Electronic Supplementary Material [1] for Polymer Chemistry

Aldehyde-Functional Polycarbonates as Reactive Platforms

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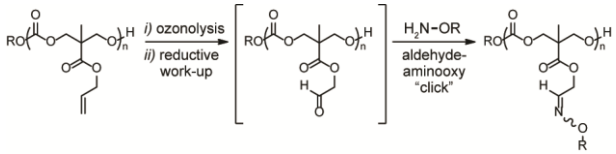
Graphical abstract



Experimental section

Materials. α-Hydroxy-ω-azido poly(ethylene glycol) 3,000 Da ($HO\text{-}PEG_{68}\text{-}N_3$) was purchased from Rapp Polymere, dried in a desiccator over P_2O_5 and stored under inert atmosphere. Benzyl alcohol and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) were dried over CaH_2, distilled, and stored under inert atmosphere. Tetrahydrofuran (THF), *N*,*N*-dimethylformamide (DMF), and dichloromethane (DCM) were purified by passage through solvent purification system (JC Meyer Solvent Systems) and used as dried solvents. The monomer, 5-methyl-5-allyloxycarbonyl-1,3-dioxan-2-one (MAC) was synthesized as reported[1], recrystallized several times before use, and dried over P_2O_5. All other solvents and chemicals were obtained from Sigma-Aldrich, TCI America, or Fisher Scientific and used as received.

Instruments. All polymerizations were preformed under inert atmosphere in a glovebox. ^1H and ^{13}C NMR spectra were recorded on Varian Mercury 300 spectrometers. Chemical shifts were referenced to the solvent resonance signals.

IR spectra were recorded on an IR Prestige 21 system (Shimadzu Corp., Japan), equipped with an ATR accessory, and analyzed using IRsolution v.1.40 software.

Gel permeation chromatography (GPC) eluted with THF was conducted on a system equipped with Waters chromatography, Inc. (Milford, MA) model 1515 isocratic pump and a model 2414 differential refractometer with a three-column set of Polymer Laboratories, Inc (Amherst, MA). Styragel columns (PL_{gel} 5 μm Mixed C, 500 Å, and 10^4 Å, 300 × 7.5 mm columns) and a guard column (PL_{gel} 5 μm, 50 × 7.5 mm). The system was equilibrated at 40 °C in THF, which served as the polymer solvent and eluent (flow rate set to 1.00 mL/min). The differential refractometer was calibrated with Polymer Laboratories, Inc., polystyrene standards (300–467,000 Da). Polymer solutions were prepared at a concentration of *ca*. 3 mg/mL with 0.05% vol toluene as flow rate marker and an injection volume of 200 μL was used. Data were analyzed using Empower Pro software from Waters Chromatography, Inc.

Glass transition temperatures (T_g) were measured by differential scanning calorimetry (DSC) on a Mettler-Toledo DSC822 (Mettler-Toledo, Inc., Columbus, OH) under N_2. Measurements of T_g were taken with a heating rate of 10 °C/min. The measurements were analyzed using Mettler-Toledo Star^e v. 10.00 software. The T_g was taken as the midpoint of the inflection tangent, upon the third scan. Thermogravimetric analysis (TGA) was performed under Ar atmosphere using a Mettler-Toledo model TGA/DSC 1, with a heating rate of 10 °C/min.

Column chromatography was performed on CombiFlash Rf4x (Teledyne ISCO) with RediSepRf Column (Teledyne ISCO).

Organocatalytic ROP of 5-Methyl-5-allyloxycarbonyl-1,3-dioxan-2-one (MAC). In a typical experiment, MAC and benzyl alcohol initiator were dissolved in dry DCM ($[MAC]_0$ = 0.5 M). DBU (1 equiv to initiator) was added to the monomer/initiator solution. After the desired time, the polymerizations were quenched by benzoic acid solution in DCM and precipitated directly into hexanes. Impurities were removed by column chromatography on silica gel in hexanes/ethyl acetate (4:1 to 1:1). The polymer containing fractions were concentrated then dissolved in a minimal amount of DCM and precipitated into hexanes. For example, MAC (1.0 g, 5.0 mmol), benzyl alcohol (26 μL, 27 mg, 0.25 mmol), DBU (37 μL, 38 mg, 0.25 mmol), DCM (10 mL), benzoic acid solution (36 mL, 46 mg, 0.38 mmol in 200 μL DCM) were used to yield BnO-$PMAC_{15}$-OH.

