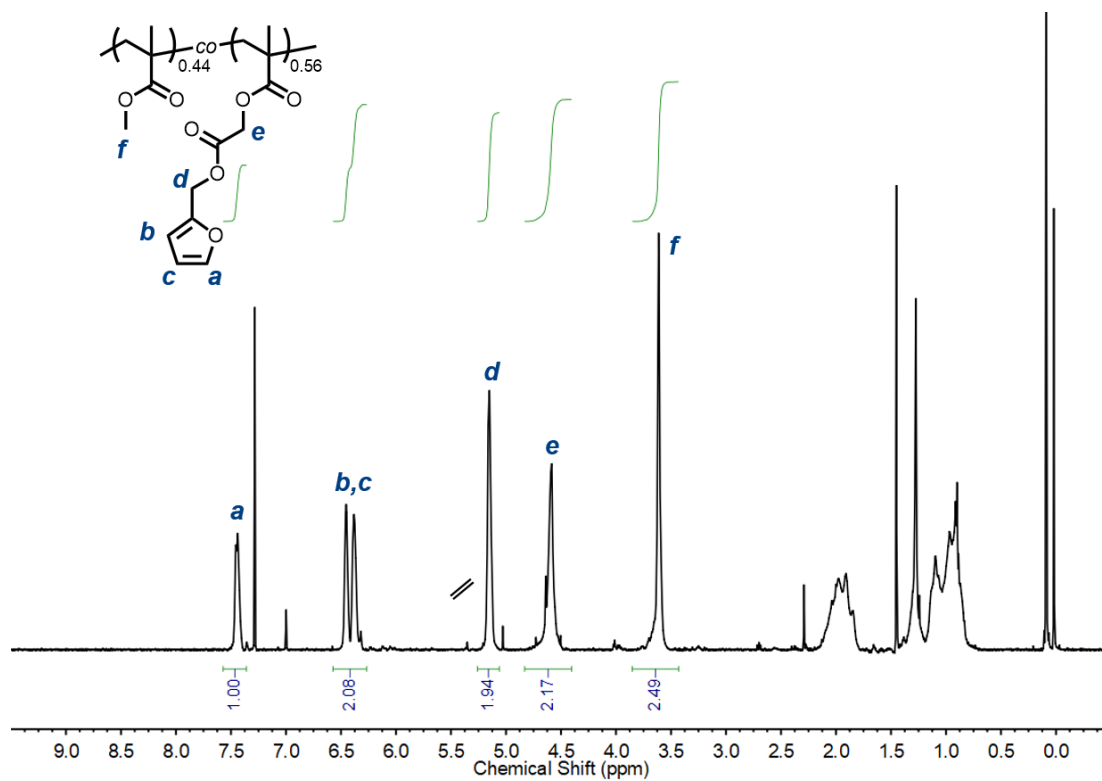
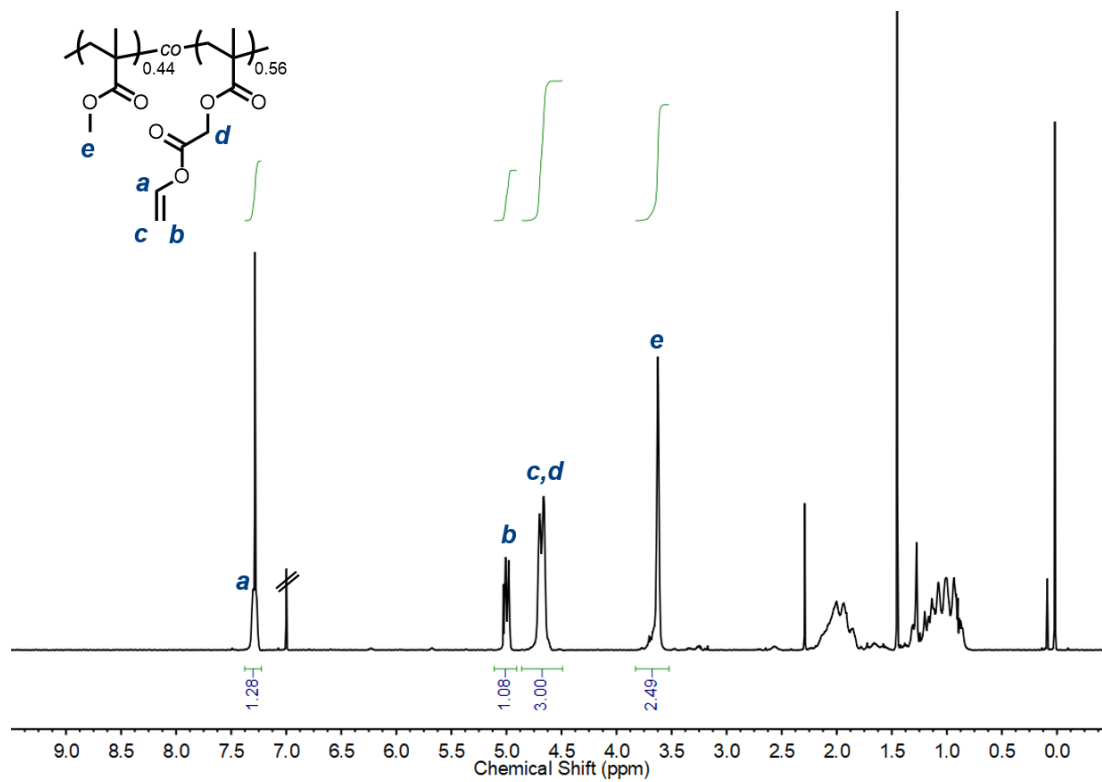


