# Supporting Information

## Modular Synthetic Platform for the Construction of Functional Single-Chain Polymeric Nanoparticles: from Aqueous Catalysis to Photo-Sensitization

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## Experimental Section

## Materials and Methods

### 1. Chemicals

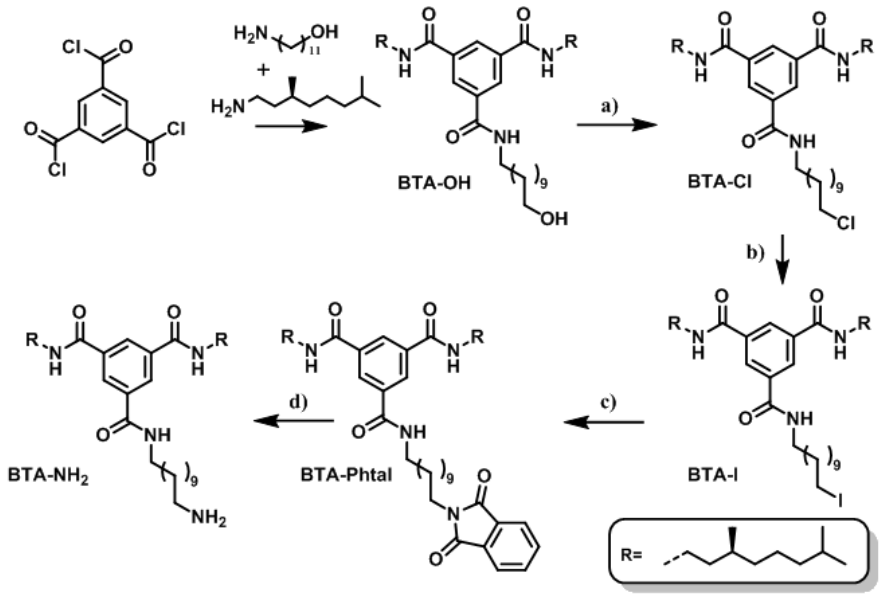
Azobisisobutyronitrile (AIBN) was recrystallized from methanol. 4-Cyano-4-((phenylcarbonothioyl)thio)pentanoic acid was kindly provided by SyMO-Chem (Eindhoven, the Netherlands). 3-Azido-7-hydroxy-2H-chromen-2-one (FluoroChem, 95%), Pentafluorophenyl acrylate (Sigma-Aldrich, 98%), Jeffamine® M-1000 (Jeffamine M1000, PO/EO mol ratio = 3/19, Lot n°: 0L504, Huntsman Holland BV), 4-(2-amino-ethyl)-piperidine-1-carboxylic acid tert-butyl ester (Sigma-Aldrich), 1,4-dioxane (Sigma-Aldrich, anhydrous, 99.8%), thionyl chloride (Sigma-Aldrich, ≥ 99.0%), phthalimide potassium salt (Sigma-Aldrich, 98%), sodium iodide (Sigma-Aldrich, 99.0%), hydrazine monohydrate ($N_2H_4$ 64-65%, reagent grade, 98%), copper(II) sulfate pentahydrate (Sigma-Aldrich, ≥ 98.0%), palladium acetate (Sigma-Aldrich, 98.0%), sodium ascorbate (Sigma-Aldrich, ≥ 98.0%), pentafluorophenyl trifluoroacetate (Sigma-Aldrich, 98.0%), 3-azido-7-hydroxycoumarin (fluorochem, 95%). 7-(4'-methyl-[2,2'-bipyridin]-4-yl)heptan-1-amine [1], allyloxycarbonyl-'caged'rhodamine 110 [2], 4-(10,15,20-tris(4-(methoxycarbonyl)phenyl)porphyrin-5-yl)benzoic acid[3] and 4-methyl-2-oxo-2H-chromen-7-yl propiolate[4] were synthesized according to a previously reported procedure.

### 2. Characterization methods

Ultraviolet-visible (UV/Vis) and circular dichroism (CD) measurements were performed on a Jasco J-815 spectropolarimeter where the sensitivity, time constant and scan rate were chosen appropriately. Corresponding temperature-dependent measurements were performed with a PFD-425S/15 Peltier-type temperature controller with a temperature range of 263-383 K and adjustable temperature slope, in all cases a temperature slope of 1 K/min was used. Fluorescence measurements were performed on a Jasco FP-6500 spectrofluorometer. Dynamic light scattering measurements were performed on a Malvern mV Zetasizer equipped with an 830 nm laser. Samples were prepared in MilliQwater, followed by ultrasonfication for 2 h, standing over night, and filtering the solution through a 0.2 mm PVDF-filter (Whatman). $^{1}H$ and $^{13}C$ NMR spectra were recorded at 25 ℃ on a Varian Mercury Vx 400 MHz, where chemical shifts were determined with respect to tetramethylsilane (TMS) as an internal reference. DMF-SEC measurements were carried out

in PL-GPC-50 plus from Polymer Laboratories (Agilent Technologies) with the refractive index detector working in DMF containing 10 mM LiBr at 50 °C at a constant flow rate of 1mL $min^{-1}$ on a Shodex GPC-KD-804 column (exclusion limit = 400 000 Da; 0.8 cmi.d. × 300 mL), which was calibrated with polyethyleneoxide (PEO) samples with a range from 282-77350 Da (Polymer Laboratories-Agilent Technologies). THF-SEC-measurements were performed on a Shimadzu-system with two Agilent Technology columns in series (PLgel 5 mm mixed C [200–2 000 000Da] and PLgel 5 mm mixed D [200–40 000 Da]) and equipped with a RI detector (Shimadzu RID-10A) and a PDA detector (Shimadzu SPD-M10A), with THF as eluent at a constant flowrate of 1.0 mL $min^{-1}$. The system was calibrated with polystyrene (PS) samples with a range of 580–100 000 Da (Polymer Laboratories). IR measurements were performed on PerkinElmer FT-IR Spectrometer. LC-MS: ThermoScientific LCQ Fleet. Infra-red emission spectroscopy: photoluminescence (PL) signals were recorded using an Edinburgh FLS920 Spectrometer with a nitrogen-cooled near-infrared photomultiplier tube (Hamamatsu R5509-72). Photoirradiation experiments employed a tungsten-halogen lamp filtered by a Schott GG385 UV filter and a Hoya LB120 daylight filter.