BnO-$PMAC_{15}$-OH. Yield = 670 mg, 87% based upon monomer conversion (75%). Crude: $M_{n,\ GPC}$ = 3,000 g/mol. PDI = 1.13. $M_{n,\ NMR}$ = 3,100 g/mol. After fractionation, fractions 11–12: $M_{n,\ GPC}$ = 1,200 g/mol. PDI = 1.08, fractions 14–16: $M_{n,\ GPC}$ = 2,800 g/mol. PDI = 1.03. ^{1}H NMR (300 MHz, $CDCl_3$, 7.26 ppm): δ 7.35 (m, OBn–Ar*H*), 5.86 (m, CH_{vinyl}), 5.33–5.20 (m, C$H_{2\text{-vinyl}}$), 5.13 (s, OBn–CH_2), 4.61 (d, OCH_2CHCH_2), 4.43–4.24 (m, OC(O)OCH_2), 3.70 (m, CH_2OH), 2.50 (t, O*H*), 1.25 (s, CH_3), 1.21 (s, C(CH_3)CH_2OH). ^{13}C NMR (75 MHz, $CDCl_3$, 77.16 ppm): δ 171.8, 154.5, 135.1, 131.6, 128.6, 118.5, 68.6, 66.0, 46.6, 17.6. IR (neat, cm^{-1}): 3150–2800 (br), 1736 (s), 1649 (w), 1470 (m), 1402 (m), 1379

(m), 1231 (s), 1138 (s), 968 (s), 785 (m), 739 (w), 698 (w). T_g = -16.0 °C (-17.5 °C, onset). TGA in N_2: 255–280 °C, 7% mass loss; 280–415 °C, 74% mass loss; 415–450 °C, 10% mass loss; 9% mass remaining above 500 °C.

Synthesis of Diblock Copolymer, α-Azido Poly(ethylene glycol)$_{68}$-*block*-poly(5-Methyl-5-allyloxycarbonyl-1,3-dioxan-2-one)$_n$, N$_3$-PEG$_{68}$-*b*-PMAC$_n$. N_3-PEG-*b*-PMAC block copolymer was synthesized using the above-mentioned method with commercially available *α*-hydroxy-*ω*-azido poly(ethylene glycol) 3,000 Da (HO-PEG$_{68}$-N_3) as an initiator ([M]/[I] = 20).

For the synthesis of PMAC-*b*-PLLA block copolymers, MAC (or L-lactide) and benzyl alcohol initiator were dissolved in dry DCM. DBU was added to the monomer/initiator solution. After the desired time (~80% conversion for MAC and >90% conversion for L-lactide), L-lactide (or MAC) was dissolved separately in DCM and added to the reaction mixture. After the desired time, the polymerizations were quenched by benzoic acid solution in DCM and precipitated directly into cold diethyl ether. Otherwise, the mixture was purified by column chromatography on silica gel in hexanes/ethyl acetate (4:1 to 1:1). The polymer containing fractions were concentrated and then dissolved in a minimal amount of DCM and precipitated into hexanes.

N_3-PEG$_{68}$-b-PMAC$_{10}$-OH. Yield = 234 mg, 90% based upon monomer conversion. $M_{n,\,GPC}$ = 5,100 g/mol. PDI = 1.09. $M_{n,\,NMR}$ = 5,000 g/mol. ^{1}H NMR (300 MHz, CD_2Cl_3, 5.32 ppm): δ 5.89 (C*H*$_{vinyl}$), 5.34–5.20 (C*H*$_{2\text{-vinyl}}$), 4.61 (OC*H*$_2$CHCH$_2$), 4.39–4.23 (OC(O)OC*H*$_2$), 3.59 (OC*H*$_2$C*H*$_2$), 3.36 (N$_3$CH$_2$C*H*$_2$O), 1.25 (s, C*H*$_3$), 1.20 (s, C(C*H*$_3$)CH$_2$OH).

BnO-PMAC$_{37}$-b-PLLA$_{20}$-OH. Yield = 162 mg, 74% based upon monomer conversion. $M_{n,\,GPC}$ = 4,300 g/mol (flow marker was shifted). PDI = 1.09. $M_{n,\,NMR}$ = 10,400 g/mol. ^{1}H NMR (300 MHz, $CDCl_3$, 7.26 ppm): δ 7.34 (OBn-Ar*H*), 5.86 (C*H*$_{vinyl}$), 5.32–5.10 (C*H*$_{2\text{-vinyl}}$, PLLA-C*H* and OBn-C*H*$_2$), 4.60 (OC*H*$_2$CHCH$_2$), 4.32–4.24 (OC(O)OC*H*$_2$ and C*H*OH), 1.55 (PLA-C*H*$_3$), 1.25 (s, PMAC-C*H*$_3$).

