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Metal-free organic catalyst for synthesis of low dispersity poly(ethylene glycol-*block*-polylactide) copolymers with well-defined structure

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Materials.

L,L-/D,L-Lactide (99%) was purchased from Corbion. DBU, bifunctional PEG with molar mass of 4.6 kDa and benzioc acid were purchased from Sigma-Aldrich, monomethoxy-PEG with molar mass of 5 kDa was purchased J&K Scientific. Benzioc acid and all organic solvents were of analytical grade.

Methods.

1. *Purification of reagents and solvents*

Method A. DBU, dichloromethane (CH_2Cl_2) and ethyl acetate were used as purchased. L,L-/D,L-Lactide was purified by recrystallization from ethyl acetate. Poly(ethylene glycol) (4.6 kDa, 5 kDa) were dried in a vacuum oven (ca. 0.1 mbar) at 150 °C for 1 hour.

Method B. Toluene and CH_2Cl_2 were purified as follows: were vacuum distilled, were refluxed with calcium hydride (CaH_2) and then were distilled to separate them from the byproducts of the reflux reaction. Dry solvents were stored over activated molecular sieves (3 Å) in an airtight flask. Lactide was twice recrystallized from dry ethyl acetate, then twice from dry toluene, dried under vacuum, and stored under an inert atmosphere until needed. Poly(ethylene glycol) (4.6 kDa, 5 kDa) were dried by azeotropic distillation with dry toluene at atmospheric pressure. DBU was used as received.

2. *Synthesis of block copolymer*

Amphiphilic linear block copolymers PEG_x-PLA_n were synthesized *via* ring-opening polymerization of L,L- / D,L-lactide monomers using poly(ethylene glycol) (4.6 kDa or 5 kDa) as a macroinitiator and DBU as a catalyst. The polymerization was carried out in solution at 25 °C, using a Schlenk line. The polymerization degree of polylactide in PEG_x-PLA_n was controlled by varying the molar ratios of the lactide monomer and hydroxy group of PEG_x [LA]/[OH]. The purified PEG_{113} (600 mg, 0.12 mmol) and lactide (605 mg, 4.2 mmol) were weighed and charged to a 150 ml round-bottom flask. The solids were then cycled thrice with vacuum and nitrogen at room temperature. Dichloromethane was added followed by sonification

to ensure dissolution of the solids (c = 130 mg ml^{-1}). DBU was weighed into a 2 ml glass vial, then CH_2Cl_2 was added *via* syringe (typically 0.1 ml) to the vial. The solution (0.0073 mg, molar ratios of OH/DBU = 2.5) was syringed into the flask to initiate the polymerization. All reactions were terminated with benzoic acid (2x molar excess relative to the DBU). The polymer was precipitated from excess cold hexane and was dried overnight in a vacuum oven.

3. *Characterization of the synthesized block copolymers.* The chemical composition of the synthesized block copolymers and polymerization degree (n, DP PLA) of the hydrophobic polylactide block were determined by ^{1}H NMR. The spectra were recorded on a 600 MHz Agilent-Varian VNMRS 700 spectrometer at 25 °C. For measurements 30 mg of the block copolymer was dissolved in 1 ml of deuterated chloroform ($CDCl_3$). The integrals of the peaks corresponding to the PEG methylene protons (–C$\boldsymbol{H}_2$–) at 3.64 ppm and the PLA methine protons (–C$\boldsymbol{H}$) at 5.20 ppm were used to calculate the values of n of the PLA block and the values of the number-average molecular mass (M_n) of the block copolymers.

4. *Gel permeation chromatography (GPC).* The number-averaged molecular weight (M_n), weight-averaged molecular weight (M_w), and polydispersity index (PDI) of the synthesized block copolymers were determined on an analytical chromatograph Knauer (Germany) equipped with a refractive index detector and Phenogel 5 μm 10^3 Å column. The column calibration was performed using polystyrene standards (Polymer Laboratories). THF was used as the mobile phase at a flow rate of 1 ml min^{-1} at 40 °C. For measurements 5 mg of the block copolymer was dissolved in 1 ml of THF.

Table S1 Synthesis conditions and characteristics of synthesized block copolymers ([OH]/[DBU]=2.5, T = 25 °C, CH_2Cl_2).

