Supporting Information

Facile Functionalization of Polyesters through Thiol-yne Chemistry for the Design of Degradable, Cell–Penetrating and Gene Delivery Dual–Functional Agents

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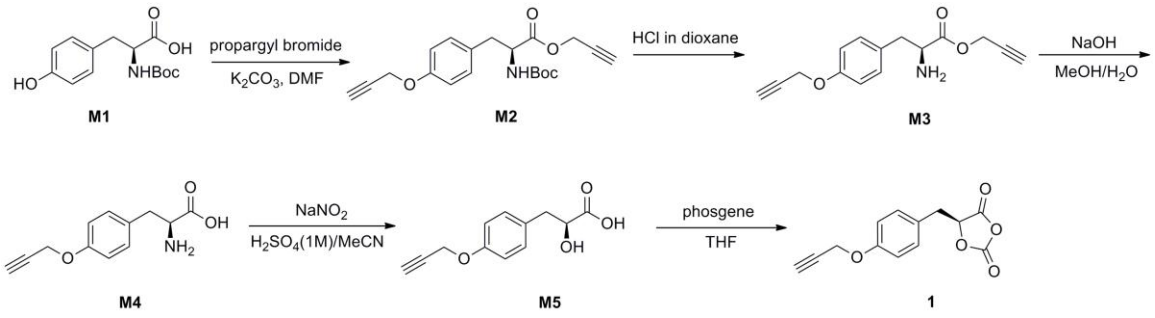
Experimental section

Materials. Boc-$_L$-tyrosine was purchased from Chem-Impex International (Des Plaines, IL, USA) and used as received. Anhydrous dichloromethane (DCM), hexane and tetrahydrofuran (THF) were dried by columns packed with alumina and stored in a glove box. Anhydrous dimethylformamide (DMF) was dried by passing the solvent through a column packed with 4Å molecular sieves. Pierce BCA assay kits were purchased from ThermoFisher Scientific (Rockford, IL, USA). pCMV-Luc plasmid DNA was purchased from Elim Biopharm (Hayward, CA, USA). Bright-Glo luciferase assay reagent was from Promega (Madison, WI, USA). YOYO-1 was purchased from Invitrogen (Carlsbad, CA, USA). TAMRA-Arg9 and TAMRA-HIV-TAT were purchased from Biocompare (San Francisco, CA, USA). All other chemicals were purchased from Sigma-Aldrich (St. Louis, MO, USA) and used as received unless otherwise specified.

Instrumentation. NMR spectra were recorded on a Varian U500 (500 MHz) or a VXR-500 (500 MHz) spectrometer. Gel permeation chromatography (GPC) experiments were performed on a system equipped with an isocratic pump (Model 1100, Agilent Technology, Santa Clara, CA, USA), a DAWN HELEOS multi-angle laser light scattering detector (MALLS detector, Wyatt Technology, Santa Barbara, CA, USA) and an Optilab rEX refractive index detector (Wyatt Technology, Santa Barbara, CA, USA). The detection wavelength of HELEOS was set at 658 nm. Separations were performed using serially connected size exclusion columns (100 Å, 500 Å, 10^3 Å and 10^4 Å Phenogel columns, 5 μm, 300 × 7.8 mm, Phenomenex, Torrance, CA, USA) at 60 °C using DMF containing 0.1 M LiBr as the mobile phase. The MALLS detector was

calibrated using pure toluene with no need for calibration using polymer standards and was used for the determination of the absolute molecular weights (MWs). The molecular weight of polymer was determined from the *d*n/*d*c value calculated offline by means of the internal calibration system processed by the ASTRA V software (Version 5.1.7.3, Wyatt Technology). Low-resolution electrospray ionization mass spectrometry experiment was performed on a Waters Quattro II mass spectrometer. Infrared spectra were recorded on a Perkin Elmer 100 serial FTIR spectrophotometer calibrated with polystyrene film. Lyophilization was conducted on a Labconco FreeZone lyophilizer (Kansas City, MO, USA). UV light was generated from an OmiCure S1000 UV lamp (EXFO, Mississauga, Canada). Small angle x-ray scattering (SAXS) experiment was performed on a Bruker M18XHF22 system (Bruker Axs Inc., Madison, WI, USA) with rotating anode generator operating at 50 kV and 50 mA and supplying a Cu Kα (λ = 1.541838 Å) radiation beam collimated using a pinhole collimator.

Scheme S1. The synthetic route of Tyr(alkynyl)-OCA (**1**)



Synthesis of (*S*)-2-Amino-3-(4-(prop-2-yn-1-yloxy)phenyl)propionic acid propargyl ester (M3). Boc-$_L$-tyrosine (9.30 g, 33.1 mmol, 1 equiv.) and Potassium carbonate (13.75 g, 99.5 mmol, 3 equiv.) were suspended in anhydrous DMF (80 mL). Propargyl bromide (11 mL, 98.8 mmol, 3 equiv., 80 wt.% in toluene) was added dropwise at 0^{o}C. The reaction mixture was

stirred for 24 h at room temperature. Water (300 mL) and ethyl ether (250 mL) were added. The aqueous phase was extracted with ethyl ether (3 × 150 mL). The combined organic phase was dried over anhydrous sodium sulfate and evaporated to give a yellow oil ((S)-prop-2-yn-1-yl 2-((tert-butoxycarbonyl)amino)-3-(4-(prop-2-yn-1-yloxy)phenyl)propanoate, **M2**), which was used in the next step without further purification. The deprotection of **M2** was performed with HCl/dioxane (4 M, 150 mL) at room temperature for 24 h. After the solvent was removed under reduced pressure, a yellowish solid (**M3**, 9.36 g, 96% for two steps) was obtained. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 7.21 (d, 2H, Ar*H*), 6.93 (d, 2H, Ar*H*), 4.80 (d, 2H, -COOC*H*$_2$C≡CH), 4.77 (d, 2H, -PhOC*H*$_2$C≡CH), 4.26 (t, 1H, -*CH*NH$_2$), 3.69 (t, 1H, -COOCH$_2$C≡C*H*), 3.58 (t, 1H, -PhOCH$_2$C≡C*H*), 3.07-3.18 (m, 2H, -C*H*$_2$PhOCH$_2$C≡CH). ^{13}C NMR (DMSO-d_6, 500 MHz): δ 168.3, 156.5, 130.7, 126.9, 114.8, 77.4-79.2, 55.3, 53.2, 34.8. ESI-MS (m/z): Calcd $C_{15}H_{15}NO_3$ 257.1 (M); found: 258.2 $(M+H)^+$.