Figure S11. ¹H NMR spectra of P(MMA-co-VMAc) and transesterification products with furfuryl alcohol.

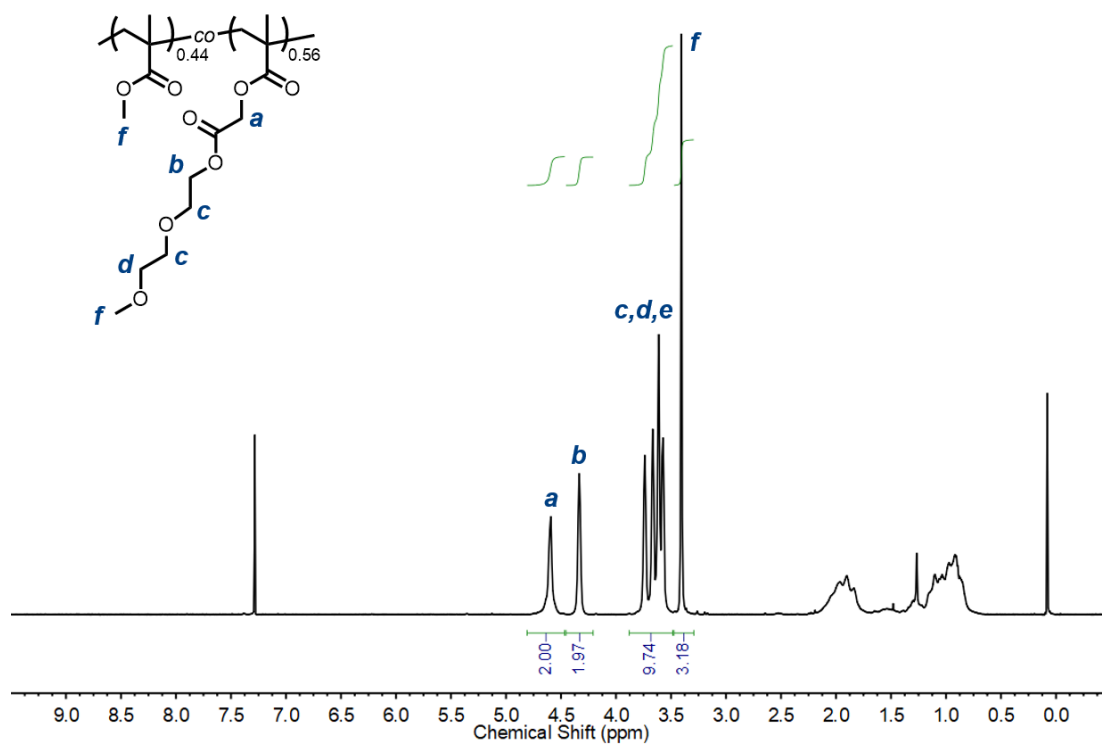
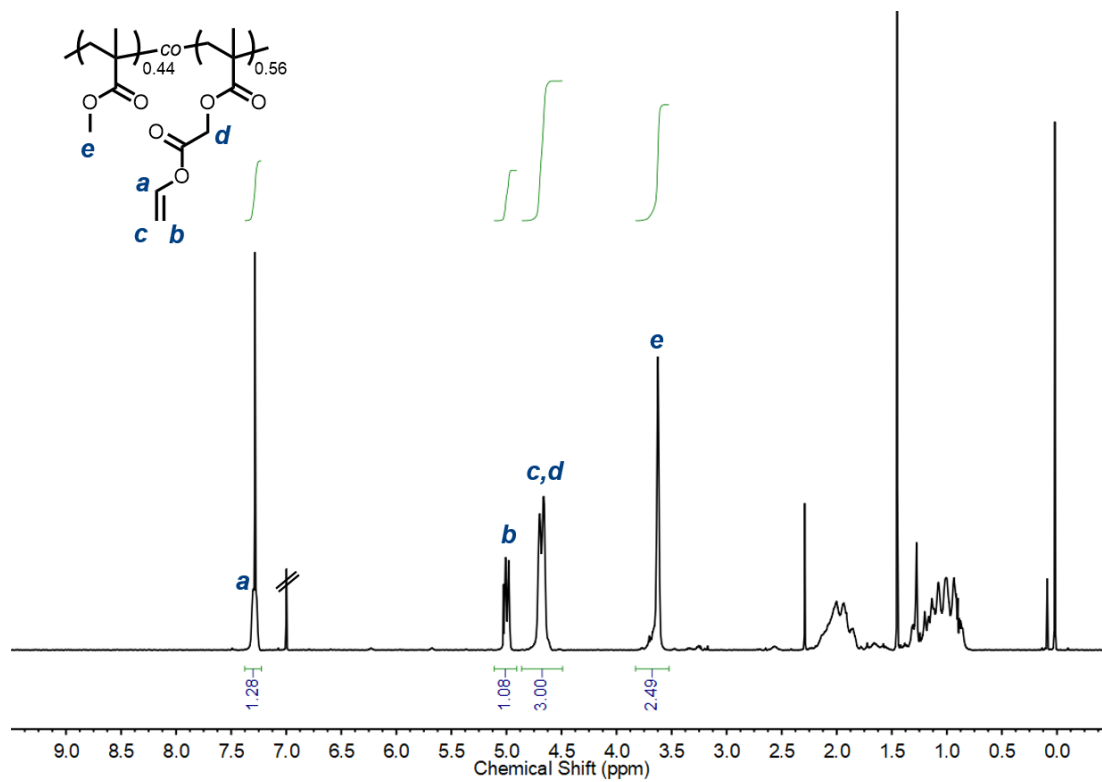


