Supporting Information for

Developing Pd(II) based amphiphilic polymeric nanoparticles for pro-drug activation in complex media

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1. Materials and Methods

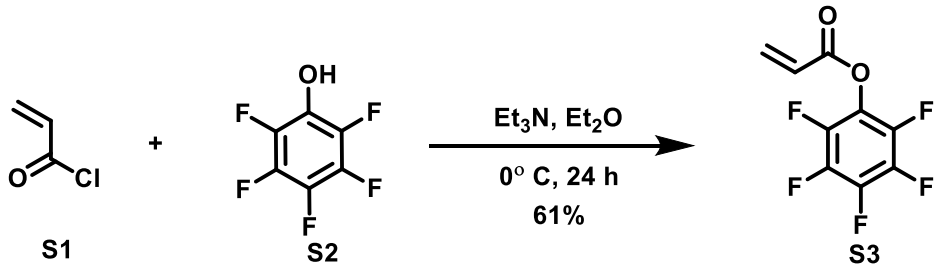
Pentafluorophenol was purchased from ABCR GmbH und Co. KG. 4-Cyano-4-(phenylcarbonothioylthio)pentanoic acid and lauryl peroxide was purchased from Merck Life Science NV. Jeffamine M-1000® was provided by Huntsman Holland BV. Commercially available AIBN was recrystallized from methanol. Rhodamine 110 hydrochloride was purchased from Fisher scientific. 4,4'-Dimethyl-2,2'-dipyridyl was obtained from Merck Life Science NV. All other chemicals were purchased either from Merck or TCI chemicals. Deuterated solvents were purchased from Cambridge isotope laboratories. The dialysis membrane was regenerated cellulose tubing purchased from Spectra/Por® with a molecular weight cut-off of 6-8 kDa. All solvents were purchased from Biosolve. Gibco DMEM (glucose concentration 1 g/L, with sodium pyruvate, without L-glutamine, without phenol red) and MEM medium were purchased from Fischer scientific. Dialysis of triphenylphosphine (TPP) functionalized polymers was done in degassed solvents in a wide screw-capped 1 L container, keeping it tightly closed. Dialysis solvents were refreshed regularly with new degassed solvents to prevent oxidation of phosphines. Chloroform used for triphenylphosphine polymers' complexation was dried using Mbraun solvent purification system (MB-SPS 800) and was degassed thoroughly by six freeze-pump thaw cycles. All the flasks and needles used for TPP complexation were pre-dried in the oven at 135 °C overnight, and experiments were performed under an argon atmosphere. Automated column chromatography was performed on Grace Reveleris X2 Flash Chromatography System using Flashpure BUCHI prepacked silica columns. BTA amine was previously synthesized in our lab according to the reported protocol. [1] All pro-dyes and pro-drugs were synthesized following the previously reported protocol.[2–7]

2. Characterisation methods

^{1}H, ^{13}C, and ^{31}P NMR measurements were recorded on Bruker 400 MHz spectrometer at ambient temperature, and chemical shifts were recorded concerning TMS as the internal standard for ^{1}H and ^{13}C spectra and 85% H_3PO_4 in D_2O as an external standard for ^{31}P NMR spectra. Fluorescence measurements were performed on an Agilent Cary Eclipse fluorescence spectrophotometer using 1 cm × 1 cm pathlength quartz cuvettes. UV- Vis measurements were performed on JASCO V-750 spectrometer using 1 cm pathlength quartz cuvettes, and CD measurements were performed on Jasco J-815 spectropolarimeter using 0.5 cm pathlength quartz cuvettes. Liquid chromatography - UV was performed using Shimadzu UFLC-XR with PDA detector with water + 0.1% formic acid and ACN + 0.1% formic acid as eluents on Kinetex column C18 5 μm EVO 100 Å. HPLC Method 1 for pro-dyes **1** - **3**: eluent A: water (0.1% formic acid); eluent B: acetonitrile (0.1% formic acid); and A/B = 90:10 isocratic 2 min, 90:10 to 0:100 in 2 min, isocratic 2 min, 0:100 to 90:0 in 2 min, and isocratic 2.0 min (flow = 0.2 mL/min). Method 2 for pro-5FU: A/B = 95:5 isocratic 15 min. Method 3 for pro-paclitaxel: A/B = 80:20 isocratic 0.5 min, A/B = 80:20 to 0:100 in 10 min, isocratic 2 min, and 0:100 to 80:20 in 5 min, isocratic 1.5 min (flow = 0.2 mL/min). Method 4 for pro-dox: A/B = 95:5 isocratic 3 min, A/B = 95:5 to 20:80 in 8 min, isocratic 1 min, and 20:80 to 95:5 in 3 min, isocratic 4 min (flow = 0.2 mL/min). Size exclusion chromatography (SEC) measurements of poly(pentafluorophenyl)acrylate were recorded using Shimadzu LC-2030C 3D with RID-20 refractive index detector and PDA detector at a flow rate of 1 mL min^{-1} with THF as eluent with Agilent mixed-C and mixed-D column in series at 40 °C. Exclusion limit = 2.000.000 g mol^{-1}, 7.5 mm i.d. × 300 mm. Calibration was performed using polystyrene standards from polymer laboratories. DMF-SEC measurements of functionalized polymers were performed using PL-GPC-50 plus (Varian Inc. Company) equipped with a refractive index detector. DMF with 10 mM LiBr was used as eluent at a flow rate of 1 mL min^{-1} on the Shodex GPC-KD-804 column at 50 °C. Exclusion limit = 100.000 Da, 0.8 cm i.d. × 300 mm calibrated using poly (ethylene oxide) from polymer laboratories. Palladium quantification was performed on Agilent MP-AES 4200 (Microwave plasma atomic emission spectrometer) elemental analyzer calibrated using Palladium Standard for ICP. Dynamic light scattering experiments were performed using Malvern Zetasizer with 830 nm laser and an angle of scattering 90°.

3. Synthesis

3.1 Pentafluorophenylacrylate[1]



Acryloyl chloride **S1** (4.4 mL, 1 eq, 54 mmol) was dissolved in dry diethyl ether (50 mL) and was added slowly via a dropping funnel to a combined mixture of pentafluorophenol **S2** (10 g, 1 eq, 54 mmol) and triethylamine (8.3 mL, 1.1 eq, 60 mmol) dissolved in 150 mL of dry diethyl ether cooled under ice bath. After 3 h, the reaction was brought to room temperature and was

stirred overnight. After confirming the completion of the reaction via TLC, the white precipitate formed was filtered off and the filtrate was collected. The solvent was removed using rotary evaporator to obtain crude product as pale-yellow liquid. The crude product was purified by column chromatography (100 g FlashPure irregular silica column, n-heptane) and **S3** was obtained as colourless liquid. Yield: 8 g, 61%

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.72 (dd, *J* = 17.3, 1.0 Hz, 1H), 6.37 (dd, *J* = 17.3, 10.5 Hz, 1H), 6.18 (dd, *J* = 10.5, 1.0 Hz, 1H).