Synthesis of 2-Amino-3-(4-(prop-2-yn-1-yloxy)phenyl)propionic Acid (M4). The compound **M3** (9.36 g, 31.9 mmol) from the previous step was dissolved in H_2O/methanol (1:1, v/v, 100 mL) containing NaOH (4.00 g, 100 mmol). The reaction solution was stirred for 16 h at room temperature and then neutralized by adding concentrated HCl. Water (50 mL) was added and the mixture was kept at 4^{o}C overnight. The precipitate was filtered, washed with ice-cold H_2O, and lyophilized. A white powder was obtained (**M4**, 5.09 g, 73 % yield). ^{1}H NMR (DMSO-d_6, 500 MHz): δ 7.19 (d, 2H, Ar*H*), 6.91 (d, 2H, Ar*H*), 4.74 (d, 2H, -PhOC*H*$_2$C≡CH), 4.07 (t, 1H, -*CH*NH$_2$), 3.52 (t, 1H, -PhOCH$_2$C≡C*H*), 3.03-3.11 (m, 2H, -C*H*$_2$PhOCH$_2$C≡CH). ^{13}C NMR (DMSO-d_6, 500 MHz): δ 170.3, 156.7, 130.9, 127.7, 115.1, 79.6, 78.5, 55.6, 53.3, 34.9. ESI-MS (m/z): Calcd $C_{12}H_{13}NO_3$ 219.1 (M); found: 220.1 $(M+H)^+$.

Synthesis of 2-Hydroxy-3-(4-(prop-2-yn-1-yloxy)phenyl)propionic Acid (M5). In a 50-mL round-bottom flask, **M4** (4.38 g, 20.0 mmol) was dissolved in a mixture of sulfuric acid (40 mL, 1 M) and acetonitrile (40 mL). Sodium nitrite (2.76 g, 40.0 mmol) dissolved in water (20 mL) was added slowly to the **M4** solution. The mixture was stirred under nitrogen for 16 h and then extracted with dichloromethane (200 mL × 3). The combined organic layers were dried, filtered, and concentrated under vacuum, giving the product as a solid (3.15 g, 72 %). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.18 (d, 2H, Ar*H*), 6.92 (d, 2H, Ar*H*), 4.66 (d, 2H, -PhOC*H*$_2$C≡CH), 4.45 (m, 1H, -*CH*OH), 2.90-3.14 (m, 2H, -C*H*$_2$PhOCH$_2$C≡CH), 2.52 (t, 1H, -PhOCH$_2$C≡C*H*), ^{13}C NMR ($CDCl_3$, 500 MHz): δ 178.3, 156.7, 130.7, 129.0, 115.1, 78.7, 75.8, 71.2, 55.9, 39.3. ESI-MS (m/z): Calcd $C_{12}H_{12}O_4$ 220.1 (M); found: 218.9 $(M-H)^-$.

Synthesis of 5-[4-(Prop-2-yn-1-yloxy)benzyl]-1,3-dioxolane-2,4-dione (Tyr(alkynyl)-OCA, 1). To an anhydrous THF solution (40 mL) containing **M5** (3.15 g, 14.3 mmol), phosgene (23 mL, 32.2 mmol, 15 wt. % in toluene) was added dropwise at 0^{o}C. The mixture was stirred at room temperature for 16 h. The solvent was removed under vacuum. The residue was purified by silica gel chromatography in a glovebox with DCM as the eluent (Note: The silica gel was pre-treated by drying it at 150^{o}C for 8 h under vacuum). The solution was collected and the DCM was evaporated under reduced pressure to give a yellow solid. The crude OCA was recrystallized in hexane/CH_2Cl_2 in glove box. A colorless OCA monomer **1** was obtained in crystalline form (2.02 g, yield: 57.4 %). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.17 (d, 2H, Ar*H*), 6.96 (d, 2H, Ar*H*), 5.27 (t, 1H, alpha-*H*), 4.68 (d, 2H, -PhOC*H*$_2$C≡CH), 3.19-3.35 (m, 2H, -C*H*$_2$PhOCH$_2$C≡CH), 2.52 (t, 1H, -PhOCH$_2$C≡C*H*), ^{13}C NMR ($CDCl_3$, 500 MHz): δ 166.5, 157.8, 147.9, 131.0, 124.5, 115.7, 80.1, 78.4, 75.9, 56.0, 35.8. The crystal structure of **1** was analyzed by SAXS (Figure S9).

General Procedure for the Polymerization of Tyr(alkynyl)-OCA. In a glovebox, **1** (49.3 mg, 0.2 mmol) was dissolved in DCM (1 mL) followed by the addition of pyrenebutanol (40 μL, 0.1 M) and DMAP (40 μL, 0.1 M). The conversion of **1** was monitored by measuring the intensity of the anhydride peak of OCA at 1810 cm^{-1} by FTIR. After the polymerization was complete, the Tyr(alkynyl)-PAHA (poly(**1**)) was precipitated with ether and dried under vacuum (37.6 mg, 93% yield).

Kinetic Study of the Polymerization of Tyr(alkynyl)-OCA (1). In a glove box, **1** (246.6 mg, 1.0 mmol) was dissolved in DCM (9.8 mL). Pyrenebutanol (0.1 M in DCM, 100 μL) and DMAP (0.1 M in DCM, 100 μL) were added to the stirred OCA solution. At selected time points, a portion of the reaction solution (1 mL) was added into 4-*tert*-butylbenzoyl chloride (10 μL, 0.05 mmol) to terminate the reaction. The solvent was then removed under vacuum and then analyzed by ^{1}H NMR. The conversion of OCA was determined by comparing the OCA concentration in the polymerization solution versus the initial OCA concentration.