Figure S12. ¹H NMR spectra of P(MMA-co-VMAc) and transesterification products with diethylene glycol monomethyl ether.

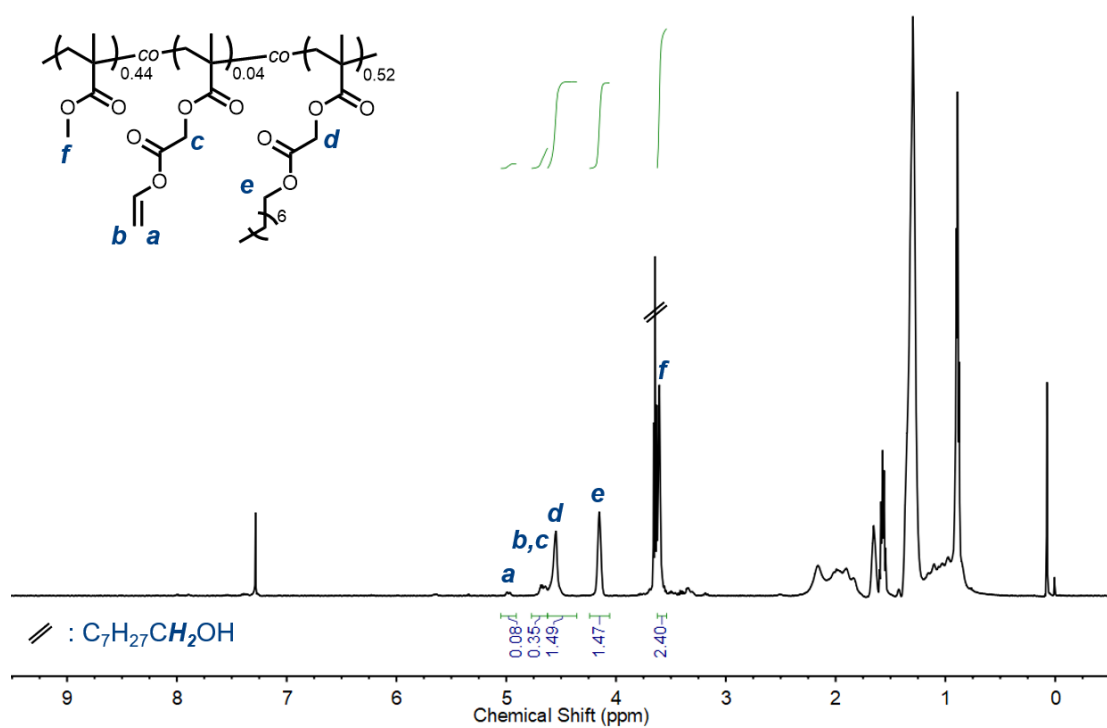