BnO-PLLA$_{20}$-b-PMAC$_{15}$-OH. Yield = 197 mg, 71% based upon monomer conversion. $M_{n,\ GPC}$ = 5,600 g/mol. PDI = 1.12. $M_{n,\ NMR}$ = 6,000 g/mol. ^{1}H NMR (300 MHz, CD_2Cl_3, 5.32 ppm): δ 7.35 (OBn-Ar*H*), 5.89 (C*H*$_{vinyl}$), 5.35–5.13 (C*H*$_{2\text{-vinyl}}$, PLLA-C*H* and OBn-C*H*$_2$), 4.61 (OC*H*$_2$CHCH$_2$), 4.40–4.25 (OC(O)OC*H*$_2$ and C*H*OH), 3.69 (C*H*$_2$OH), 1.55 (PLA-C*H*$_3$), 1.26 (s, PMAC-C*H*$_3$).

Ozonolysis of PMAC [synthesis of poly(5-methyl-5-oxoethyloxycarbonyl-1,3-dioxan-2-one, PMOC]. PMAC$_{15}$ (20 mg, 0.10 mmol repeat unit, 1 equiv) was dissolved in DCM (2.0 mL), and the solution was cooled to –78 ºC (dry ice/acetone cooling bath). Ozone was bubbled through the cooled solution until a slight blue color was obtained (10 min). When a slight blue color was not recognizable, an aliquot was collected, dried *in vacuo*, and analyzed by ^{1}H NMR to determine conversion. N_2 was then bubbled through for 10 min., and then dimethyl sulfide (37 µL, 31 mg, 0.50 mmol, 5 equiv) was added. The reaction was slowly allowed to warm to room temperature and stir overnight. The resulting solution was used without further purification or was precipitated in diethyl ether to yield PMOC as a white solid (quantitative). For kinetic study of ozonolysis, aliquots were collected, dried *in vacuo*, and analyzed by ^{1}H NMR at the allotted period of time (1, 3, 5, 7, 9, or 11 min). $M_{n,\ NMR}$ = 3,100 g/mol. ^{1}H NMR (300 MHz, CD_2Cl_2, 5.32 ppm): δ 9.52 (br, C*H*O), 7.36 (br, OBn–Ar*H*), 4.74 (m, OC*H*$_2$CHO), 4.34 (m, OC(O)OC*H*$_2$), 1.33 and 1.27 (br s, C*H*$_3$). ^{1}H NMR (300 MHz, TFA-d, 11.5 ppm) δ 9.63 (br, C*H*O), 7.37 (br, OBn–Ar*H*), 5.07 (br s, OC*H*$_2$CHO), 4.56 (br s, OC(O)OC*H*$_2$), 1.47 (br s, C*H*$_3$). ^{13}C NMR (75 MHz, TFA-d, 164.2 ppm): δ 201.7, 176.2, 158.2, 88.1, 72.0, 49.5, 18.4. IR (neat, cm^{-1}): 3675–3075 (br), 3075–2775 (br), 2843 (w), 2725 (w), 1736 (s), 1468 (m), 1402 (m), 1383 (m), 1233 (s), 1142 (s), 961 (s), 858 (m), 783 (m), 738 (w), 700 (w). T_g = 49.0 °C (41.0 °C, onset). TGA in N_2: 210–355 °C, 76% mass loss; 355–420 °C, 9% mass loss; 15% mass remaining above 500 °C

Functionalization of aldehyde-functional polycarbonates (PMOC). Isolated or *in situ*-generated PMOC (50 mg, 0.25 mmol for repeat unit) in DCM (5.0 mL) was mixed with aminooxy compound [*O*-benzylhydroxylamine hydrochloride (80 mg, 0.50 mmol) for

conjugate **1**, *O*-(carboxymethyl)hydroxylamine (55 mg, 0.50 mmol) for conjugate **2**] and NaOAc (136 mg, 1.0 mmol) in MeOH (5.0 mL). The mixture was stirred for 1.5 h at 45 ºC. The conjugate **1** was purified by precipitation into water. The conjugate **2** was concentrated and diluted with nanopure water. The resulting solution was purified by dialysis against nanopure water for 2 days and lyophilized.