^{19}F NMR (376 MHz, $CDCl_3$): δ -152.28 – -153.07 (m), -158.04 (t, *J* = 21.7 Hz), -162.08 – -162.96 (m)

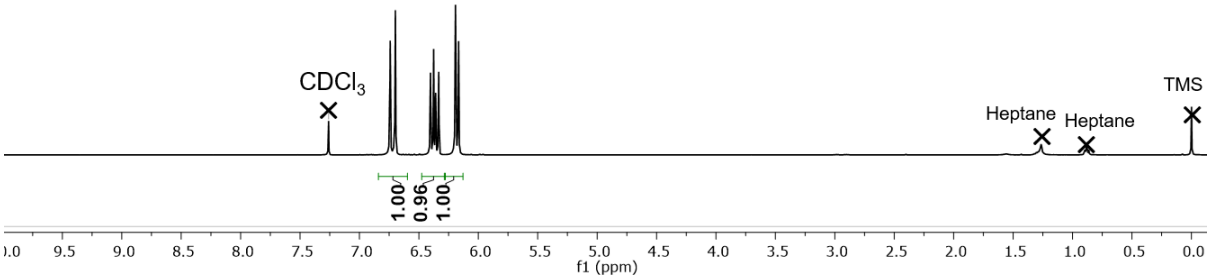


Fig. S1. ^{1}H-NMR spectrum of pentafluorophenyl acrylate in $CDCl_3$

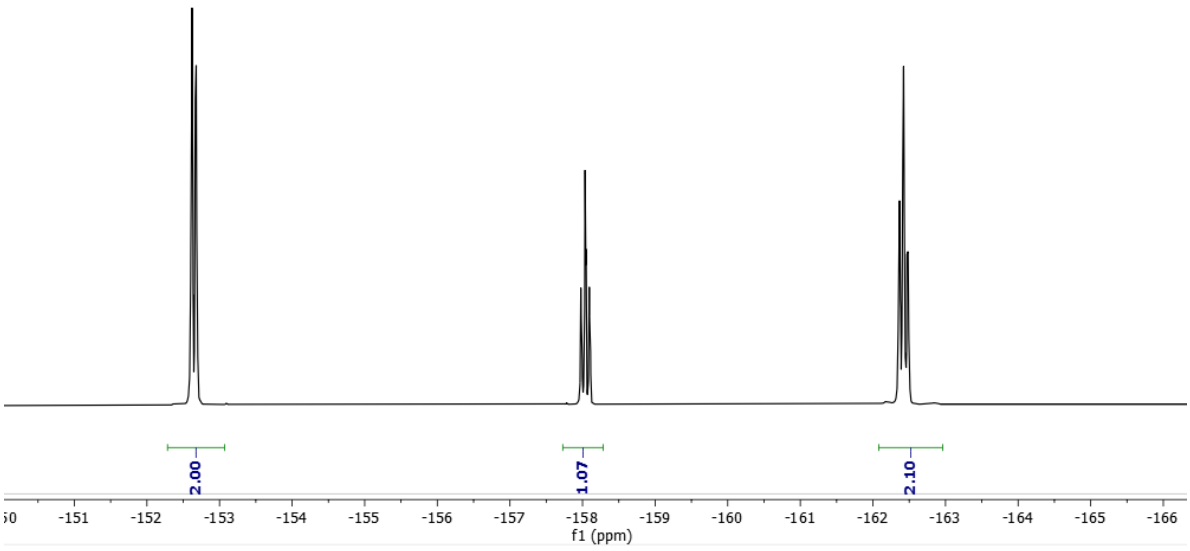
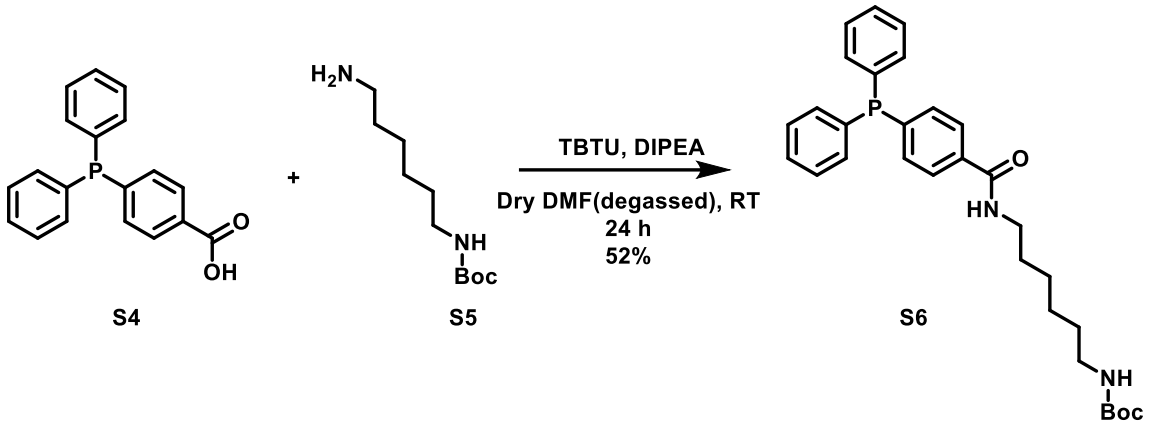


Fig. S2. ^{19}F-NMR spectrum of pentafluorophenyl acrylate in $CDCl_3$

3.2 *tert*-Butyl (6-(4-(diphenylphosphaneyl)benzamido)hexyl)carbamate



4-Diphenylphosphinobenzoic acid **S4** (800 mg, 1 eq, 2.6 mmol) was dissolved in dry and degassed DMF (20 mL) followed by the addition of DIPEA (500 µL, 1.1 eq, 2.8 mmol) and TBTU (840 mg, 1 eq, 2.6 mmol). After stirring the reaction mixture for 15 min, *N*- boc-1,6 hexadiamine **S5** (583 µL, 1 eq, 2.6 mmol) was added. The reaction mixture was then stirred overnight at room temperature under argon atmosphere. Completion of the reaction was monitored by TLC by mini work up in Eppendorf using ethyl acetate. After completion of the reaction, 40 mL degassed water was added to the reaction mixture and water phase was extracted using degassed ethyl acetate (40 mL × 3) and dried over Na_2SO_4. The solvent was removed using rotary evaporator and residue was purified using column chromatography (12 g, FlashPure HP silica column, MeOH/CH_2Cl_2: 0/100 - 10/90) to obtain white solid. Yield: 680 mg, 52%