**Synthesis of BTA-$NH_2$:**




Conditions for the synthesis of BTA-$NH_2$: a) $SOCl_2$, DMF (cat.), 70 ℃; b) NaI, acetone, reflux; c) potassium phthalimide, DMF, 90 ℃; d) hydrazine monohydrate, THF, 60 ℃.

**BTA-OH**:

BTA-OH was synthesized following a previously reported procedure.[5]

**BTA-Cl:**

BTA-OH (1.1 g, 1.67 mmol) was charged in to a 25 mL flask and dissolved in 5 mL thionyl chloride. One droplet of DMF was added as catalyst. The mixture was stirred at 70 ℃ overnight and the mixture was subsequently allowed to cool to room temperature. The mixture was dropwise added into 200 mL of a NaOH-$Na_2CO_3$ (1.0 M-1.0 M) solution. The mixture was extracted by $CHCl_3$ (100 mL) and then washed with 1M NaOH solution (100 mL), water (2 × 100 mL) and brine (100 mL). The organic layer was dried with $MgSO_4$ and the solvent was evaporated *in vacuo*. After purification by column chromatography (20% ethyl acetate, 80% chloroform), a sticky white solid was obtained. Yield 0.85g, 75%. $^1$H-NMR (400 MHz, $CDCl_3$): δ = 8.34 (s, 3H, aromatic), 6.49 (m, 3H, NH), 3.54 (m, 2H, Cl-$CH_2$), 3,48 (m, 6H, NH-$CH_2$), 1.78 ~0.85 (m, 56H, $CH_2$, $CH_3$). $^{13}$C-NMR (400 MHz, $CDCl_3$): δ = 165.6, 135.2, 127.9, 40.4, 39.2, 38.5, 37.1, 36.6, 32.6, 30.7, 29.5, 29.4, 29.2, 28.8, 27.9, 27.0, 26.9, 24.6, 22.7, 22.6, 19.5. Maldi-TOF Calcd. $[M+H]^+$= 676.51, Obs. $[M+H]^+$= 676.52.

**BTA-I:**

BTA-Cl (0.85g, 1.26 mmol) and 6 g NaI was charged into a 250 mL flask and dissolved in 100 mL acetone, the mixture was then refluxed for 48 hours. After cooling to room temperature, the acetone was removed *in vacuo*. The solid residue was extracted by 100 mL $CHCl_3$ and washed with water (2 × 200 mL). The organic layer was dried over $Na_2SO_4$, the solvent was evaporated *in vacuo* and the product was obtained as a sticky light-yellow solid. Yield 0.88g, 91%. $^1$H-NMR (400 MHz, $CDCl_3$): δ = 8.34 (s, 3H, aromatic), 6.47 (m, 3H, NH), 3.48 (m, 6H, NH-$CH_2$), 3,19 (m, 2H, I-$CH_2$), 1.70 ~ 0.85 (m, 56H, $CH_2$, $CH_3$). $^{13}$C-NMR (400 MHz, $CDCl_3$):δ =165.8, 165.7, 135.3, 127.9, 60.3, 40.4, 39.2, 38.5, 37.1, 36.6, 33.5, 30.8, 30.5, 29.5, 29.4, 29.4, 29.3, 28.5, 27.9, 27.0, 24.6, 22.7, 22.6, 22.6, 19.5. Maldi-TOF Calcd. $[M+H]^+$= 768.45, Obs. $[M+H]^+$= 768.45.

**BTA-Phtal:**

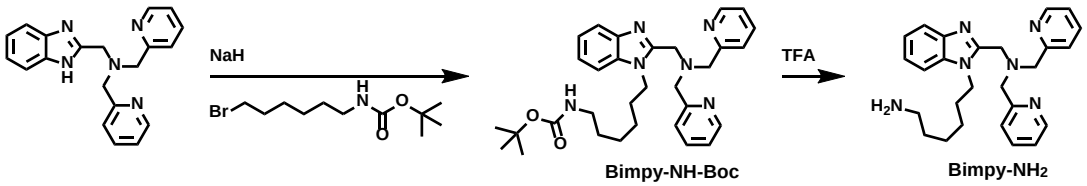
BTA-I (0.88 g, 1.15 mmol) and 500 mg potassium phthalimide was dissolved in 20 mL DMF. The mixture was stirred at 90 ℃ overnight. After cooling to room temperature, the mixture was added into 200 mL water and then extracted by ethyl acetate (100 mL). The organic phase was washed with water (2 × 200 mL) and saturated KCl (100 mL). After drying by $MgSO_4$, the crude product was purified by column chromatography (ethyl acetate:chloroform = 3:7). Yield 0.72 g, 80%. $^1$H-NMR (400 MHz, $CDCl_3$): δ = 8.34 (s, 3H, aromatic), 7.84 (m, 2H, aromatic), 7.72(s, 2H, aromatic), 6.64 (m, 3H, NH), 3.64 (m, 2H, N-$CH_2$), 3,44 (m, 6H, NH-$CH_2$), 1.90 ~ 0.85 (m, 56H, $CH_2$, $CH_3$). $^{13}$C-NMR (400 MHz, $CDCl_3$): δ =168.5, 165.7, 135.2, 133.8, 132.2, 127.9, 123.1, 77.3, 40.4, 39.2, 38.5, 38.0, 37.1, 36.6, 30.7, 29.5, 29.4, 29.4, 29.2, 29.1, 28.5, 27.9, 26.9, 26.8, 24.6, 22.7, 22.6, 22.6, 19.5. Maldi-TOF Calcd. $[M+H]^+$ = 786.57, $[M+Na]^+$ = 809.56, Obs. $[M+H]^+$ = 786.57, $[M+Na]^+$ = 809.56.