Conjugate **1**. Yield = 61 mg, 80%. $M_{n,\,GPC}$ = 2,400 g/mol (flow marker was shifted). PDI = 1.10. $M_{n,\,NMR}$ = 4,700 g/mol. ^{1}H NMR (300 MHz, $CDCl_3$, 7.26 ppm): δ 7.43 (br, *H*C=NO), 7.30 (br, OBn–Ar*H*), 6.72 (br, *H*C=NO), 5.07 and 5.04 (s, OBn–CH_2), 4.98 (m, OCH_2CHNO), 4.64 (m, OCH_2CHNO), 4.25 (m, OC(O)OCH_2), 1.22 (s, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$, 77.16 ppm): δ 171.9, 165.2, 154.5, 147.0, 144.7, 137.4, 137.2, 128.8, 128.6, 128.5, 128.3, 76.7, 76.5, 68.7, 62.0, 60.0, 46.8, 46.7, 17.6. IR (neat, cm^{-1}): 3100–2800 (br), 1746 (s), 1497 (w), 1470 (m), 1454 (m), 1400 (m), 1377 (m), 1236 (s), 1140 (s), 974 (s), 909 (s), 864 (w), 785 (m), 729 (s), 698 (s). T_g = 0.0 °C (-0.2 °C, onset). TGA in N_2: 200–320 °C, 85% mass loss; 320–500 °C, 5% mass loss; 10% mass remaining above 500 °C

Conjugate **2**. Yield = 52 mg, 76%. $M_{n,\,NMR}$ = 4,200 g/mol. ^{1}H NMR (300 MHz, CD_3OD, 4.78) δ 7.45 (br, *H*C=NO), 7.26 (br, OBn–Ar*H*), 6.71 (br, *H*C=NO), 5.05 (s, OBn–CH_2), 4.92 (m, OCH_2CHNO), 4.62 (m, OCH_2CHNO), 4.37 (m, CH_2COOH), 4.22 (m, OC(O)OCH_2), 4.34 (m, CCH_2OH), 1.18 (s, CH_3). ^{13}C NMR (75 MHz, D_2O): δ 174.2, 155.7, 150.0, 148.2, 130.0, 72.8, 69.9, 62.8, 61.0, 47.6, 17.9. IR (neat, cm^{-1}): 3700–3100 (br), 3020–2840 (br), 1738 (s), 1601 (s), 1458 (m), 1406 (m), 1236 (s), 1142 (s), 1059 (m), 1024 (m), 968 (m), 922 (w), 883 (w), 866 (w), 785 (m), 698 (w). T_g = 76.0 °C (-71.0 °C, onset). TGA in N_2: 155–220 °C, 28% mass loss; 220–330 °C, 36% mass loss; 320–500 °C, 9% mass loss; 27% mass remaining above 500 °C.

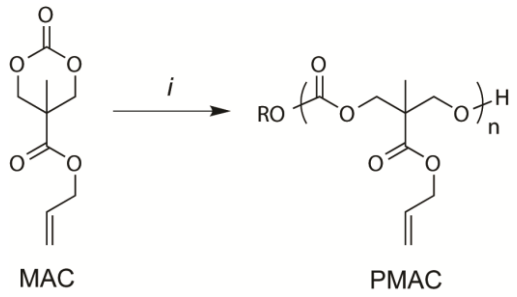
Synthesis of alkene- and aldehyde-functional polycarbonates (PMAC-*co*-PMOC) and functionalization by consecutive aldehyde-aminooxy and thiol-ene "click" reactions. $PMAC_{15}$ (20 mg, 0.10 mmol for repeat units, 1 equiv) was dissolved in DCM (2.0 mL), and the solution was cooled to -78 ºC (dry ice/acetone cooling bath). Ozone was bubbled through

the cooled solution. After the allotted period of time (3 and 5 min), N_2 was then bubbled through for 10 min., and then dimethyl sulfide (37 μL, 31 mg, 0.50 mmol, 5 equiv) was added. The reaction was slowly allowed to warm to room temperature and stir overnight. The resulting PMAC-*co*-PMOC solution in DCM was mixed with aminooxy compound (*O*-benzylhydroxylamine, 0.20 mmol) and NaOAc (0.40 mmol) in MeOH (5.0 mL). The mixture was stirred for 1.5 h at 45 ºC. The conjugate **3** was purified by precipitation into water.