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 7.8 Hz, 2H), 7.38 – 7.27 (m, 12H), 6.34 (b, 1H), 4.53 (b, 1H), 3.44 (q, *J* = 6.7 Hz, 2H), 3.12 (q, *J* = 6.7 Hz, 2H), 1.62 (m, 4H), 1.53 (m, 2H), 1.42 (s, 9H), 1.40 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 167.31, 156.26, 141.94, 141.81, 136.56, 136.46, 134.93, 134.09, 133.90, 133.77, 133.58, 129.18, 128.81, 128.74, 126.97, 126.90, 40.16, 39.69, 36.62, 30.20, 29.60, 28.56, 26.22, 26.02.

^{31}P NMR (162 MHz, $CDCl_3$) δ -5.56.

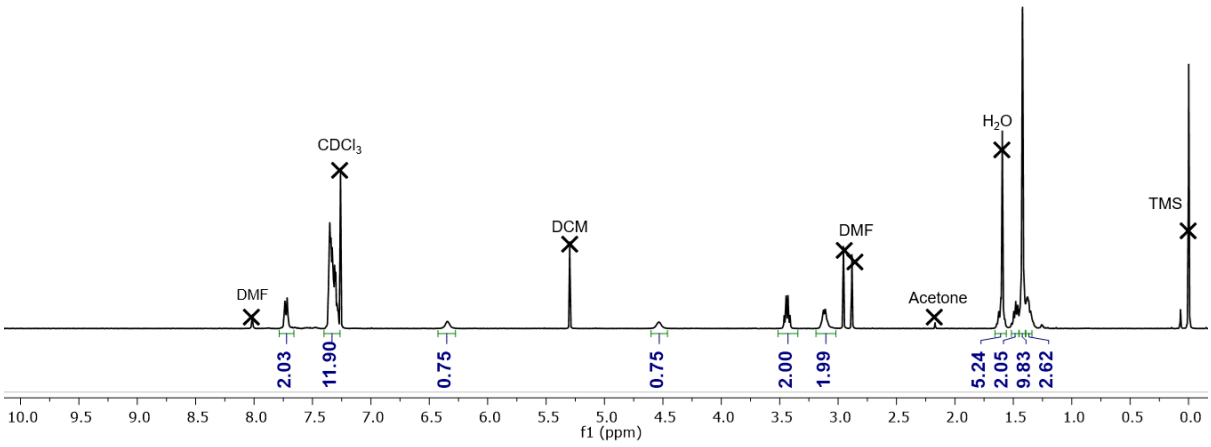


Fig. S3. ^{1}H-NMR spectrum of *tert*-butyl (6-(4-(diphenylphosphaneyl)benzamido)hexyl)carbamate in $CDCl_3$

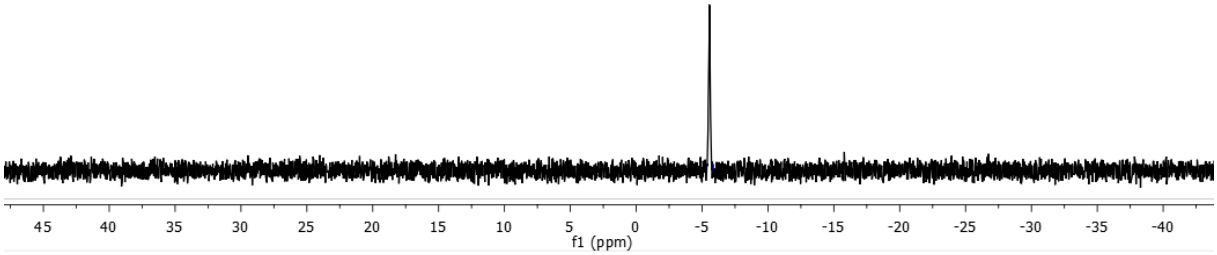


Fig. S4. ^{31}P-NMR spectrum of *tert*-butyl (6-(4-(diphenylphosphaneyl)benzamido)hexyl)carbamate in $CDCl_3$

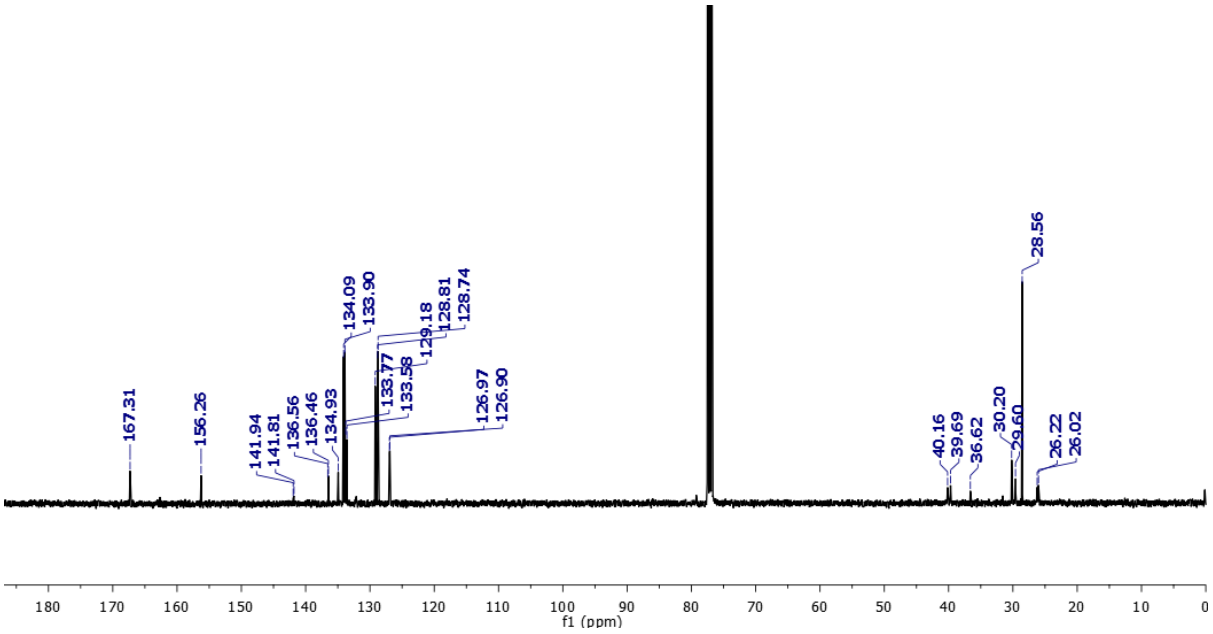
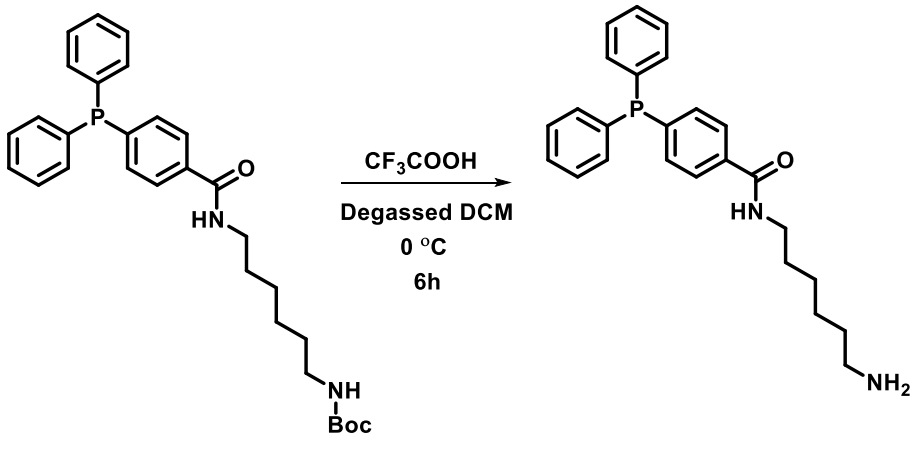