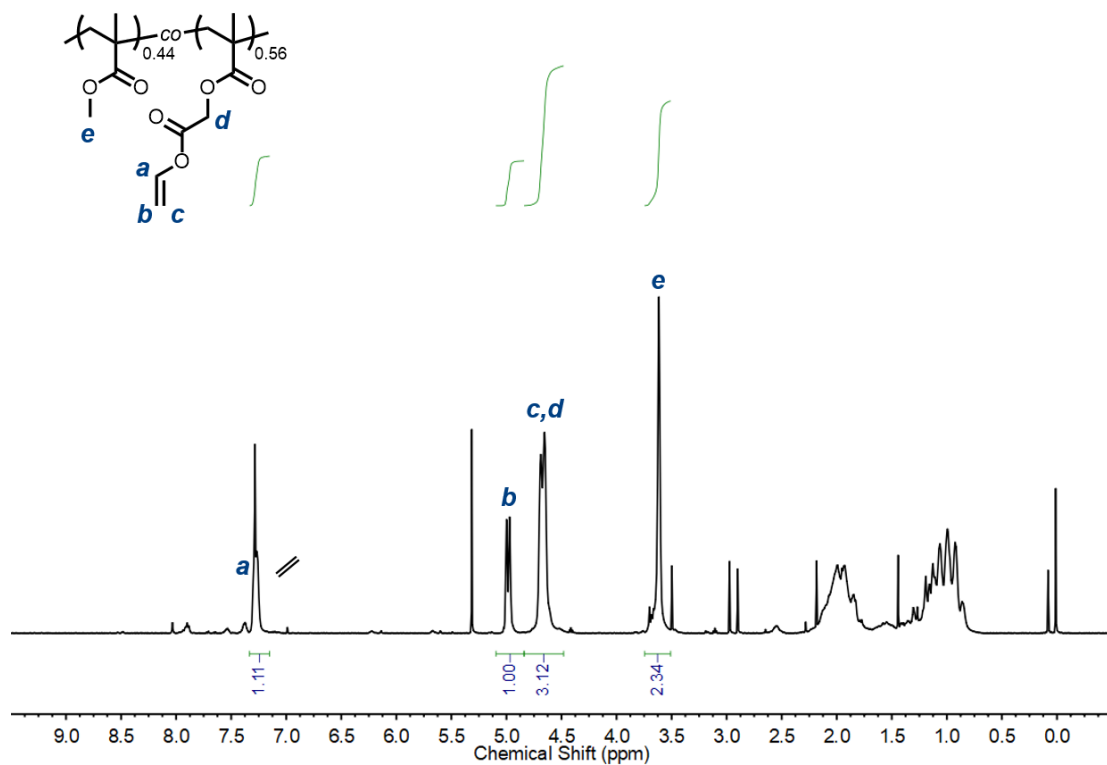


Figure S13. ^1H NMR spectra of P(MMA-co-VMAc) and transesterification products with octanol.