Synthesis of Poly(Tyr(alkynyl)-OCA)$_{50}$-graft-aminoethanethiol (poly(1)$_{50}$-*g*-AET$_2$). Poly(**1**)$_{50}$ (10.7 mg, 0.05 mmol of alkyne groups) was dissolved in DMF/DI water (1.1 mL, 9:2, v/v) in a quartz bottle, to which 2-aminoethanethiol hydrochloride (AET, 48 mg, 0.4 mmol of thiol groups, 8 equiv. of alkyne groups) and 2,2-dimethoxy-2-phenylacetophenone (DMPA, 2.8 mg, 0.01 mmol) were added. The solution was degassed by N_2 for 5 min. The reaction solution was stirred at room temperature and irradiated with a 365-nm UV lamp (20 mW/cm^2) for 60 min. The solvent was removed under vacuum. The residue was dissolved in DI water (5 mL). The crude product was purified by ultrafiltration using Amicon Ultra-4 centrifugal filter unit (MWCO

3 kDa, Millipore, Billerica, MA, US) and lyophilized (20.4 mg, 90% yield). The modification efficiency was determined to be 100% based on ^{1}H NMR analysis.

Synthesis of Rhodamine-Labeled Poly(1)$_{50}$-*g*-AET$_2$. Poly(**1**)$_{50}$-*g*-AET$_2$ (11.4 mg, 50 μmol of primary amine) was dissolved in DMSO (1 mL). Rhodamine B isothiocyanate (RhB-NCS, 1.4 mg, 2.5 μmol) in DMSO was added to the polymer solution. After that, the reaction vial was wrapped with aluminum foil. The reaction solution was stirred at room temperature for 24 h followed by ultrafiltration to yield rhodamine-labeled poly(**1**)$_{50}$-*g*-AET$_2$ (8.2 mg, 72 % yield).

Cell Penetration Study. HeLa cells were seeded in 96-well plates at 1 × 10^4 cells/well. The medium was replaced by serum-free DMEM (100 μL/well) 24 h later, and the rhodamine-poly(**1**)$_{50}$-*g*-AET$_2$ was added at various amounts (5, 10, and 20 μg/well). After incubation for certain period of time (1, 2 and 4 h), cells were washed three times with cold PBS containing 20 U/mL heparin and then lysed with 100-μL RIPA buffer. The rhodamine-poly(**1**)$_{50}$-*g*-AET$_2$ content in the lysate was quantified by spectrofluorimetry (E_x = 560 nm, E_m = 590 nm); the protein level in the cell lysate was determined by the BCA kit. The uptake level was expressed as ng of polyester per mg of cellular protein. TAMRA-labeled Arg9 and HIV-TAT, rhodamine-labeled PLL and PLR served as the controls.

Preparation and Characterization of Poly(1)$_{50}$-*g*-AET$_2$/DNA Complexes. Poly(**1**)$_{50}$-*g*-AET$_2$ and pCMV-Luc were separately dissolved in water at 1 mg/mL. Complexes were allowed to form by addition of the poly(**1**)$_{50}$-*g*-AET$_2$ solution to DNA at different N/P ratios followed by vortex for 30 s and incubation at 37°C for 30 min. The complexes were loaded onto 1% agarose

gel. The DNA condensation by the poly(**1**)$_{50}$-*g*-AET$_2$ was evaluated by analyzing DNA migration after electrophoresis at 100 V for 40 min and staining with ethidium bromide (EB). Sizes and Zeta potentials of the complexes were monitored by Zetasizer Nano(Malvern Instruments Ltd., Malvern, Worcestershire, UK).

Intracellular Delivery of Poly(1)$_{50}$-*g*-AET$_2$/DNA Complexes. DNA (1 mg/mL) was labeled with YOYO-1 (20 μM) at one dye molecule per 50 bp DNA.[1] The resulting YOYO-1-DNA was then allowed to form complexes with the poly(**1**)$_{50}$-*g*-AET$_2$ at the N/P ratio of 20:1. PLL/DNA and PLR/DNA complexes at the N/P ratio of 20 were prepared by using the same method. HeLa cells were seeded on 96-well plates at 1×10^4 cells/well, and cultured for 24 h to reach confluence. The medium was replaced by serum-free DMEM (100 μL/well). The complexes were added at the determined DNA amount (0.01, 0.05, 0.1, and 0.2 μg YOYO-1-DNA/well). After incubation at 37 °C for different time (0.5, 1, 2, and 4 h), the medium was aspirated and cells were washed three times with cold PBS containing 20 U/mL heparin before lysis with RIPA lysis buffer (100-μL). YOYO-1-DNA content in the lysate was quantified by spectrofluorimetry (λ_{ex} = 485 nm, λ_{em} = 530 nm) and the protein content was measured using the BCA kit. Uptake level was expressed as ng YOYO-1-DNA per μg of protein. To explore the mechanism involved during cellular internalization, cells were pre-incubated with endocytosis inhibitors including sodium azide (10 mM)/deoxyglucose (50 mM), chlorpromazine (30 μM), genistein (370 μM), methyl-β-cyclodextrin (mβCD, 5 mM), wortmannin (23 μM), or dynasore (80 μM) for 30 min prior to the addition of the polymer/DNA complex and throughout the 2-h uptake experiment at 37°C. Results were expressed as percentage uptake of the control where cells were incubated with complexes in the absence of inhibitors.

To observe the intracellular distribution of the polymer/DNA complexes, HeLa cells were incubated with polyester/YOYO-1-DNA complexes in serum-free DMEM at 0.5 μg DNA/well (6-well plate) for 1 h and 4 h, respectively. Cells were then stained with Lysotracker®-Red (Invitrogen) and DAPI according to the manufacturer's protocol, and were visualized by confocal laser scanning microscopy (CLSM).