Fig. S5. ^{13}C-NMR spectrum of *tert*-butyl (6-(4-(diphenylphosphaneyl)benzamido)hexyl)carbamate in $CDCl_3$

3.3 N-(6-Aminohexyl)-4-(diphenylphosphaneyl) benzamide



S7 S8

tert-Butyl (6-(4-(diphenylphosphaneyl)benzamido)hexyl)carbamate **S7** (50 mg, 1 eq, 0.099 mmol) was dissolved in degassed DCM (1 mL) followed by the addition of TFA (1 mL) and was stirred at 0 °C for 6 h. After completion of the reaction determined by TLC, the reaction mixture was concentrated in vacuum. Excess of TFA was removed by co-evaporation with DCM (6 times). Further, the product was redissolved in DCM (10 mL) and washed with sat. $NaHCO_3$ (15 mL × 2), brine (10 mL) and was dried over $MgSO_4$. The solvent was evaporated using rotary evaporator and dried under vacuum to get sticky white solid which was stored under argon at −19 °C. Yield: quantitative, 36 mg. Some phosphine oxidation was observed from ^{31}P NMR.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, *J* = 7.7 Hz, 2H), 7.38 – 7.27 (m, 12H), 6.11 (b, 1H), 3.45 (q, *J* = 6.7 Hz, 2H), 2.69 (t, *J* = 6.7 Hz, 2H), 1.66 – 1.57 (m, 2H), 1.51 (2H), 1.45 (m, 2H), 1.41 – 1.29 (m, 4H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 167.31, 141.79, 141.65, 136.40, 136.30, 134.86, 133.95, 133.75, 133.57, 133.38, 129.07, 128.69, 128.62, 126.89, 126.82, 41.94, 39.98, 33.30, 29.60, 26.76, 26.49.

^{31}P NMR (162 MHz, $CDCl_3$) δ -5.61.

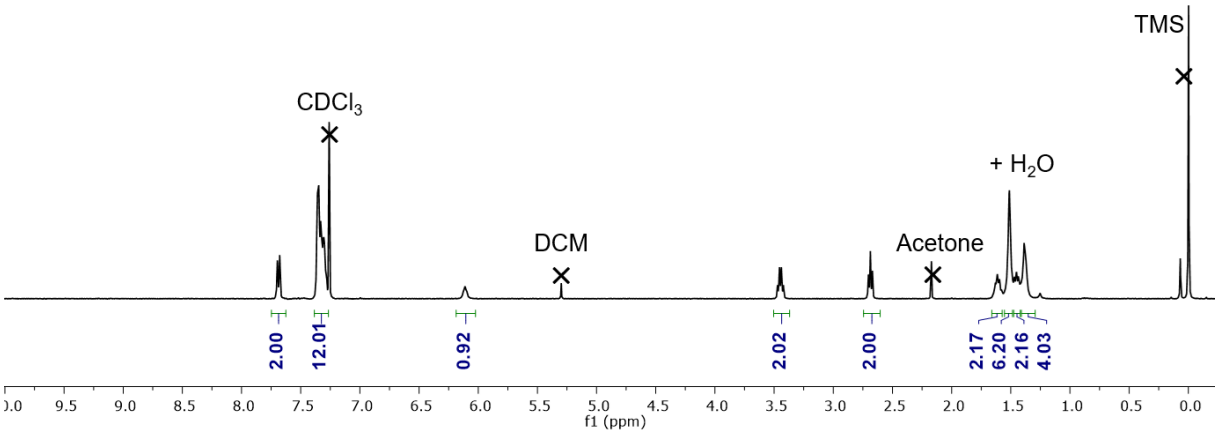


Fig. S6. ^{1}H-NMR spectrum of N-(6-aminohexyl)-4-(diphenylphosphaneyl) benzamide in $CDCl_3$