Sample (targeted)	Method	[LA]/ [DBU]	t/min	X/% [a]	M_n/kDa [b]	M_w/kDa [b]	PDI [b]	DP PLA [a]
PEG_{113}-P(D,L)LA_{14}	A	17	10	92	6.7	7.3	1.10	12
PEG_{113}-P(D,L)LA_{14}	B		10	93	7.1	7.6	1.07	13
PEG_{113}-P(L)LA_{36}	A	45	15	88	8.2	8.8	1.07	30
PEG_{113}-P(D,L)LA_{36}	B		15	91	8.6	9.2	1.06	33
PEG_{113}-P(L)LA_{70}	A	86	60	60	8.4	8.9	1.07	32
PEG_{113}-P(D,L)LA_{70}	B		30	93	11.4	12.6	1.15	65
PEG_{113}-P(D,L)LA_{120}	A	150	120	54	10.1	11.2	1.11	66
PEG_{113}-P(L)LA_{120}	B		120	88	12.9	16.5	1.15	105

[a] Results based on ^{1}H NMR: X is monomer conversion (%) and DP is polymerization degree of the polylactide block; [b] Results based on GPC measurements against a polystyrene standard, PDI is polydispersity index.

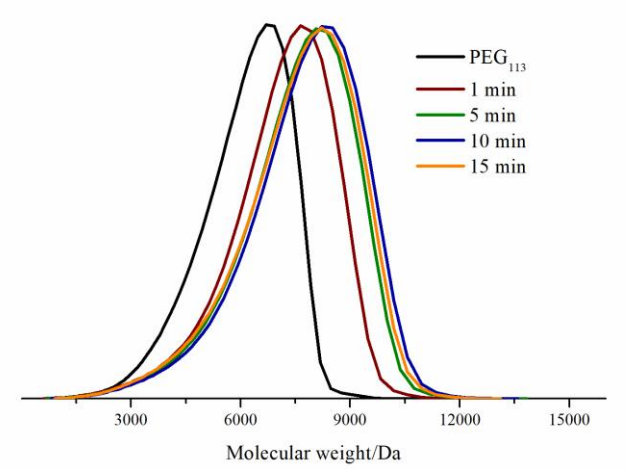

Figure S1 GPC measured molecular weight distributions of PEG_{113}-P(D,L)LA_{14} at various time points.

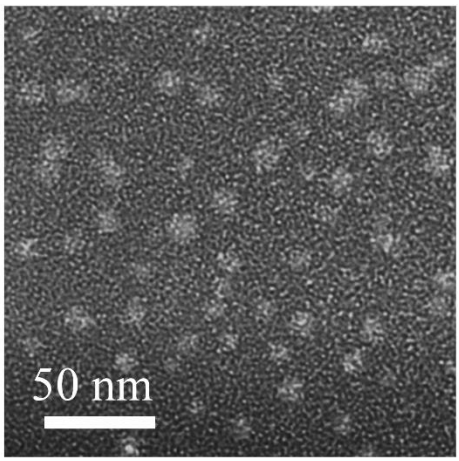

Figure S2 A representative TEM image of the PEG_{113}-P(D,L)LA_{36} nanoparticles. The concentration of dispersion c = 0.5 mg ml^{-1}.

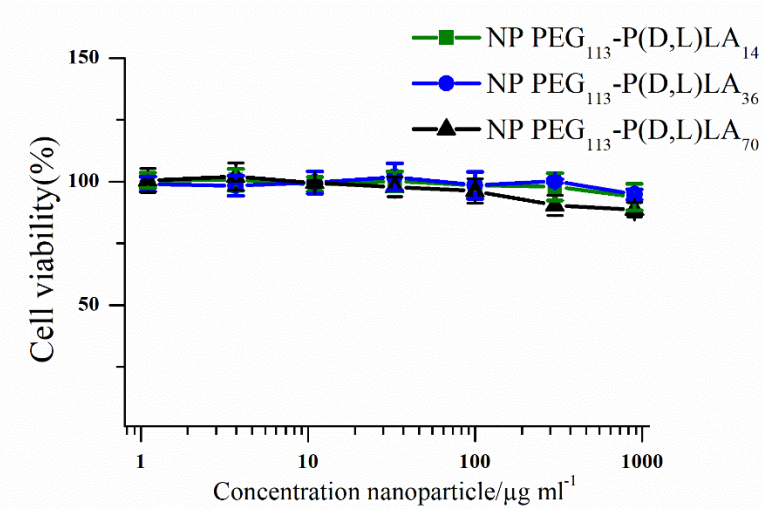

Figure S3 Cell viability determined by the MTT assay for PEG_{113}-P(D,L)LA_n nanoparticles on WI38 cell line. Results are expressed as average +/- standard deviation.