**BTA-$NH_2$:**

BTA-Phtal (0.72 g, 1.10 mmol) was dissolved in 30 mL THF and 2 mL hydrazine monohydrate was added. The mixture was allowed to stir at 60 ℃ overnight during which time an off-white solid precipitated. The solvent and the excess of hydrazine were removed *in vacuo*. $CHCl_3$ (100 mL) and 1 M NaOH (100 mL) were added to the residue and the organic layer was separated and washed with 1 M NaOH (2 × 100 mL), $H_2O$ (200 mL) and brine (100 mL). The organic layer was dried over $MgSO_4$ and the solvent was removed *in vacuo*. The crude product was purified by column chromatography (neutral aluminium oxide,

DCM:MeOH:$NH_3$ (aq., 25%) = 9:1:0.1). Yield 0.45g, 60%. $^1$H-NMR (400 MHz, $CDCl_3$): δ = 8.35 (s, 3H, aromatic), 6.63 (m, 3H, NH), 3,48 (m, 6H, NH-$CH_2$), 2.67 (m, 2H, $NH_2$-$CH_2$), 1.78 ~0.85 (m, 56H, $CH_2$, $CH_3$). $^{13}$C-NMR (400 MHz, $CDCl_3$): δ =165.7, 139.4, 135.2, 135.2, 127.9, 40.3, 39.2, 38.5, 37.1, 36.6, 30.7, 29.4, 27.9, 26.9, 24.6, 22.7, 22.6, 19.5. Maldi-TOF Calcd. $[M+H]^+$= 657.56, Obs. $[M+H]^+$= 657.63.

**Synthesis of Bimpy-$NH_2$**

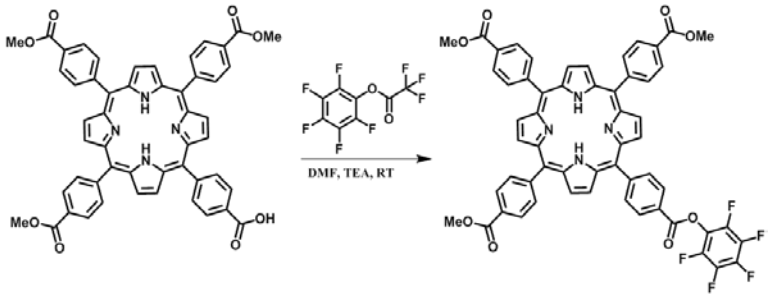



Sodium hydride 60% dispersion in mineral oil (0.012 g, 0.30 mmol, 1.5 eq.) was added to a 5-mL vial, vacuum-purged with argon, then washed with 2 mL of anhydrous pentane (dried over 4Å molecular sieves). The resulting white solid was suspended in 1 mL anhydrous DMF (dried over 3Å mol. sieves) and a 1 mL DMF solution of BimPy (0.066 g, 0.20 mmol, 1.0 eq.) was added dropwise at room temp. After the bubbling stopped, the dark orange reaction was heated at 80°C for 1 hr, then allowed to cool down to RT. The 6-(Boc-amino)hexyl bromide (0.112 g, 0.40 mmol, 2.0 eq.) was diluted in 1 mL DMF and injected dropwise to the dark brown reaction, which was further heated to 80°C for 1 hr. The black reaction mixture was allowed to cool down prior to being quenched with saturated aqueous ammonium chloride and extracted 2 × 10 mL with chloroform. The organics were washed with 5 mL of sodium carbonate, dried over anh. $MgSO_4$, filtered and concentrated under reduced pressure to brown sticky gum. HPLC-MS (15 min. gradient 25-30% MeCN/$H_2O$ with 0.1% formic acid) revealed the presence of product (m/z = 529.50, 551.42; calc. for $M+H^+$ = 529.33, $M+Na^+$ = 551.31), which was isolated by preparative LC-MS (isocratic 30% MeCN/$H_2O$ with 0.1% formic acid). After removal of solvents by rotary evaporation at 45°C (with a flow of air over the liquid!) we obtained Bimpy-NH-Bocas sticky yellow solid with blue-green fluorescence (0.073, 0.14, 69%).

$^1$H NMR (400 MHz, $CHCl_3$) δ 8.72 (d, J = 5.3 Hz, 2H), 8.01 – 7.85 (m, 4H), 7.55 – 7.42 (m, 6H), 4.65 (s, 2H), 4.37 (s, 1H), 4.33 (s, 4H), 3.06 (t, J = 6.2 Hz, 2H), 1.81 – 1.68 (m, 2H), 1.42 (s, 9H), 1.37 – 1.24 (m, 8H). $^{13}$C NMR (101 MHz, $CHCl_3$) δ 154.12, 149.79, 145.30, 141.80, 132.01, 131.40, 126.23, 124.43, 109.99, 58.33, 28.36 ppm.

Bimpy-NH-Boc (0.010 g, 0.02 mmol, 1.0 eq.) was dissolved in 0.5 mL anhydrous DCM, then treated with a few drops of TFA. After 3 hours, Ninhydrin test revealed the presence of primary amines, so the solvent was removed by placing the vial under a gentle stream of argon. The product was used without further purification. HPLC-MS m/z= 215.25, 429.33, 451.33; calc. for $(M+2H^+)/2$ = 215.14, $M+H^+$ = 429.28, $M+Na^+$ = 451.26.

**Synthesis of PorPF**




4-(10,15,20-Tris(4-(methoxycarbonyl)phenyl)porphyrin-5-yl)benzoic acid (TMPA, 16.6 mg, 20 μmol) was dissolved in 1 mL DMF and 0.1 mL triethyl amine was added. Pentafluorophenyl trifluoroacetate (28 mg, 0.1 mmol) was then added, and stirring was continued at room temperature for 1 hour when TLC showed fully conversion. $^{19}$F NMR showed that the excess pentafluorophenyl trifluoroacetate was hydrolized. After evaporating the DMF, the crude product was purified by column chromatography. Yield 15.5 mg, 78%. - $^1$H-NMR (400 MHz, $CDCl_3$): δ = 8.86-8.82 (m, 8H), 8.63-8.60 (m, 2H), 8.48-8.40 (m, 8H), 8.32-8.29 (m, 6H), 4.12 (s, 9H). $^{19}$F-NMR (400 MHz, $CDCl_3$): δ = -152.30, -157.65, -162.08. Maldi-TOF Calcd. $[M]^+$= 998.24, Obs. $[M]^+$= 998.24.