***In Vitro* Transfection.** Cells were seeded on 96-well plates at 1×10^4 cells/well and incubated for 24 h prior to the transfection studies. The medium was replaced by serum-free DMEM, into which polymer/DNA complexes were added at 0.1 μg DNA/well. After incubation for 4 h, the medium was replaced by serum-containing DMEM and cells were further cultured for 20 h. Luciferase expression was assayed using a Bright-Glo luciferase assay kit while cellular protein level was determined using a BCA kit. Results were expressed as relative light unit (RLU) for each mg of cellular protein. To explore the involvement of endosomal entrapment and escape during transfection, we performed the transfection experiment in the presence of chloroquine or Bafilomycin A1. Briefly, complexes were incubated with cells in DMEM supplemented with chloroquine (100 μM) or bafilomycin A1 (50 nM) for 4 h. The media were replaced by serum-containing DMEM and cells were further cultured for 20 h before assessment for luciferase expression.

Cytotoxicity of Poly(1)$_{50}$-*g*-AET$_2$. HeLa cells were seeded in a 96-well plate at 1×10^4 cells/well and incubated for 24 h. The medium was changed to serum-free DMEM. Poly(**1**)$_{50}$-*g*-AET$_2$ was added at 200, 100, 50, 20, 10, and 5 μg/mL, respectively. After incubation for 4 h, the medium

was replaced by serum-containing DMEM. Cells were further incubated for 20 h. Cell viability was assessed with the MTT assay. PLL and PLR were served as the controls. Cells without poly$(1)_{50}$-*g*-AET_2 treatment were served as the control. The toxicity results were expressed as percentage viability of control cells.