A solution of conjugate **3** (20 mg, 5.5 μmol, 55 μmol for alkene functionalities), ethyl 2-mercaptoacetate (61 μL, 66 mg, 550 μmol), and DMPA (3.0 mg, 11 μmol) in 0.70 mL of DMSO was irradiated under UV irradiation (365 nm, 6 W) for 2 h. The reaction mixture was purified by dialysis (MWCO 6–8 kDa) in THF overnight. A viscous liquid was collected after the removal of solvent *in vacuo*.

Conjugate **3**. Yield = 20 mg, 85%. $M_{n,\,NMR}$ = 3,600g/mol. ^{1}H NMR (300 MHz, DMSO-d_6, 7.26 ppm): δ 7.49 (br, *H*C=NO), 7.32 (br, OBn–Ar*H*), 6.86 (m, *H*C=NO), 5.84 (m, CH_{vinyl}), 5.29–5.13 (m, C$H_{2\text{-vinyl}}$), 5.08 and 5.02 (s, OBn–CH_2), 4.85 and 4.66 (s, OCH_2CHNO), 4.57 (s, OCH_2CHCH_2), 4.23 (m, OC(O)OCH_2), 1.17 (s, CH_3).

Conjugate **4**. Yield = 19 mg, 76%. $M_{n,\,NMR}$ = 4,600 g/mol. ^{1}H NMR (300 MHz, $CDCl_3$, 7.26 ppm) δ 7.47 (br, *H*C=NO), 7.34 (br, OBn–Ar*H*), 6.75 (br, *H*C=NO), 5.86 (m, CH_{vinyl}), 5.33–5.33 (m, C$H_{2\text{-vinyl}}$), 5.12 and 5.09 (s, OBn–CH_2), 4.94 and 4.69 (s, OCH_2CHNO), 4.62 (s, OCH_2CHCH_2), 4.28 (m, OC(O)OCH_2), 4.23–4.14 (m, OCH_2CH_2CH_2S and OCH_2CH_3), 3.20 (s, SCH_2C(O)O), 2.69 (m, OCH_2CH_2CH_2S), 1.94 (m, OCH_2CH_2CH_2S), 1.25 (m, CH_3 and OCH_2CH_3).



Scheme S1 Ring-opening polymerization (ROP) of 5-methyl-5-allyloxycarbonyl-1,3-dioxan-2-one, MAC. *Conditions*: (i) ROH, DBU, DCM, 29 °C in the glovebox.