**RAFT polymerization of pentafluorophenyl acrylate (PFPA)**

$pPFPA_{100}$: A Schlenk tube was charged witha stir bar, pentafluorophenylacrylate (4.0 g, 16.80 mmol, 261 eq.),4-cyano-4-((phenylcarbonothioyl)thio)pentanoic acid(0.018 g, 0.064 mmol, 1.0 eq.), azobis-isobutyronitrile (AIBN, 1.59 mg, 9.65 μmol, 0.15 eq.), and dioxane (4.0 mL). The solution was degassed under ice cooling by gently bubbling argon through the solution for 30 minutes. Subsequently, the Schlenk tube was placed into a preheated oil bath at 80 °C. After 2 hours 45 minutes, the polymerization was stopped by placing the Schlenk tube in a liquid-nitrogen bath. The monomer conversion was determined to be 38.4 % by measuring $^{19}$F NMR of the reaction mixture (see Figure S1). $pPFPA_{100}$ was isolated by precipitation in methanol (three times) and by drying under vacuum to yield a slightly pink

powder. The theoretical $M_n$ was calculated by using the linear RAFT equation: $M_n$ = ($[M]_0/[RAFT]_0$) × monomer conversion × $M_W$(Monomer)+ $M_W$(RAFT agent), $[M]_0$, $[RAFT]_0$, $M_W$ (monomer) and $M_W$ (RAFT agent) represent monomer and RAFT agent concentrations, molar mass of monomer and RAFT agent, respectively. The monomer conversion was directly determined after polymerization by $^{19}$F-NMR (see Figure S1). The degree of polymerization (*DP*) was calculated to be 100. SEC/THF (GPC data is based on polystyrene standard calibration): $M_n$ = 14.8 kDa, $Đ$ = 1.19.

Following a similar procedure, $pPFPA_{170}$ ($M_n$ = 23.7 kDa, $Đ$ = 1.30, DP~170) and $pPFPA_{150}$ ($M_n$ = 20.6 kDa, $Đ$ = 1.18, DP~150) were synthesized.

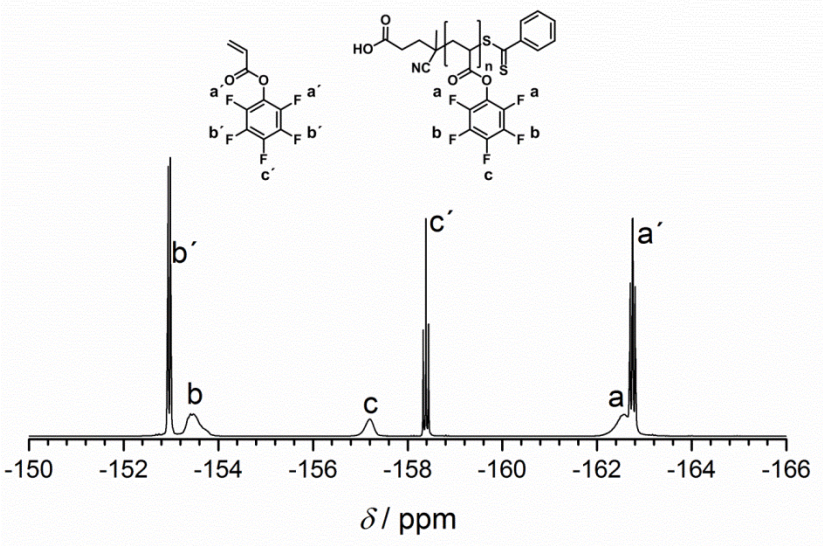



Figure S1: $^{19}$F NMR spectra of the reaction mixture, a', b', c' belong to PFPA monomer, a, b, c belong to the resulting polymer pPFPA. The conversion can be calculated to be 38.4%, corresponding to an average degree of polymerization of 100.

**Statistical copolymers from polymer analogues reactions - general remarks:**

The conversion of pPFPA with sequentially added amines was followed by $^{19}$F-NMR in the following fashion: A sample was taken after the reaction with each amino-functionalized compound (reaction time: in case of Jeffamine: 16 h, in all other cases 2 h). The NMR solvent was removed under a stream of nitrogen, dry THF was added and the sample was back injected into the reaction mixture. Note: Since the mass of the compounds employed has directinfluenceon the percentages on the polymeric backbone, care should be taken in the weighting and addition process.

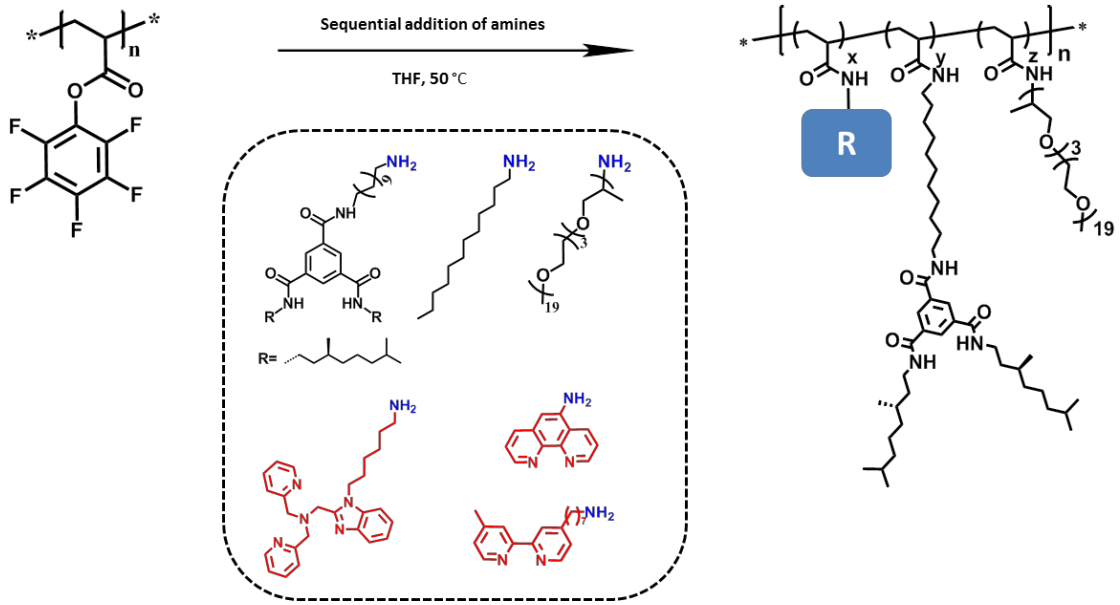



Figure S2: Synthesis **of P1-P5** and **P9** by post-polymerization modification of pPFPA.