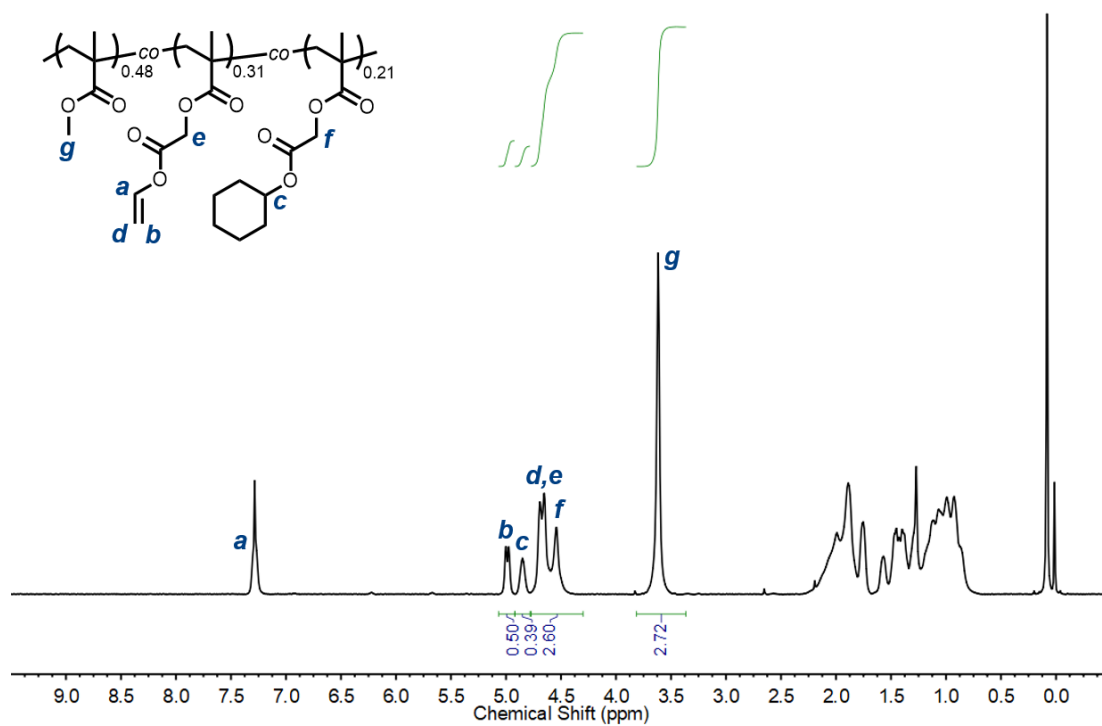
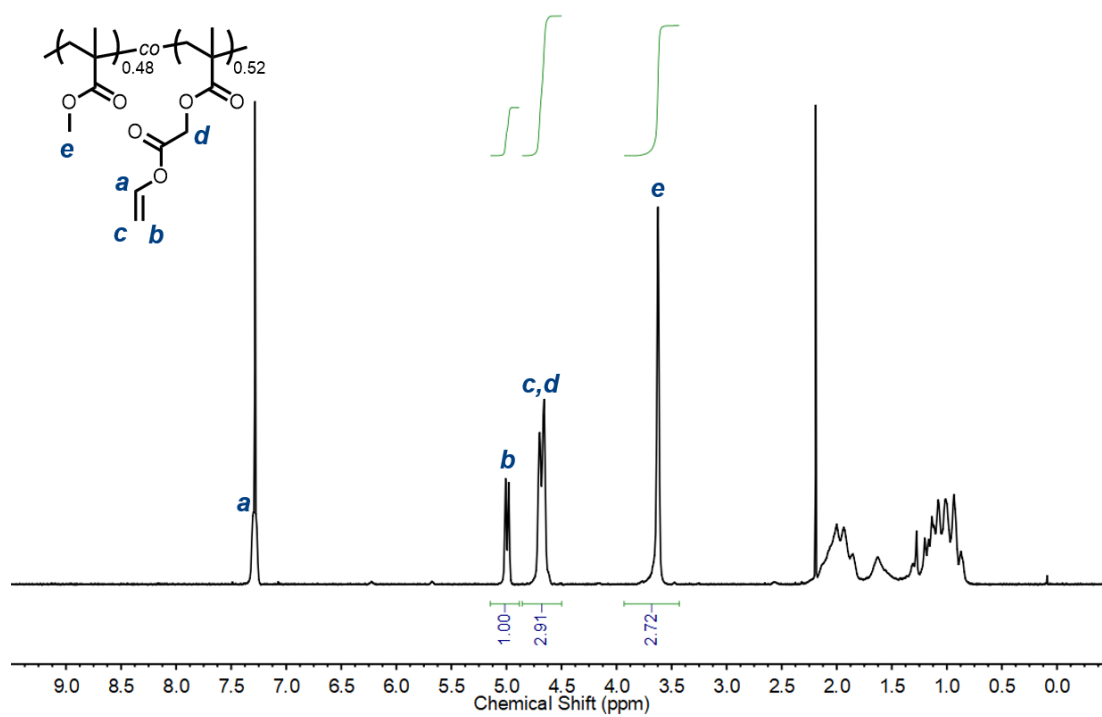


Figure 14. ^1H NMR spectra of P(MMA-*co*-VMAc) and transesterification products with cyclohexanol.

References

1. J. C. Foster, S. C. Radzinski, X. Zou, C. V. Finkielstein and J. B. Matson, *Mol. Pharm.*, 2017, **14**, 1300-1306.