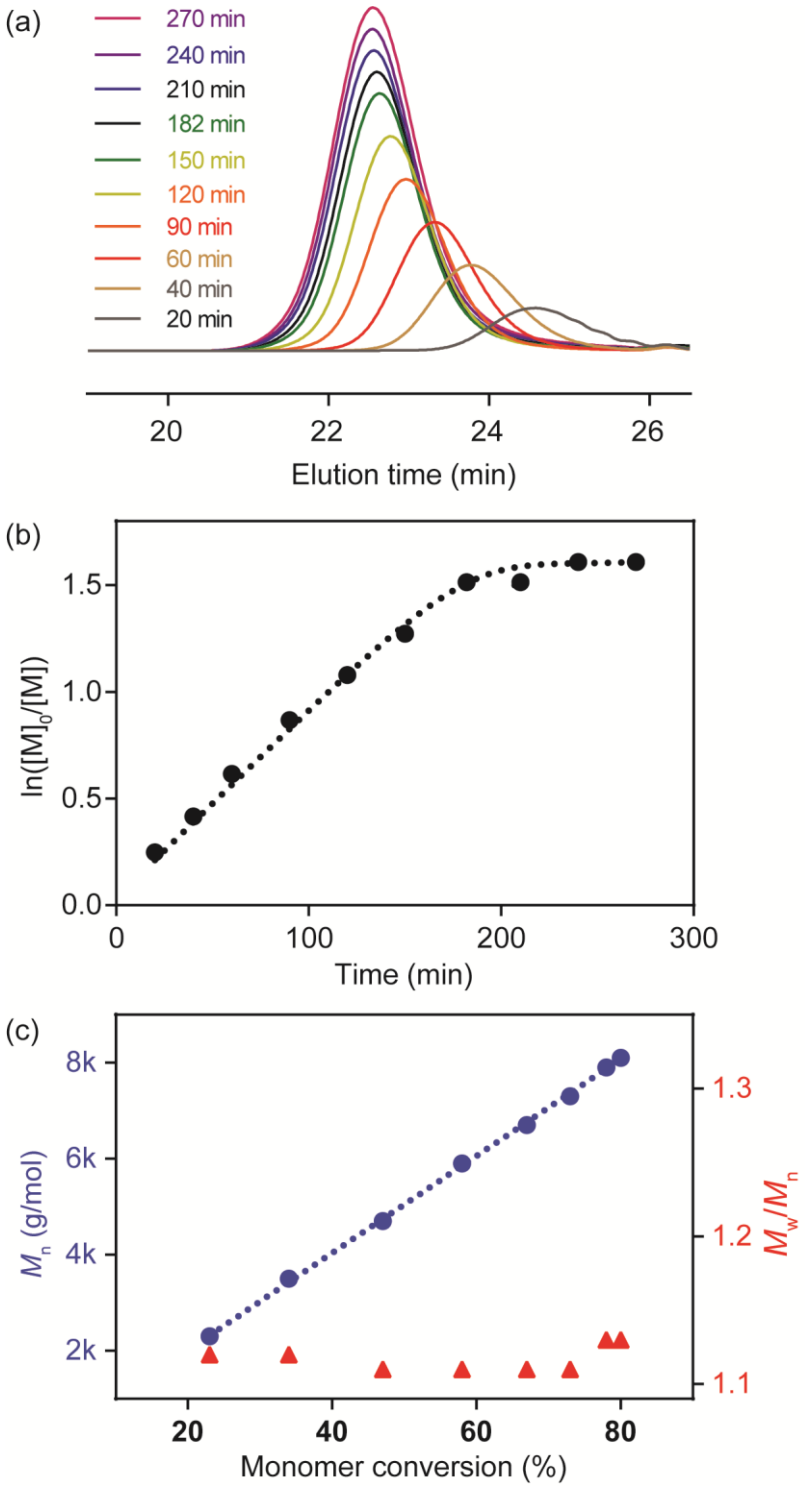


Fig. S1 (a) GPC profiles (THF as eluent, 1 mL/min) as a function of polymerization time, for the ROP of MAC; (b) Plot of $\ln([M]_0/[M])$ against time, obtained from ^{1}H NMR spectroscopy data; (c) Plot of number-average molecular weight (M_n) and polydispersity (M_w/M_n) against % monomer conversion in the ROP of MAC. *Conditions*: $[MAC]_0$ = 0.5 M in DCM at 29 °C in the glovebox, [MAC] : [BnOH] : [DBU] = 50 : 1 : 1.