Supplementary Figures

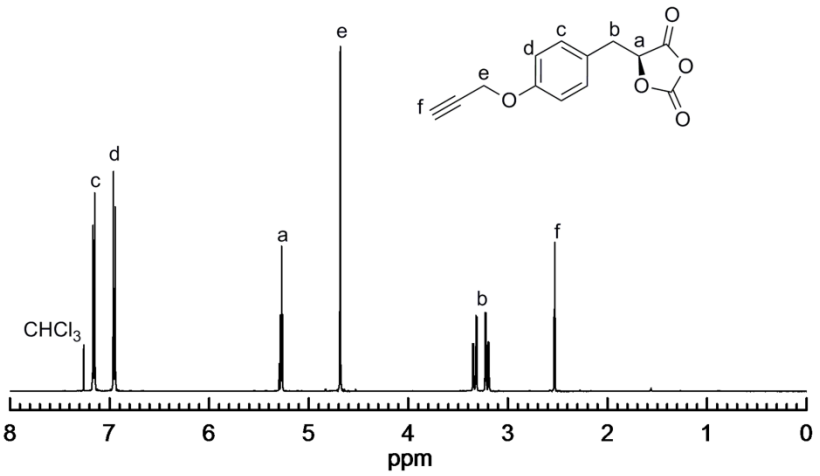


Figure S1 ^{1}H NMR spectrum of the Tyr(alkynyl)-OCA (**1**) in $CDCl_3$

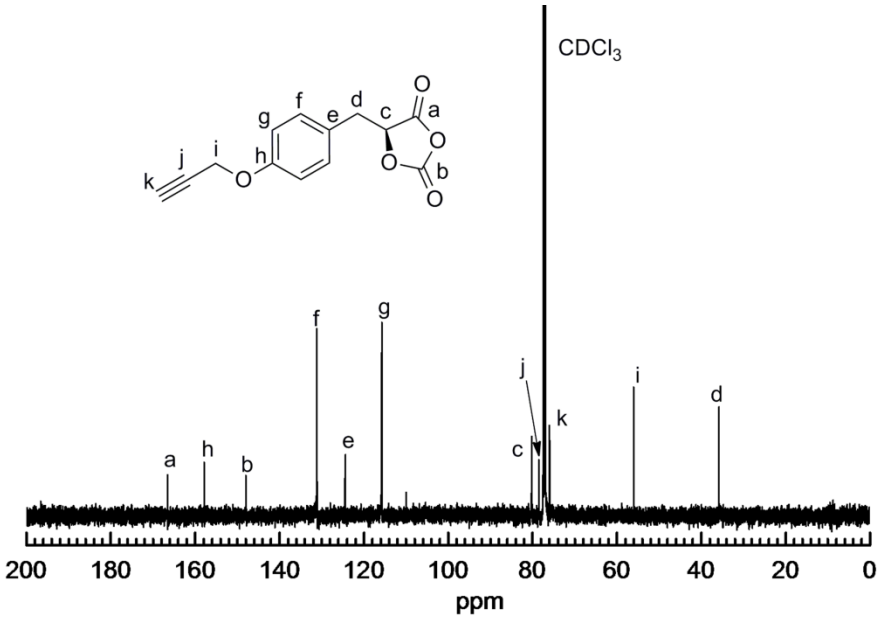


Figure S2 ^{13}C NMR spectrum of the Tyr(alkynyl)-OCA (**1**) in $CDCl_3$

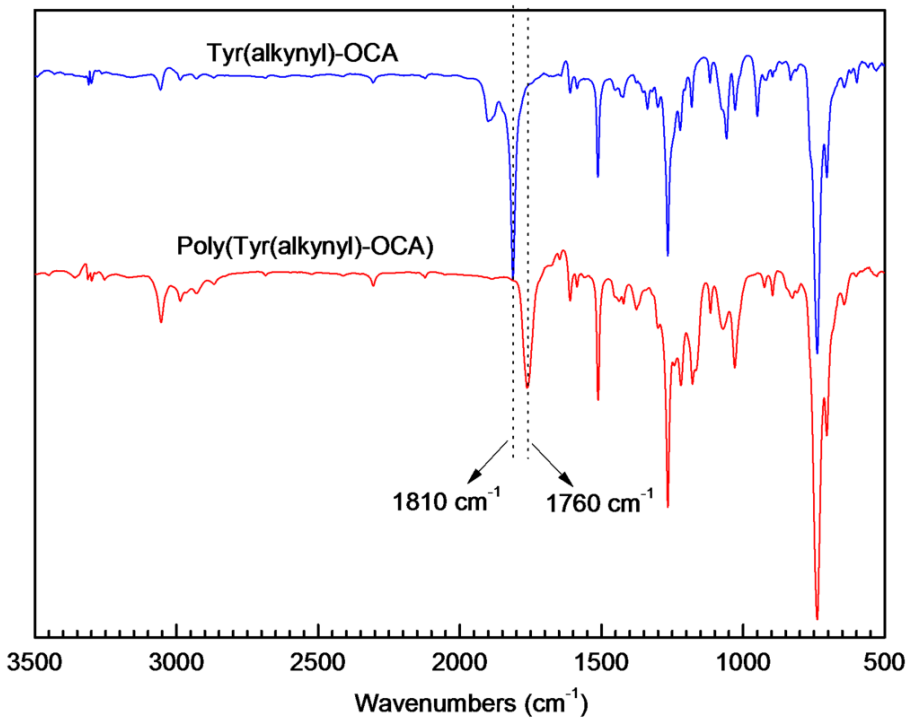


Figure S3 FTIR spectra of Tyr(alkynyl)-OCA (**1**) and poly(Tyr(alkynyl)-OCA) (poly(**1**)). After the polymerization is complete, the anhydride band of **1** at 1810 cm^{-1} disappears and an ester band poly(**1**) at 1760 cm^{-1} is observed.

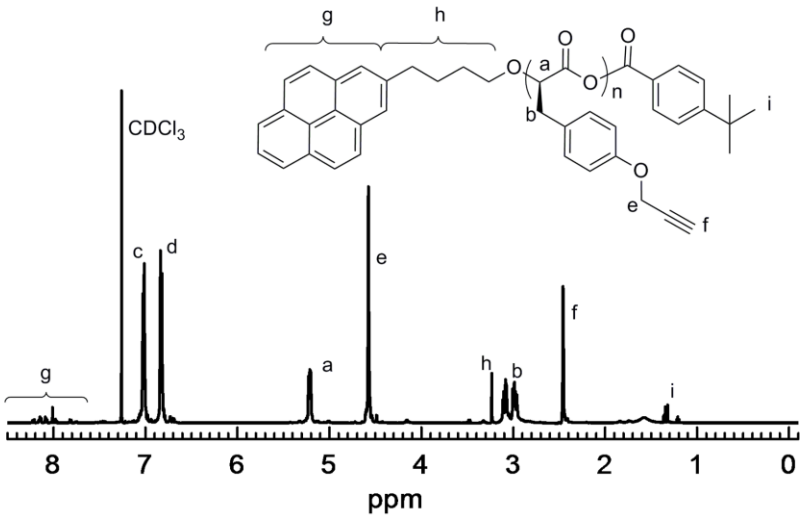


Figure S4 ^{1}H NMR spectrum of poly(**1**) in $CDCl_3$. In the reaction pyrenebutanol was used as the initiator and 4-*tert*-butylbenzoyl chloride was used as the end-capping reagent.

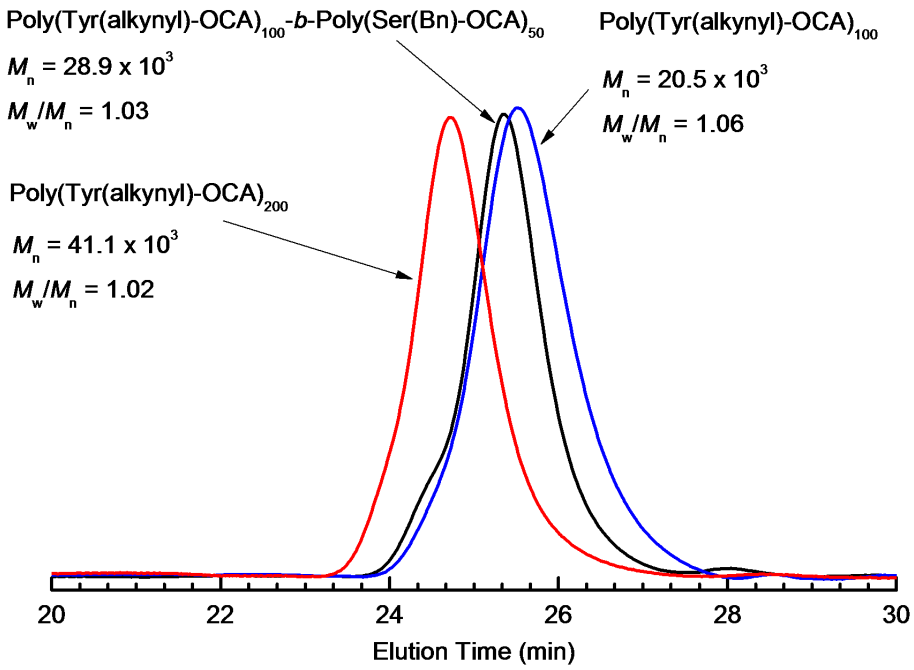


Figure S5 Overlay of GPC curves of poly(**1**) prepared at a M/I ratio of 100 (blue) and after addition of a second portion of 50 equivalent Ser(Bn)-OCA (black) or 100 equivalent **1** (red).