The synthesis of **P1-P5** and **P9** is similar, therefore the synthesis of **P1** is chosen as an example:

**pPFPA$_{100}$** (100 mg, 4.16 µmol, 1.0 eq.) and a stirrer were placed in a flask, dissolved in 3 mL of dry THF and the mixture was heated to 50 °C under a nitrogen atmosphere. BTA-amine (27.9 mg, 0.042 mmol, 10.0 eq.) dissolved in 2 mL of dry THF was added into the reaction mixture and stirred for 2 h. Next, dodecan-1-amine (3.85 mg, 0.021 mmol, 5.0 eq.) dissolved in 2 mL of dry THF was added into the reaction mixture and stirredfurther for another 2 h. Finally, pre-dried Jeffamine M1000 (563 mg, 0,541 mmol, 130 eq.) dissolved in 2 mL of dry THF was added into the mixture and stirred at 50 °C overnight. After cooling, the reaction solution was dialyzed against THF, twice against methanol, and again against THF. The solvent of the final mixture was removed under reduced pressure. The chemical structure of **P1** was further confirmed by $^1$H NMR. SEC/DMF: $M_n$ =28.1 kDa, $Đ$= 1.16.

It should be noted that **P1**, **P2** and **P5** were synthesized by using **pPFPA$_{100}$** as precursor polymer, **P3** was synthesized from **pPFPA$_{170}$**, **P4** and **P6-P9** were synthesized from **pPFPA$_{150}$**.

The synthesis of **P6-P8** employed a stepwise modification strategy:

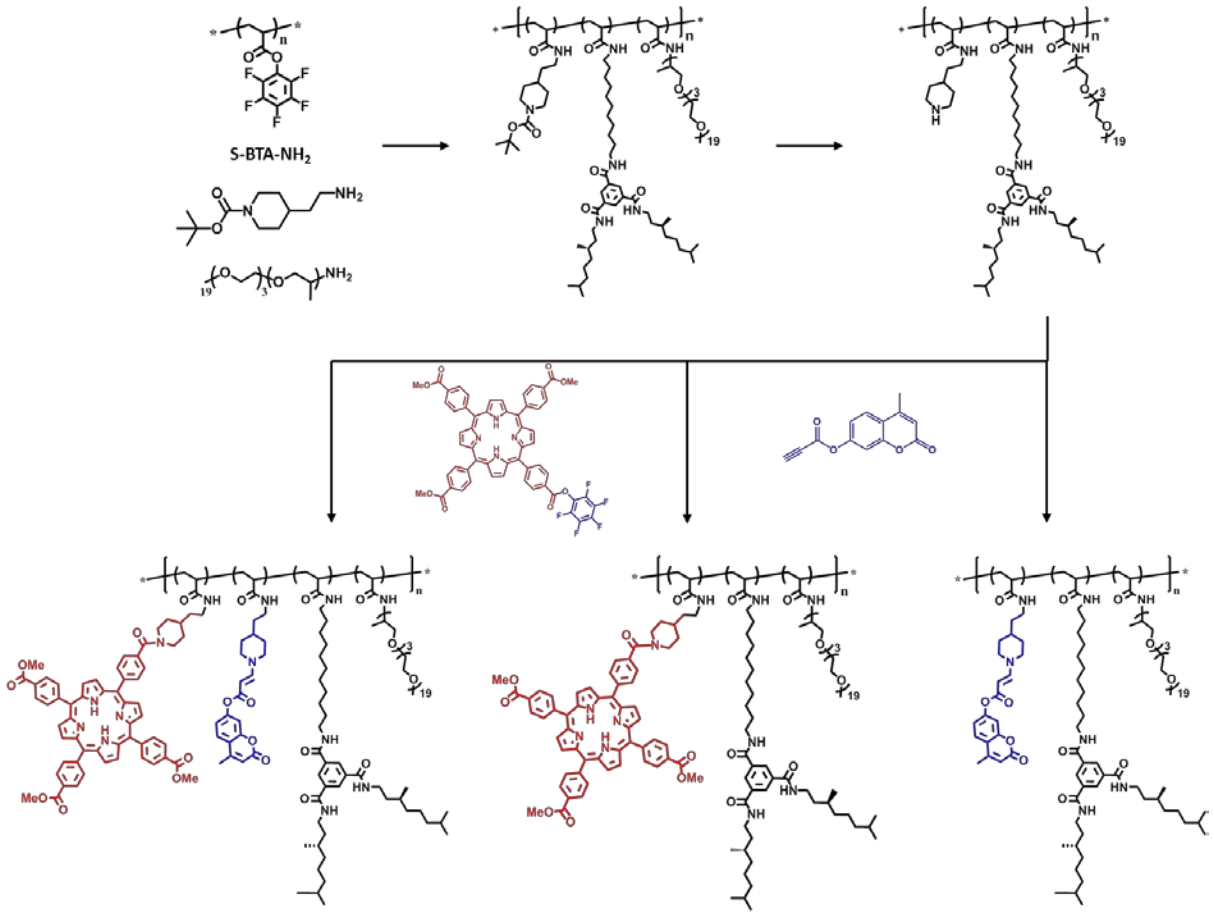



Figure S3: Synthesis of **P6-P8** by a two step modification strategy.

Using **P7** as an example:

**pPFPA$_{150}$** (40 mg, 1.67 μM, 1.0 eq.) and a stirrer were placed in a flask, dissolved in 2 mL of dry THF and the mixture was heated to 50 °C under a nitrogen atmosphere. (*S*)-BTA-amine (9.9 mg, 15 μM, 9.0 eq.) dissolved in 2 mL of dry THF was added into the reaction mixture and stirred for 2 h. Next, tert-butyl 4-(2-aminoethyl)piperidine-1-carboxylate (2.30 mg, 10 μmol, 6.0 eq.) dissolved in 1 mL of dry THF was added into the reaction mixture and stirred overnight. Finally, pre-dried Jeffamine M1000 (400 mg, 0.4 mmol, 240 eq.) dissolved in 2 mL of dry THF was added into the mixture and stirred at 50 °C until $^{19}$F-NMR showed that the reaction was complete. Then, 0.5 mL trifluoroacetic acid (TFA) was added to deprotect

the BOC group at room temperature. After 1 hour reaction, the mixture was dialyzed against THF, twice against methanol, again against THF and the solvent of the final mixture was removed under reduced pressure to obtain $P_{precursor}$. The $P_{precursor}$ was dissolved in 2 mL THF, coumarin-alkyne (1.5 mg, 6.58 μmol, 4.0 eq.) was added. The reaction mixture was stirred at room temperature and monitored by TLC, which indicated that full conversion was reached after 2 hours. Then excess of PorPF (6 mg, 6 μmol, 3.6 eq.) was added and reacted at 50 °C overnight. The mixture was then dialyzed against THF then methanol, followed by precipitating in pentane to obtain **P7**, $M_n$ =37.1 kD, $Đ$= 1.47.