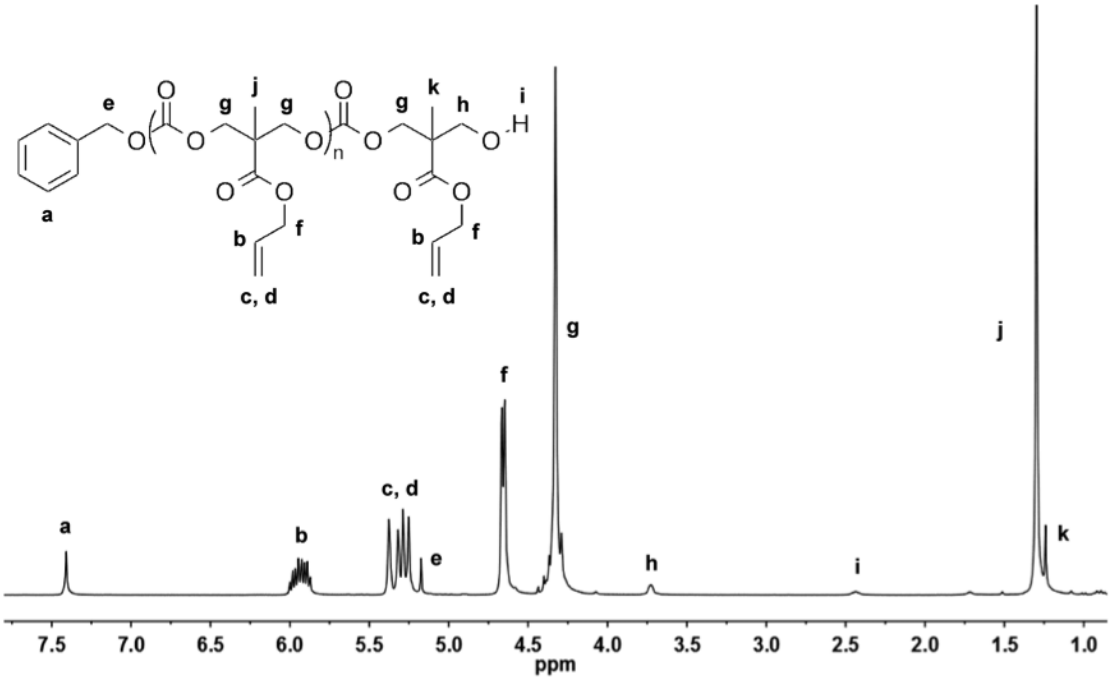


Fig. S2 ^{1}H NMR spectrum of BnO-PMAC$_{15}$-OH initiated from benzyl alcohol using DBU. *Conditions*: [MAC]$_0$ = 0.5 M in DCM a 29 °C in the glovebox, [MAC] : [BnOH] : [DBU] = 20 : 1 : 1.

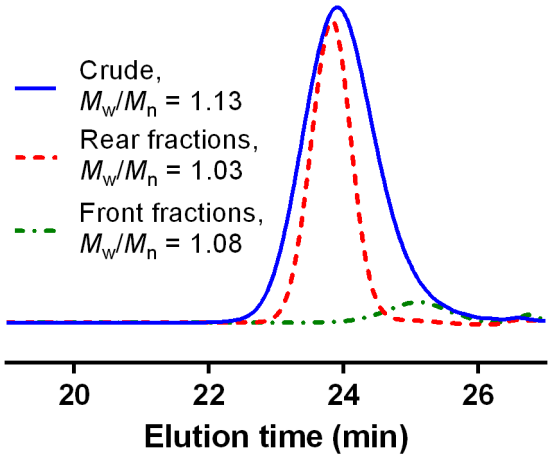


Fig. S3 GPC profiles (THF as eluent, 1 mL/min) of BnO-PMAC$_{15}$-OH before and after purification using column chromatography. *Conditions*: [MAC]$_0$ = 0.5 M in DCM at 29 °C in the glovebox, [MAC] : [BnOH] : [DBU] = 20 : 1 : 1.

Table S1 Block copolymers of MAC

Polymer	M_n (NMR) (g/mol)	M_n (GPC) (g/mol)	PDI
N_3-PEG_{68}-*b*-$PMAC_{10}$-OH	5 000	5 100	1.09
BnO-$PMAC_{37}$-*b*-$PLLA_{20}$-OH	10 400	4 300[a)]	1.09
BnO-$PLLA_{20}$-*b*-$PMAC_{15}$-OH	6 000	5 600	1.12

[a)]GPC flow marker was shifted.

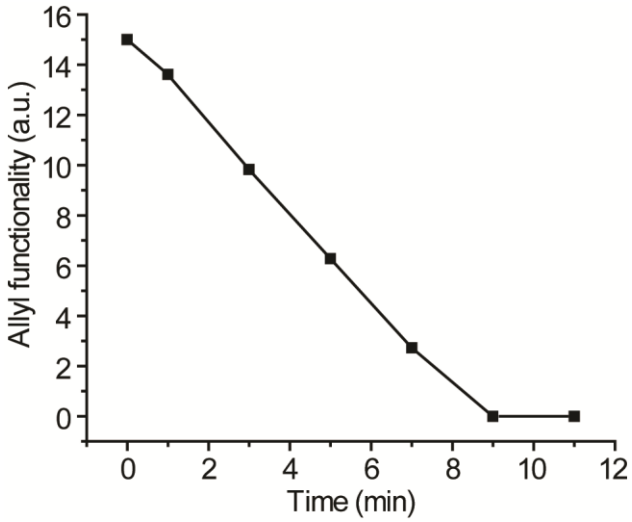


Fig. S4 Ozonolysis kinetics of $PMAC_{15}$ *Conditions*: PMAC (20 mg) in DCM (2 mL), (i) O_3, DCM, -78 ºC; (ii) aliquots were dried *in vacuo* before measuring ^{1}H NMR spectra.

Table S2 Thermal properties and solubility of synthesized polymers

	Thermal properties (ºC)			Solubility	
Polymer	T_g [a)]	$T_{d,\,5\%}$ [b)]	$T_{d,\,50\%}$ [b)]	*Organic solvent*	*Aqueous solvent*
$PMAC_{15}$	-16.0	277	333	most	none
$PMOC_{15}$	49.0	245	305	limited[c)]	none
1	0.0	235	262	most	none
2	76.0	183	265	limited[d)]	soluble

[a)]Glass transition temperature, measured by DSC analysis at the third scan.; [b)]Temperatures at 5 and 50% weight degradation by TGA; [c)]soluble in TFA; [d)]soluble in MeOH.