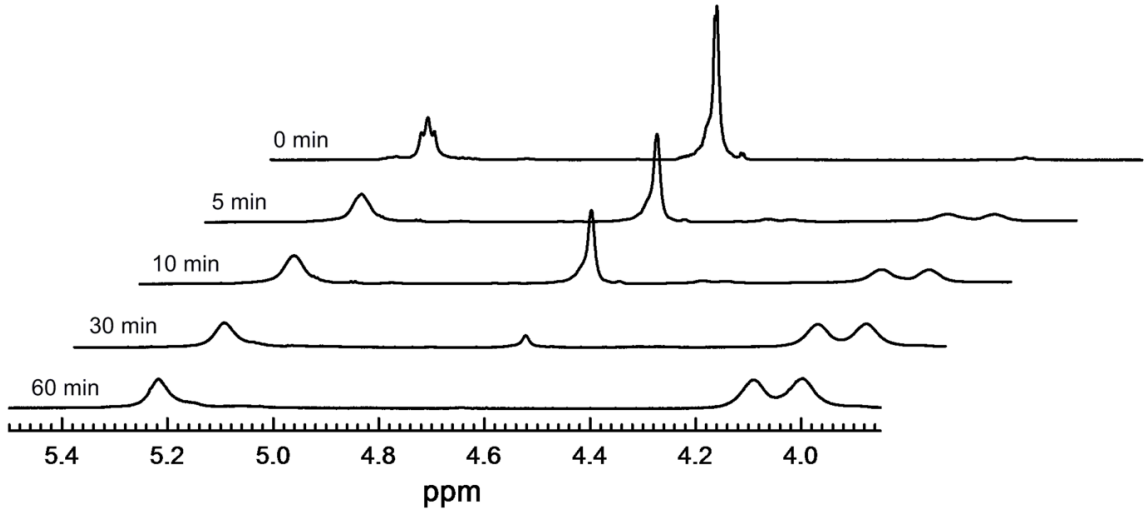


Figure S6 Monitoring the thiol-yne reaction between poly(**1**) and AET by ^{1}H NMR at selected UV-treatment time (20 mW/cm^{2}).

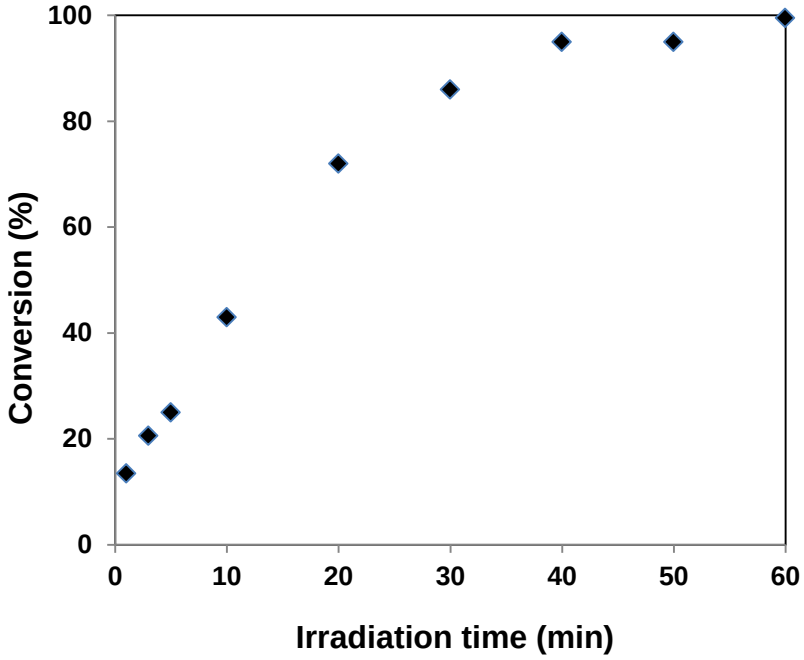


Figure S7 Conversion of alkyne versus UV-treatment time for the thiol-yne reaction of AET and poly(**1**). The molar ratio of thiol/alkyne of the reaction was set at 8.

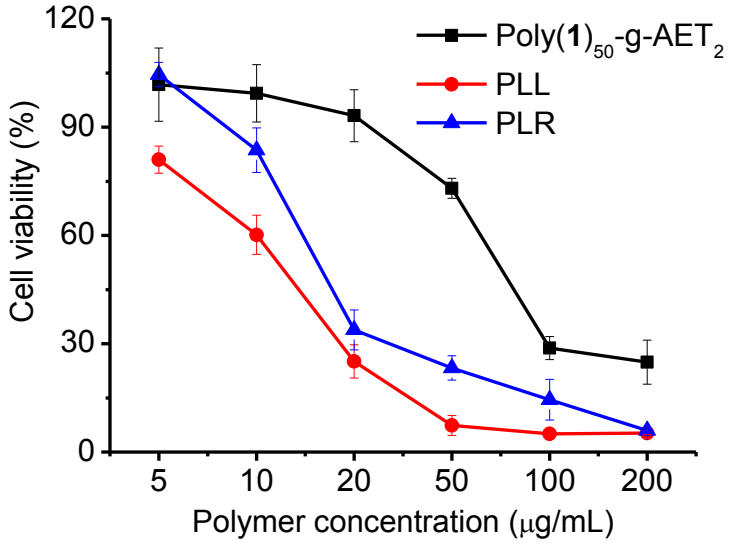


Figure S8 Viability of HeLa cells incubated with Poly(**1**)$_{50}$-*g*-AET$_2$, PLL and PLR for 24 h.

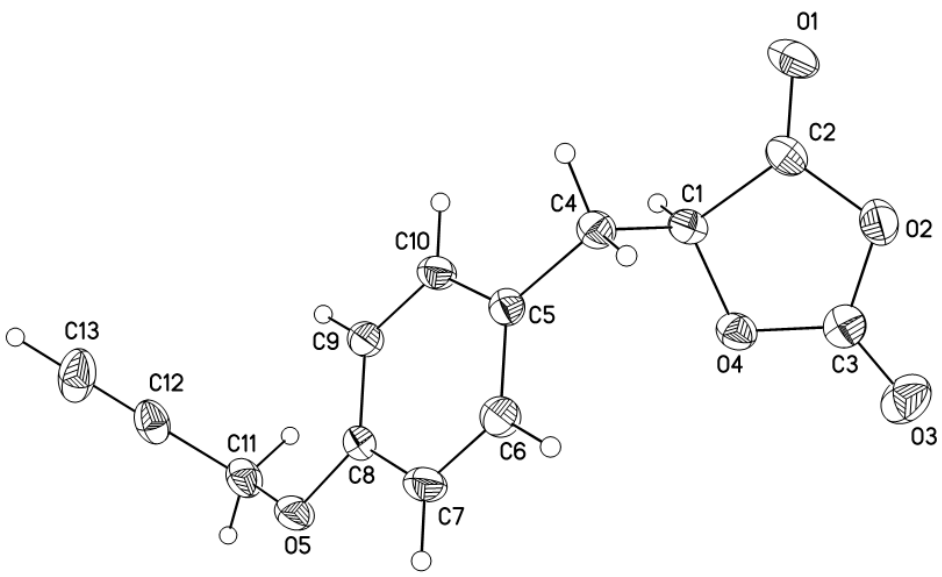


Figure S9 X-Ray diffraction image of **1**.