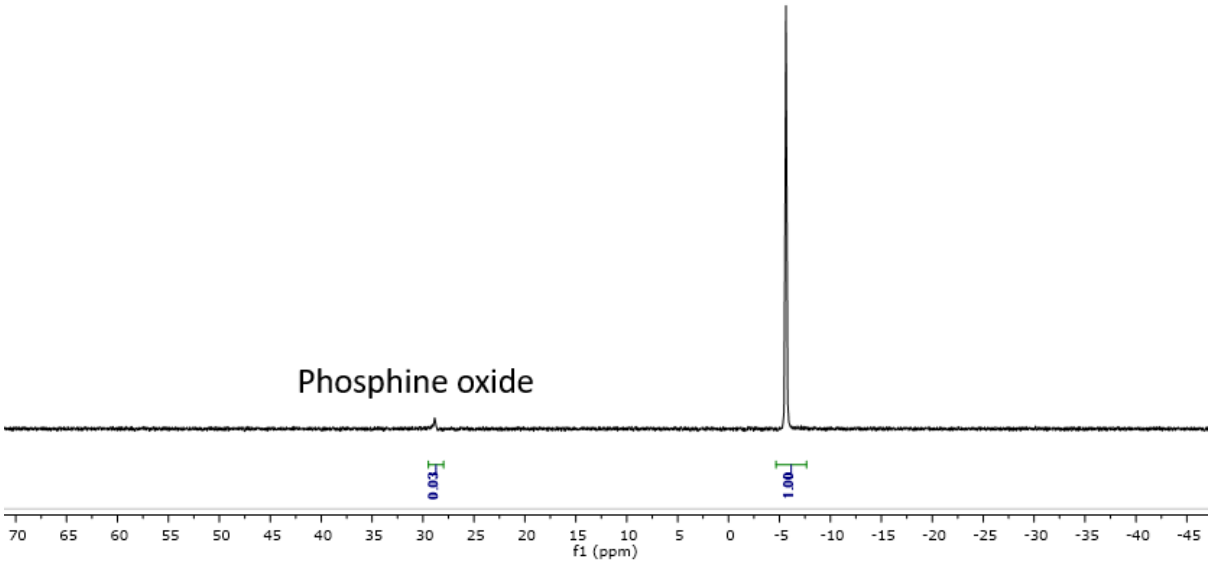


Fig. S7. ^{31}P-NMR spectrum of N-(6-aminohexyl)-4-(diphenylphosphaneyl) benzamide in $CDCl_3$

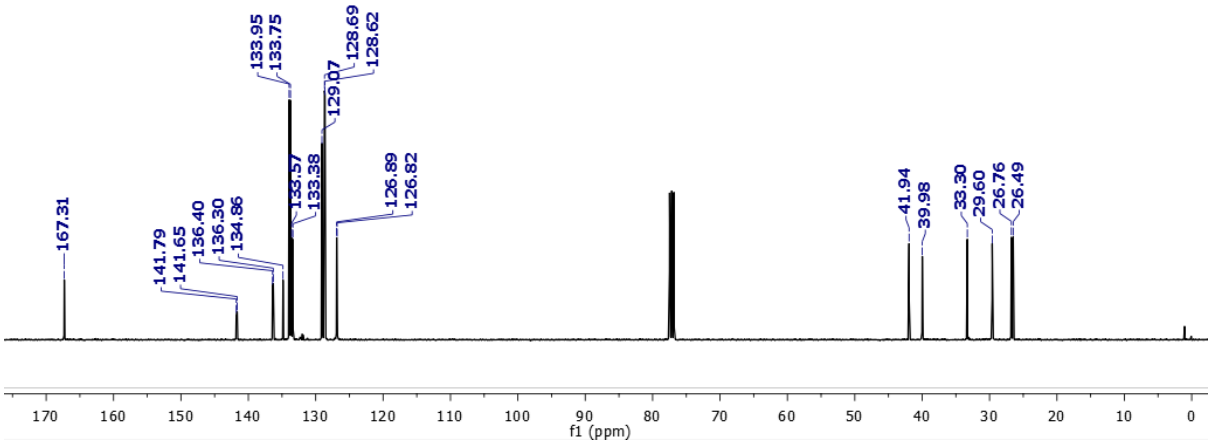


Fig. S8. ^{13}C-NMR spectrum of N-(6-aminohexyl)-4-(diphenylphosphaneyl) benzamide in $CDCl_3$

3.4 2,4-Dinitro-1-(prop-2-yn-1-yloxy) benzene[2]

S9 S10 S11

2,4-Dinitrophenol **S9** (460 mg, 1 eq, 2.5 mmol) was dissolved in DMF (5 mL) together with propargyl bromide **S10** (354 mg, 1.2 eq, 3 mmol) and K_2CO_3 (414 mg,1.2 eq, 3 mmol), reaction

mixture was stirred overnight at 50 °C. After confirming the completion of reaction by TLC, water (10 mL) was added to reaction mixture and was extracted with diethyl ether (10 mL ×3) and dried over $MgSO_4$, followed by concentration using rotary evaporator. The product was purified by flash column chromatography (10 g FlashPure irregular Silica column, Heptane/DCM: 80/20) to afford a pale-yellow solid. Yield: 399 mg, 72%

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.77 (d, *J* = 2.8 Hz, 1H), 8.46 (dd, *J* = 9.2, 2.8 Hz, 1H), 7.41 (d, *J* = 9.3 Hz, 1H), 4.99 (d, *J* = 2.4 Hz, 2H), 2.67 (t, *J* = 2.4 Hz, 1H).

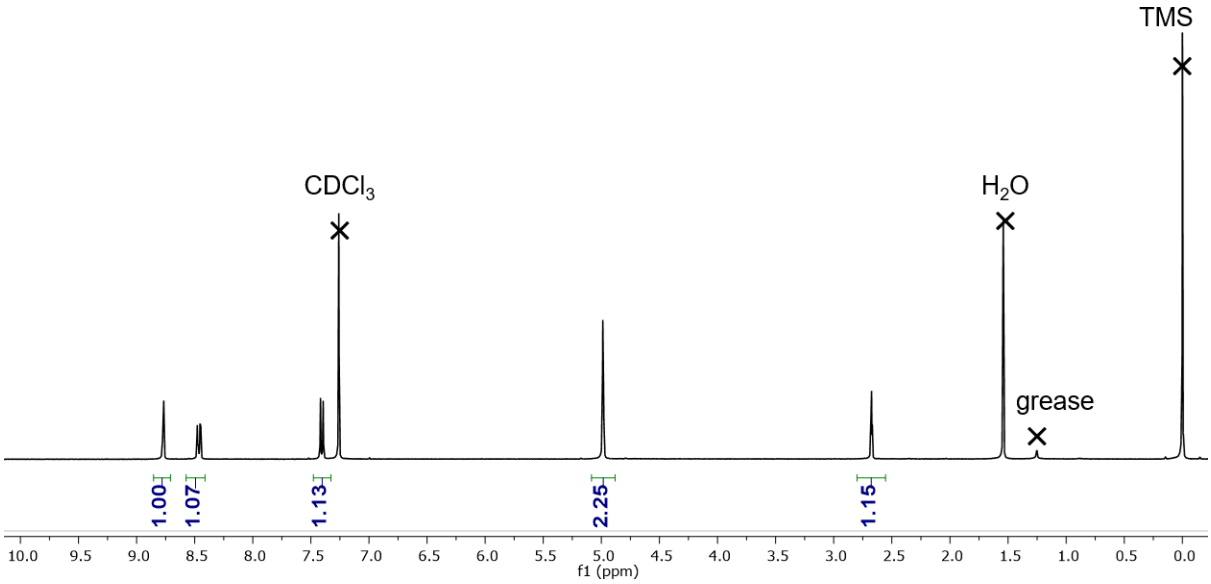
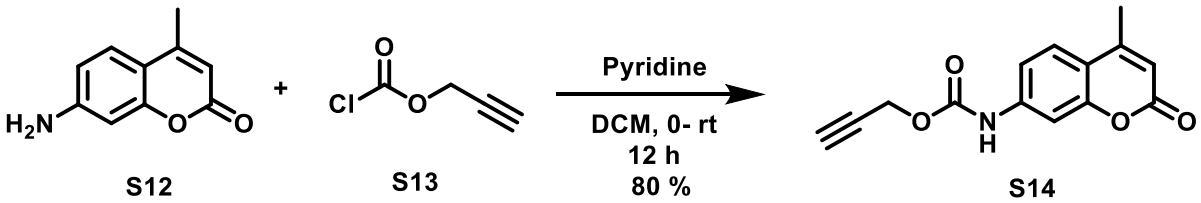