In the case of **P6** and **P8**, $P_{precursor}$ with desired ratio of piperidine moieties were prepared. Either coumarin-alkyne or PorPF was used in the second step of modification.

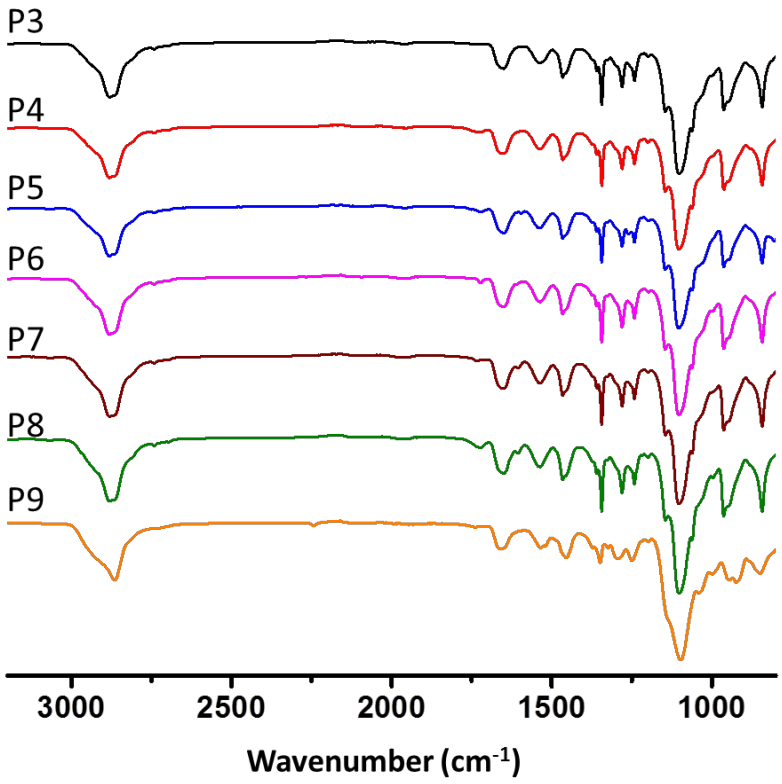



Figure S4: Infra-red spectra of **P3-P9** measured in the bulk.

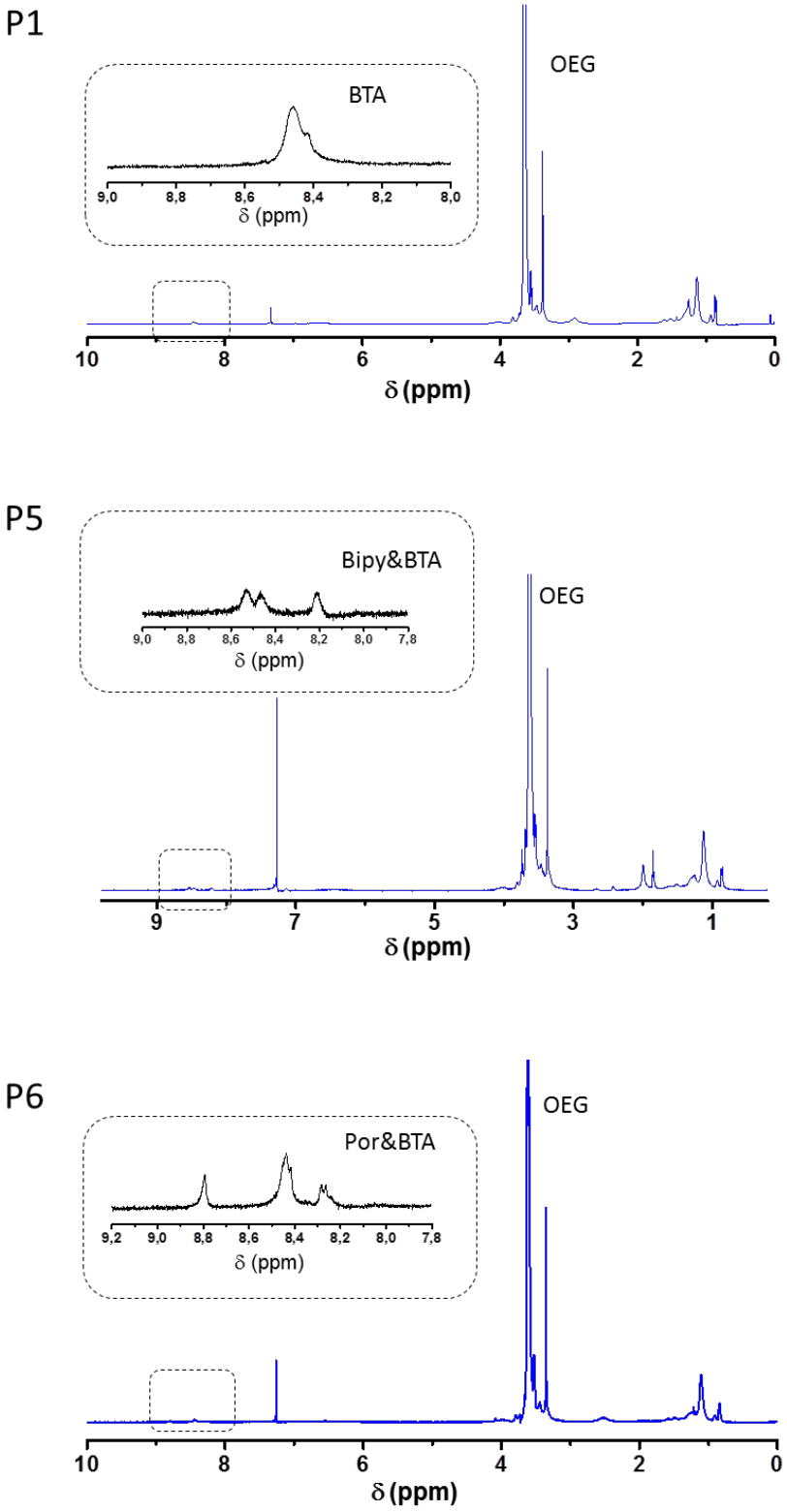



Figure S5: Representative $^{1}H$ NMR spectra of the synthesized polymers.