Table S1. Crystal data and structure refinement for bc08tas.

Identification code	bc08tas	
Empirical formula	$C_{13}H_{10}O_5$	
Formula weight	246.21	
Temperature	193(2) K	
Wavelength	1.54178 Å	
Crystal system	Monoclinic	
Space group	P 21	
Unit cell dimensions	a = 4.7496(2) Å	□= 90°.
	b = 9.1048(4) Å	□= 96.134(2)°.
	c = 13.4215(7) Å	□ = 90°.
Volume	577.08(5) $Å^3$	
Z	2	
Density (calculated)	1.417 Mg/m^3	
Absorption coefficient	0.934 mm^{-1}	
F(000)	256	
Crystal size	0.578 x 0.203 x 0.197 mm^3	
Theta range for data collection	3.31 to 66.88°.	
Index ranges	-5<=h<=5, -10<=k<=10, -13<=l<=15	
Reflections collected	7041	
Independent reflections	1964 [R(int) = 0.0279]	
Completeness to theta = 66.88°	97.6 %	
Absorption correction	Integration	
Max. and min. transmission	0.8762 and 0.6805	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	1964 / 1 / 164	
Goodness-of-fit on F^2	1.062	
Final R indices [I>2sigma(I)]	R1 = 0.0243, wR2 = 0.0646	
R indices (all data)	R1 = 0.0244, wR2 = 0.0647	
Absolute structure parameter	0.12(14)	
Extinction coefficient	0.0124(15)	
Largest diff. peak and hole	0.121 and -0.126 $e.Å^{-3}$	

Table S2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3)
for bc08tas. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	-5987(2)	6058(1)	5207(1)	50(1)
O(2)	-3100(2)	7398(1)	4348(1)	43(1)
O(3)	385(3)	8914(1)	3985(1)	57(1)
O(4)	-250(2)	8415(1)	5575(1)	36(1)
O(5)	4712(2)	10755(1)	9710(1)	44(1)
C(1)	-2116(3)	7486(1)	6079(1)	32(1)
C(2)	-4019(3)	6858(1)	5215(1)	35(1)
C(3)	-845(3)	8312(2)	4589(1)	38(1)
C(4)	-3617(3)	8362(2)	6826(1)	33(1)
C(5)	-1501(3)	9001(1)	7629(1)	30(1)
C(6)	-550(3)	10432(2)	7569(1)	40(1)
C(7)	1521(3)	10979(2)	8272(1)	44(1)
C(8)	2662(3)	10106(1)	9054(1)	32(1)
C(9)	1724(3)	8681(1)	9135(1)	34(1)
C(10)	-343(3)	8146(2)	8420(1)	35(1)
C(11)	6232(3)	9835(2)	10443(1)	40(1)
C(12)	4732(3)	9582(2)	11323(1)	41(1)
C(13)	3594(5)	9343(2)	12038(1)	60(1)

Table S3. Bond lengths [Å] and angles [°] for bc08tas.

O(1)-C(2)	1.1841(17)
O(2)-C(3)	1.3678(18)
O(2)-C(2)	1.3766(17)
O(3)-C(3)	1.1827(18)
O(4)-C(3)	1.3275(17)
O(4)-C(1)	1.4442(16)
O(5)-C(8)	1.3747(15)
O(5)-C(11)	1.4280(17)
C(1)-C(2)	1.5049(18)
C(1)-C(4)	1.5171(17)
C(1)-H(1)	1.0000
C(4)-C(5)	1.5096(18)
C(4)-H(4A)	0.9900
C(4)-H(4B)	0.9900
C(5)-C(10)	1.3823(19)
C(5)-C(6)	1.3847(19)
C(6)-C(7)	1.381(2)
C(6)-H(6)	0.9500
C(7)-C(8)	1.3804(19)
C(7)-H(7)	0.9500
C(8)-C(9)	1.3798(19)
C(9)-C(10)	1.3856(19)
C(9)-H(9)	0.9500
C(10)-H(10)	0.9500
C(11)-C(12)	1.461(2)
C(11)-H(11A)	0.9900
C(11)-H(11B)	0.9900
C(12)-C(13)	1.171(2)
C(13)-H(13)	0.9500

C(3)-O(2)-C(2)	109.17(10)
C(3)-O(4)-C(1)	110.47(10)
C(8)-O(5)-C(11)	117.42(11)
O(4)-C(1)-C(2)	102.11(10)