Fig. S9. ^{1}H-NMR spectrum of 2,4-dinitro-1-(prop-2-yn-1-yloxy)benzene in $CDCl_3$

3.5 Prop-2-yn-1-yl (4-methyl-2-oxo-2H-chromen-7-yl) carbamate[3]



7-Amino-4-methyl coumarin **S12** (100 mg, 1 eq, 0.57 mmol) was dissolved in 4 mL dry DCM under ice bath followed by the addition of pyridine (61 µL, 1.3 eq, 0.75 mmol). Propargyl carbonyl chloride **S13** (85 mg, 1.2 eq, 0.72 mmol) was added to this reaction mixture resulting in a yellow suspension. The reaction mixture was stirred at 0 °C for 3 h and was brought to room temperature and stirred overnight under argon atmosphere. After completion of the reaction monitored by TLC, 1 N HCl (30 mL) was added to the reaction mixture, the pale-yellow precipitate formed was filtered, and washed with diethyl ether until the yellow colour was faded. The product was purified by column chromatography to afford white powder. (Silica, MeOH/ DCM: 10/90) Yield: 117 mg, 80 %

^{1}H NMR (400 MHz, DMSO-d_6): δ 10.37 (s, 1H), 7.71 (d, J = 8.7 Hz, 1H), 7.53 (d, J = 2.1 Hz, 1H), 7.41 (dd, J = 8.7, 2.1 Hz, 1H), 6.25 (d, J = 1.4 Hz, 1H), 4.81 (d, J = 2.5 Hz, 2H), 3.61 (t, J = 2.4 Hz, 1H), 2.39 (d, J = 1.2 Hz, 3H).

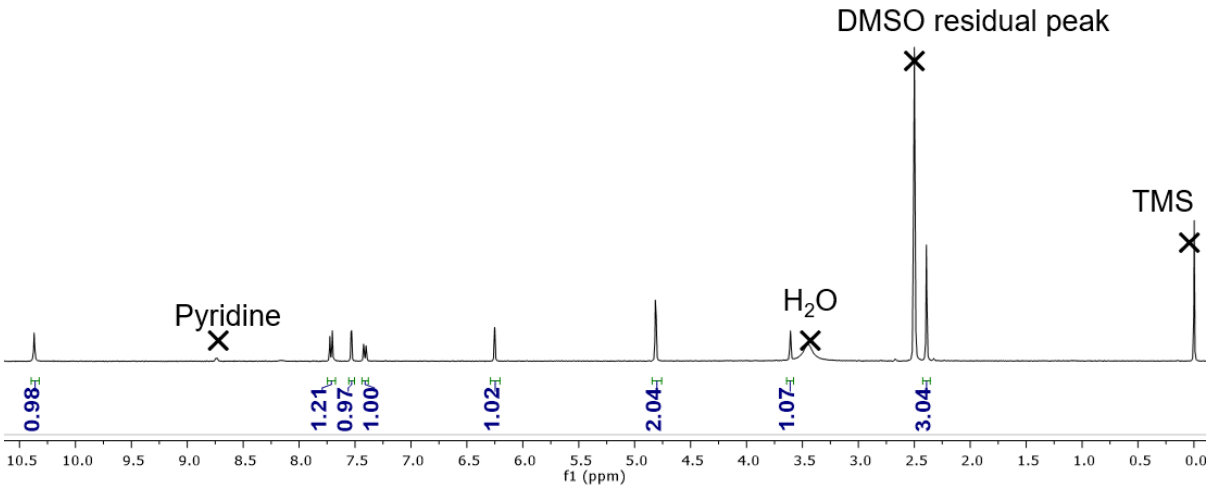
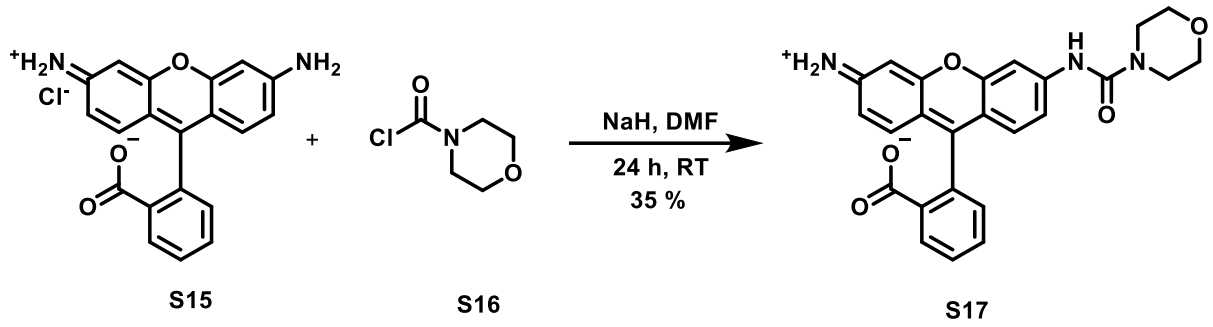


Fig. S10. ^{1}H-NMR spectrum of prop-2-yn-1-yl (4-methyl-2-oxo-2H-chromen-7-yl) carbamate in DMSO-d_6