**CD measurements:**

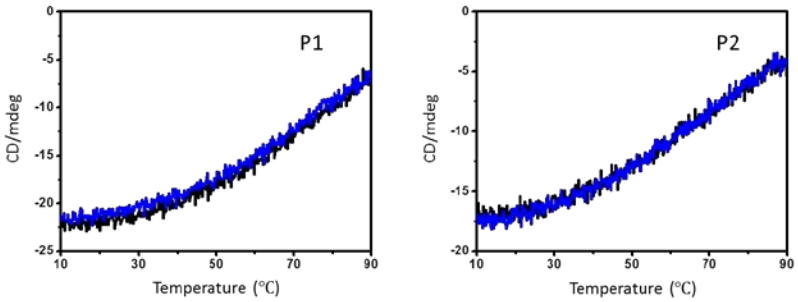



Figure S6: CD cooling and heating curves of **P1** and **P2** ($c_{BTA}$= 50 μM; 0.5 cm cuvette) in water. Temperature from 10 ℃to 90 ℃, monitored at 223 nm (cooling rate and heating rate at 1 K/min).

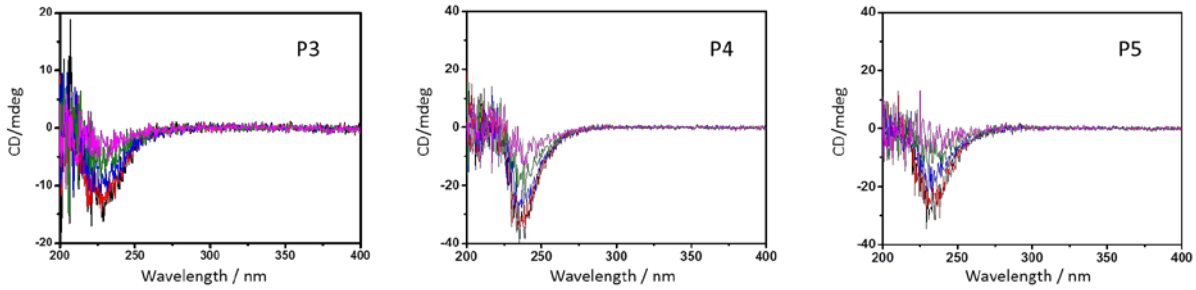



Figure S7: CD spectra of **P3** ($c_{BTA}$= 60 μM, [polymer]= 1.0 mg/mL), **P4** ($c_{BTA}$= 133μM, [polymer]= 1.3 mg/mL) and **P5** ($c_{BTA}$= 150 μM, [polymer]= 1.5 mg/mL) in PBS buffer.

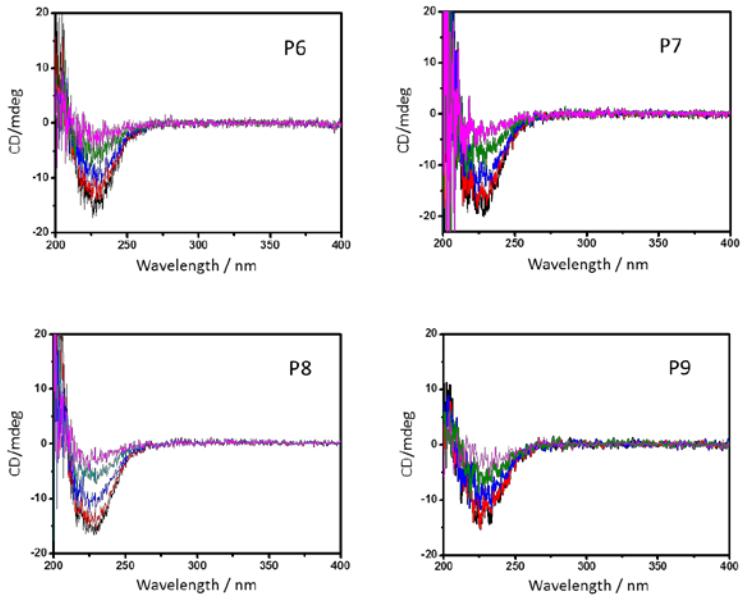



Figure S8: CD spectra of **P6**, **P7**, **P8** and **P9** (all polymers at [polymer]= 0.5 mg/mL) in water.

(In both Figure S3 and S4, black: 10 ℃, red: 30℃, blue: 50℃, green: 70℃, pink: 90℃)

DLS measurements:

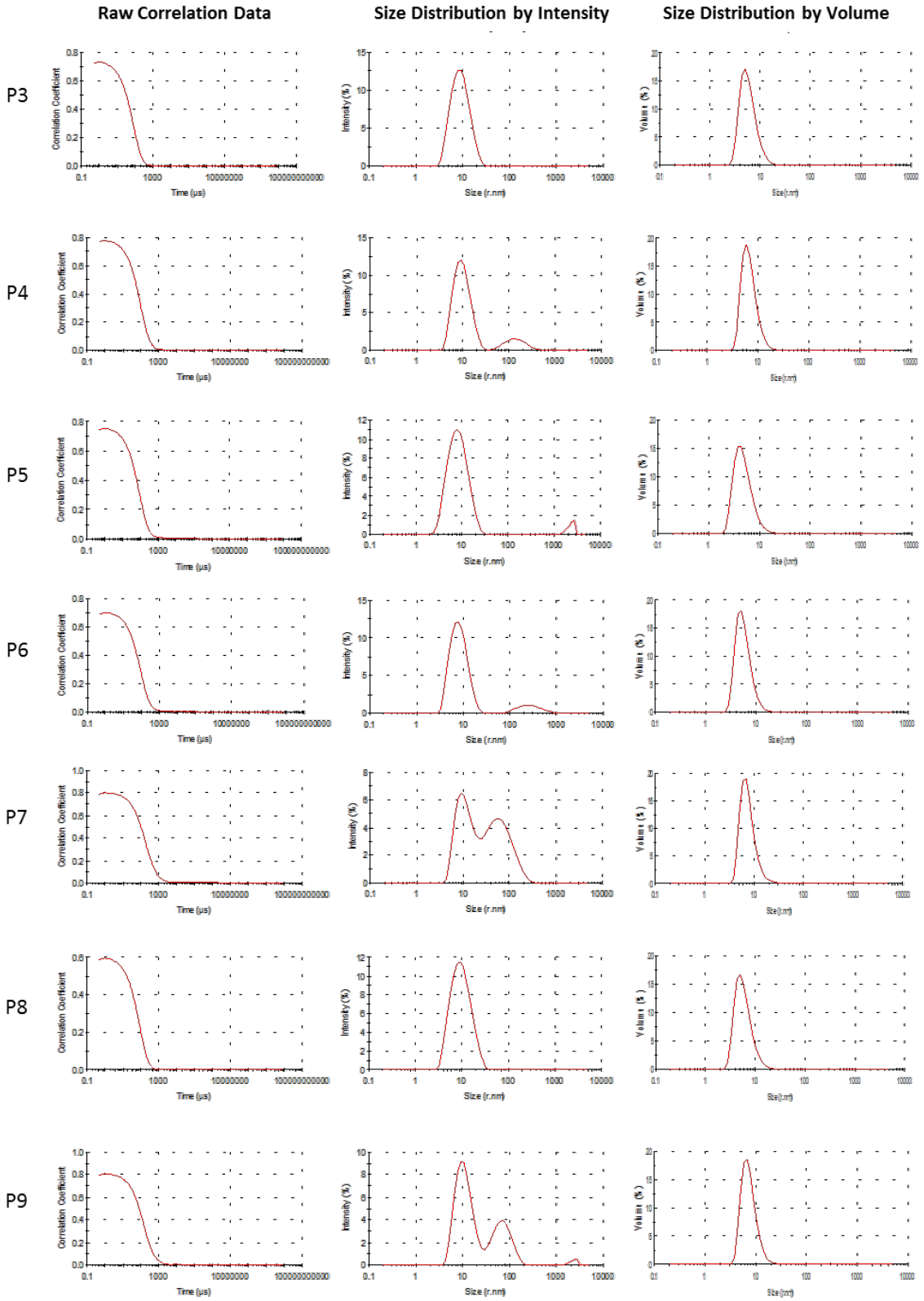



Figure S9: DLS data of **P3**-**P9**: (left) Raw correlation data; (middle) Size distribution by intensity; (right) Size distribution by volume.

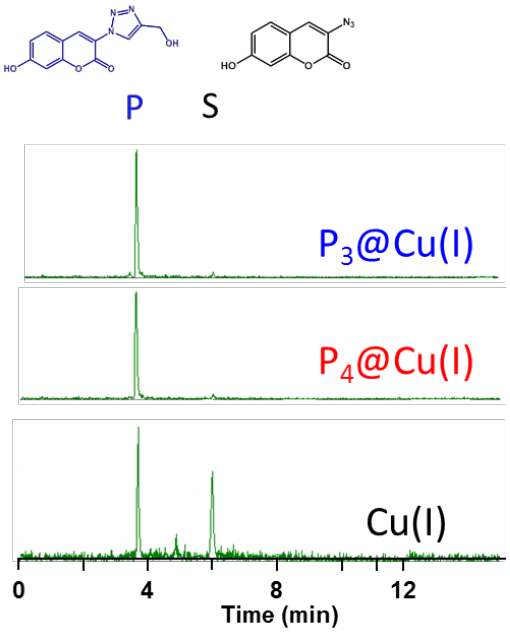



Figure S10: The LC-MS data of CuAAC catalysis. The reaction mixture after 1 hour reaction was directly used for LC-MS measurements.

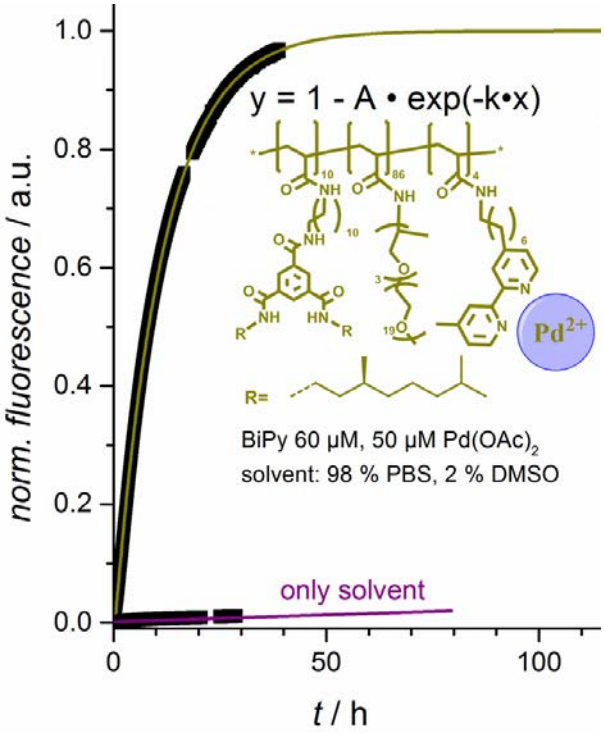



Figure S11: The fluoresence-time curves of depropargylation of **1**. (Green, with **P5**@Pd catalyst; purple, without **P5**@Pd catalyst)

[1] Schatzschneider, U.; Barton, J. K. *J. Am. Chem. Soc.* **2004**, *126*, 8630-8631.
[2] Li, J.; Yu, J.; Zhao, J.; Wang, J.; Zheng, S.; Lin, S.; Chen, L.; Yang, M.; Jia, S.; Zhang, X.; Chen, P. R. *Nat. Chem.* **2014**, *6*, 352-361.
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