O(4)-C(1)-C(4)	110.92(10)
C(2)-C(1)-C(4)	115.02(10)
O(4)-C(1)-H(1)	109.5
C(2)-C(1)-H(1)	109.5
C(4)-C(1)-H(1)	109.5
O(1)-C(2)-O(2)	122.21(13)
O(1)-C(2)-C(1)	130.49(13)
O(2)-C(2)-C(1)	107.30(11)
O(3)-C(3)-O(4)	125.60(15)
O(3)-C(3)-O(2)	123.51(14)
O(4)-C(3)-O(2)	110.89(11)
C(5)-C(4)-C(1)	110.51(10)
C(5)-C(4)-H(4A)	109.5
C(1)-C(4)-H(4A)	109.5
C(5)-C(4)-H(4B)	109.5
C(1)-C(4)-H(4B)	109.5
H(4A)-C(4)-H(4B)	108.1
C(10)-C(5)-C(6)	117.99(13)
C(10)-C(5)-C(4)	120.76(12)
C(6)-C(5)-C(4)	121.16(12)
C(7)-C(6)-C(5)	120.80(13)
C(7)-C(6)-H(6)	119.6
C(5)-C(6)-H(6)	119.6
C(8)-C(7)-C(6)	120.34(13)
C(8)-C(7)-H(7)	119.8
C(6)-C(7)-H(7)	119.8
O(5)-C(8)-C(9)	124.49(12)
O(5)-C(8)-C(7)	115.65(11)
C(9)-C(8)-C(7)	119.86(12)
C(8)-C(9)-C(10)	119.10(12)
C(8)-C(9)-H(9)	120.5
C(10)-C(9)-H(9)	120.5
C(5)-C(10)-C(9)	121.91(12)
C(5)-C(10)-H(10)	119.0
C(9)-C(10)-H(10)	119.0
O(5)-C(11)-C(12)	113.29(11)

O(5)-C(11)-H(11A)	108.9
C(12)-C(11)-H(11A)	108.9
O(5)-C(11)-H(11B)	108.9
C(12)-C(11)-H(11B)	108.9
H(11A)-C(11)-H(11B)	107.7
C(13)-C(12)-C(11)	177.79(16)
C(12)-C(13)-H(13)	180.0

Symmetry transformations used to generate equivalent atoms:

Table S4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for bc08tas. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2} U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	45(1)	44(1)	59(1)	-12(1)	0(1)	-16(1)
O(2)	44(1)	50(1)	34(1)	-6(1)	2(1)	-2(1)
O(3)	62(1)	59(1)	55(1)	2(1)	29(1)	0(1)
O(4)	30(1)	38(1)	40(1)	-5(1)	4(1)	-4(1)
O(5)	54(1)	40(1)	35(1)	1(1)	-8(1)	-17(1)
C(1)	30(1)	27(1)	36(1)	1(1)	-2(1)	-1(1)
C(2)	34(1)	31(1)	40(1)	-6(1)	0(1)	1(1)
C(3)	37(1)	37(1)	42(1)	-2(1)	10(1)	6(1)
C(4)	30(1)	36(1)	33(1)	0(1)	0(1)	-3(1)
C(5)	29(1)	32(1)	30(1)	-1(1)	3(1)	0(1)
C(6)	51(1)	34(1)	33(1)	6(1)	-4(1)	-3(1)
C(7)	60(1)	30(1)	41(1)	4(1)	-4(1)	-13(1)
C(8)	36(1)	34(1)	27(1)	-4(1)	3(1)	-7(1)
C(9)	40(1)	30(1)	30(1)	3(1)	-2(1)	-2(1)
C(10)	40(1)	28(1)	36(1)	1(1)	0(1)	-6(1)
C(11)	36(1)	46(1)	36(1)	-6(1)	-3(1)	-4(1)
C(12)	54(1)	32(1)	35(1)	-4(1)	-2(1)	12(1)
C(13)	97(1)	43(1)	43(1)	5(1)	23(1)	21(1)

Table S5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for bc08tas.

	x	y	z	U(eq)
H(1)	-997	6678	6436	38
H(4A)	-4721	9165	6474	40
H(4B)	-4952	7716	7138	40
H(6)	-1332	11046	7037	48
H(7)	2165	11961	8217	53
H(9)	2485	8075	9674	41
H(10)	-982	7164	8476	42
H(11A)	8087	10294	10660	48
H(11B)	6597	8878	10132	48
H(13)	2671	9150	12618	72

Table S6. Torsion angles [°] for bc08tas.

C(3)-O(4)-C(1)-C(2)	-2.30(13)
C(3)-O(4)-C(1)-C(4)	-125.33(11)
C(3)-O(2)-C(2)-O(1)	178.67(13)
C(3)-O(2)-C(2)-C(1)	-0.83(14)
O(4)-C(1)-C(2)-O(1)	-177.59(14)
C(4)-C(1)-C(2)-O(1)	-57.4(2)
O(4)-C(1)-C(2)-O(2)	1.85(13)
C(4)-C(1)-C(2)-O(2)	122.06(12)
C(1)-O(4)-C(3)-O(3)	-177.71(13)
C(1)-O(4)-C(3)-O(2)	1.96(14)
C(2)-O(2)-C(3)-O(3)	179.02(13)
C(2)-O(2)-C(3)-O(4)	-0.67(15)
O(4)-C(1)-C(4)-C(5)	-61.95(13)
C(2)-C(1)-C(4)-C(5)	-177.18(12)
C(1)-C(4)-C(5)-C(10)	-79.69(15)
C(1)-C(4)-C(5)-C(6)	96.83(14)
C(10)-C(5)-C(6)-C(7)	0.8(2)
C(4)-C(5)-C(6)-C(7)	-175.76(13)
C(5)-C(6)-C(7)-C(8)	-0.6(2)
C(11)-O(5)-C(8)-C(9)	8.78(17)
C(11)-O(5)-C(8)-C(7)	-171.22(13)
C(6)-C(7)-C(8)-O(5)	179.86(12)
C(6)-C(7)-C(8)-C(9)	-0.1(2)
O(5)-C(8)-C(9)-C(10)	-179.48(12)
C(7)-C(8)-C(9)-C(10)	0.53(19)
C(6)-C(5)-C(10)-C(9)	-0.5(2)
C(4)-C(5)-C(10)-C(9)	176.17(12)
C(8)-C(9)-C(10)-C(5)	-0.2(2)
C(8)-O(5)-C(11)-C(12)	-82.55(15)
O(5)-C(11)-C(12)-C(13)	169(5)

Symmetry transformations used to generate equivalent atoms:

References

(1) Gabrielson, N. P.; Cheng, J. J. *Biomaterials* **2010,** *31*, 9117-9127.