3.6 2-(3-Iminio-6-(morpholine-4-carboxamido)-3H-xanthen-9-yl)benzoate [4]



A pre-dried three-neck round bottom flask was purged under argon, allowed to cool down and dry DMF (50 mL) was added to the flask followed by the addition of rhodamine 110 chloride **S15** (500 mg, 1 eq, 1.3 mmol). The reaction was performed under argon atmosphere and covered with aluminium foil throughout. To this solution, NaH 60% dispersion in mineral oil (119 mg, 2.2 eq, 2.9 mmol) was added portion wise over 10 min and was stirred for 1 h. After, 4-morpholinecarbonyl chloride **S16** (160 µL, 1 eq, 1.3 mmol) was added dropwise over 7 min. The color of the reaction turned fluorescent brown and was stirred overnight. The color changed to purple after 24 h and the reaction mixture was concentrated using rotary evaporator. The crude product was purified using column chromatography (Flashpure BUCHI 12 g 40 µm irregular silica column, $CHCl_3$: MeOH: CH_3COOH = 100:7:1). After column, product was redissolved in Toluene/Methanol/DMF: 100/5/0.5 (30 mL×3) and co-evaporated using rotary evaporator to remove CH_3COOH. The presence of acetic acid can result in unwanted side products in the next step that can reduce the yield drastically. The product was dried

under vacuum to afford red powder. ^{1}H NMR showed presence of toluene which will not interfere with the next step while was necessary to get rid of CH_3COOH. Yield: 200 mg, 35%

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.79 (s, 1H), 7.97 (d, *J* = 7.6 Hz, 1H), 7.74 (dt, *J* = 32.9, 7.4 Hz, 2H), 7.62 (d, *J* = 2.1 Hz, 1H), 7.09 (dd, *J* = 8.7, 2.1 Hz, 1H), 6.57 (d, *J* = 8.7 Hz, 1H), 6.43 (d, *J* = 1.9 Hz, 1H), 6.40 – 6.27 (m, 2H), 5.64 (s, 2H), 3.61 (t, *J* = 4.7 Hz, 4H), 3.43 (t, *J* = 4.8 Hz, 4H).

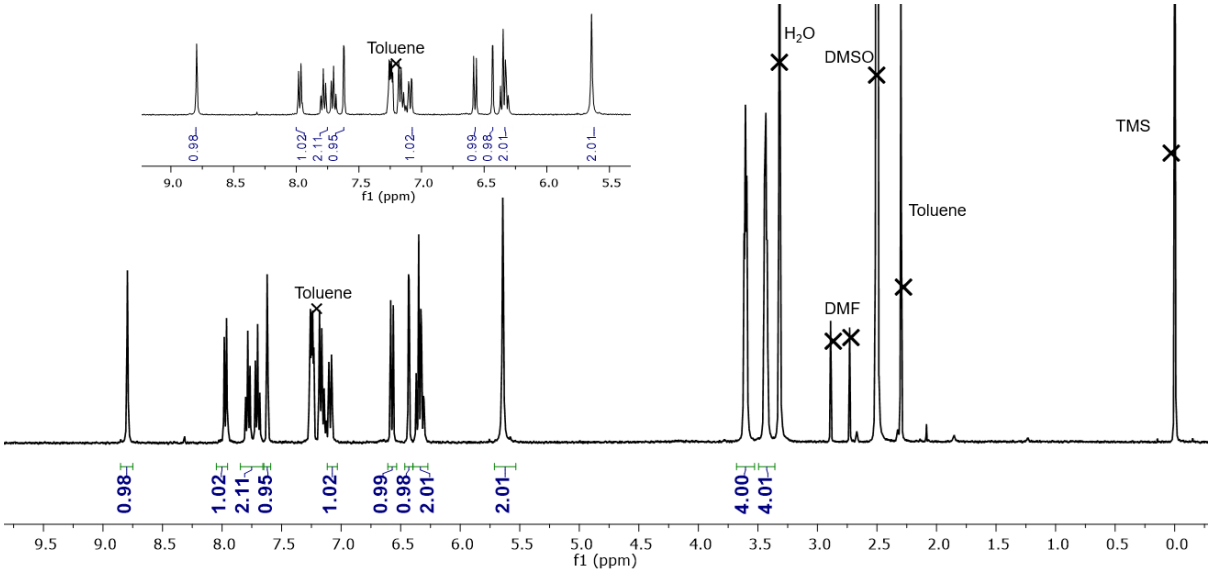
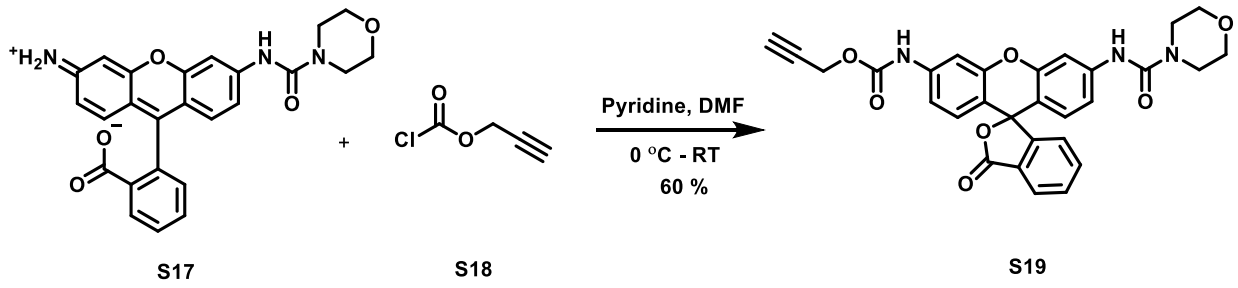


Fig. S11. ^{1}H -NMR spectrum of 2-(3-iminio-6-(morpholine-4-carboxamido)-3H-xanthen-9-yl) benzoate in DMSO-d_6

3.7 Prop-2-yn-1-yl (3'-(morpholine-4-carboxamido)-3-oxo-3H-spiro[isobenzofuran-1,9'-xanthen]-6'-yl) carbamate [4]



S17 S18 S19

2-(3-Iminio-6-(morpholine-4-carboxamido)-3H-xanthen-9-yl) benzoate **S17** (200 mg, 1 eq, 0.45 mmol) was dissolved in dry DMF (6 mL) followed by the addition of pyridine (2 mL, 53 eq, 24 mmol) under argon atmosphere at 0 °C and covered with aluminium foil. Then, propargyl chloroformate **S18** (0.5 mL, 10 eq, 5 mmol) was added dropwise through a syringe. The reaction mixture was brought to room temperature and stirred overnight, and solvent was removed using rotary evaporator. The crude product was redissolved in 15 mL chloroform and washed with 1 N HCl (20 mL × 1), water (20 mL × 1), saturated brine (10 mL × 1) solution and dried over $MgSO_4$. The crude mixture was then purified by column chromatography (Flashpure