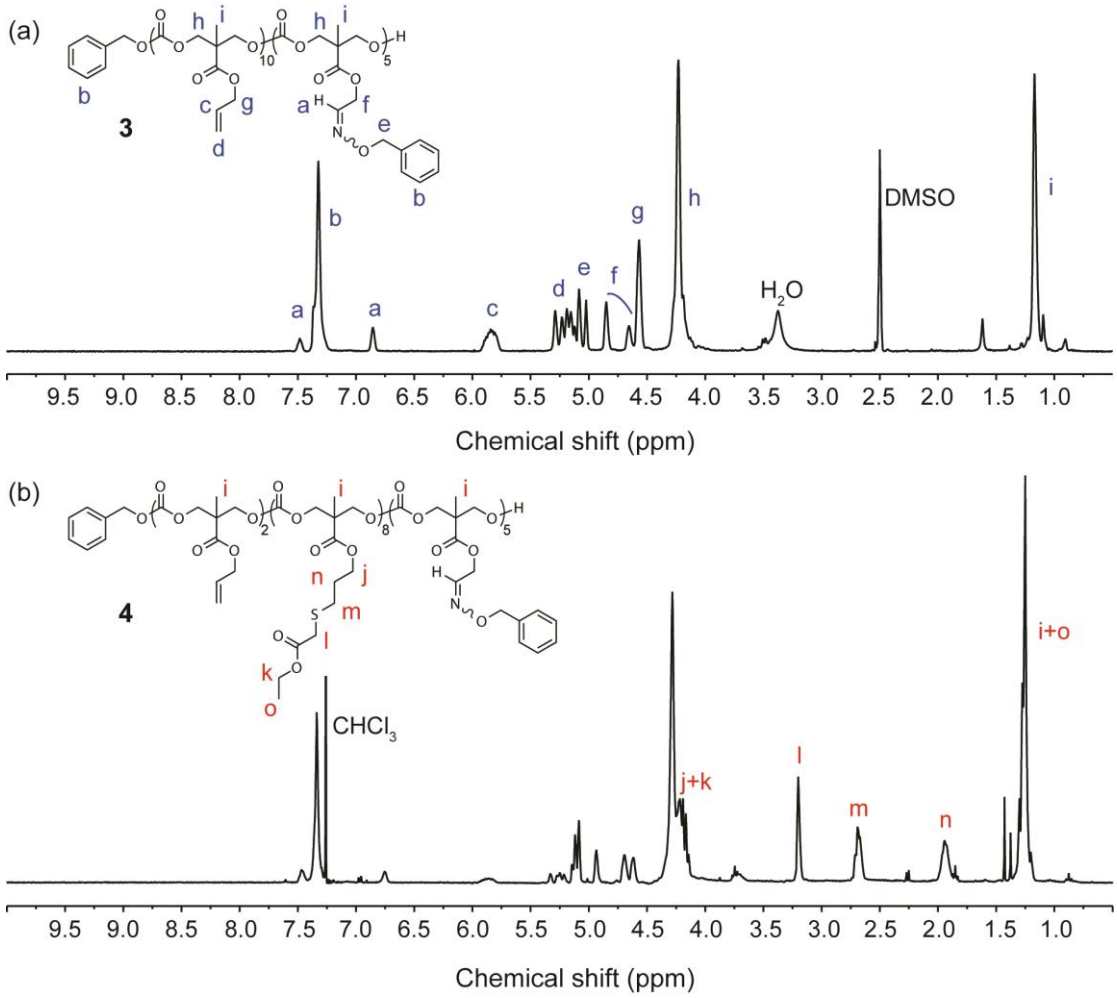


Fig. S5 ^{1}H NMR spectra of polymer **3** (partial ozonolysis of $PMAC_{15}$ and consecutive functionalization by aldehyde-aminooxy "click" reaction with *O*-benzylhydroxylamine and polymer **4** (thiol-ene reaction of polymer **3** with ethyl 2-mercaptoacetate).

Reference

1. X. Hu, X. Chen, Z. Xie, S. Liu and X. Jing, *J. Polym. Sci., Part A: Polym. Chem.*, **2007**, *45*, 5518-5528.