BUCHI 12 g 40 µm irregular silica column, EtOAc) to afford pale yellow powder. Yield = 140 mg, 60%

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, *J* = 7.5 Hz, 1H), 7.63 (dt, *J* = 19.4, 7.3 Hz, 2H), 7.48 (d, *J* = 14.2 Hz, 2H), 7.13 (d, *J* = 7.5 Hz, 1H), 6.94 (d, *J* = 7.2 Hz, 2H), 6.84 (s, 1H), 6.71 (dd, *J* = 12.9, 8.6 Hz, 2H), 6.45 (s, 1H), 4.83 – 4.74 (m, 2H), 3.76 (t, *J* = 4.9 Hz, 4H), 3.50 (t, *J* = 4.9 Hz, 4H), 2.53 (s, 1H).

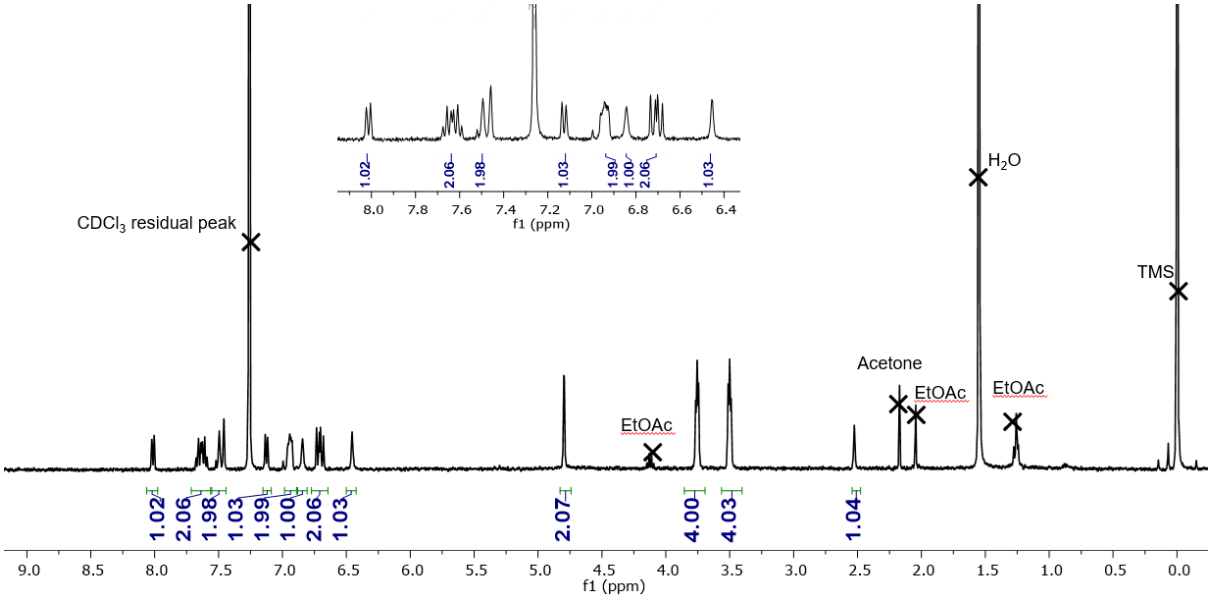
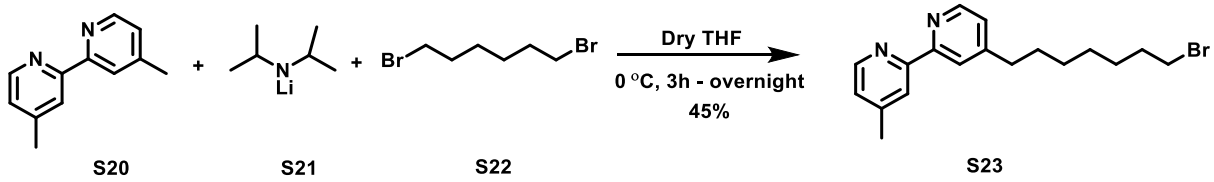


Fig. S12. ^{1}H -NMR spectrum of prop-2-yn-1-yl (3'-(morpholine-4-carboxamido)-3-oxo-3H-spiro[isobenzofuran-1,9'-xanthen]-6'-yl) carbamate in $CDCl_3$

3.8 4-(7-Bromoheptyl)-4'-methyl-2,2'-bipyridine [8]



S20 S21 S22 S23

4,4' -Dimethylbipyridine **S20** (1 g, 1 eq, 5.4 mmol) was dissolved in dry THF (30 mL) and cooled under ice bath in a Schenk flask. In another Schlenk flask cooled in ice-bath, dry THF (5 mL) was added, followed by the addition of diisopropylamine (909 µL, 1.2 eq, 6.5 mmol) under argon atmosphere. To this mixture *n*-butyllithium **S21** (2.2 mL of 2.5 M solution in hexane, 1 eq, 5.4 mmol) was added via syringe. Finally, precooled 4,4' -dimethylbipyridine in THF was added to the former solution and was stirred for 1 h. After this, 1,6-dibromohexane **S22** (1.7 mL, 2 eq, 10.8 mmol) dissolved in dry THF (3 mL) was added to the reaction mixture and was stirred for 3 h. The reaction was quenched by the addition of water (20 mL) and after stirring for 30 min, pH was adjusted to ~5 by addition of 1 N HCl. Then, this mixture was stirred overnight. Diethyl ether (20 mL) was added to the mixture and product was extracted using dichloromethane (30 mL × 5), dried over $MgSO_4$, and concentrated under vacuum at room temperature. The crude product was purified by column chromatography (Silica, Dichloromethane) Yield: 840 mg, 45 %

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (t, *J* = 5.5 Hz, 2H), 8.27 – 8.19 (m, 2H), 7.13 (dd, *J* = 4.8, 2.1 Hz, 2H), 3.40 (t, *J* = 6.8 Hz, 2H), 2.69 (t, *J* = 8.8, 6.8 Hz, 2H), 2.44 (s, 3H), 1.85 (p, *J* = 6.9 Hz, 2H), 1.74 – 1.65 (m, 2H), 1.47 – 1.32 (m, 6H).

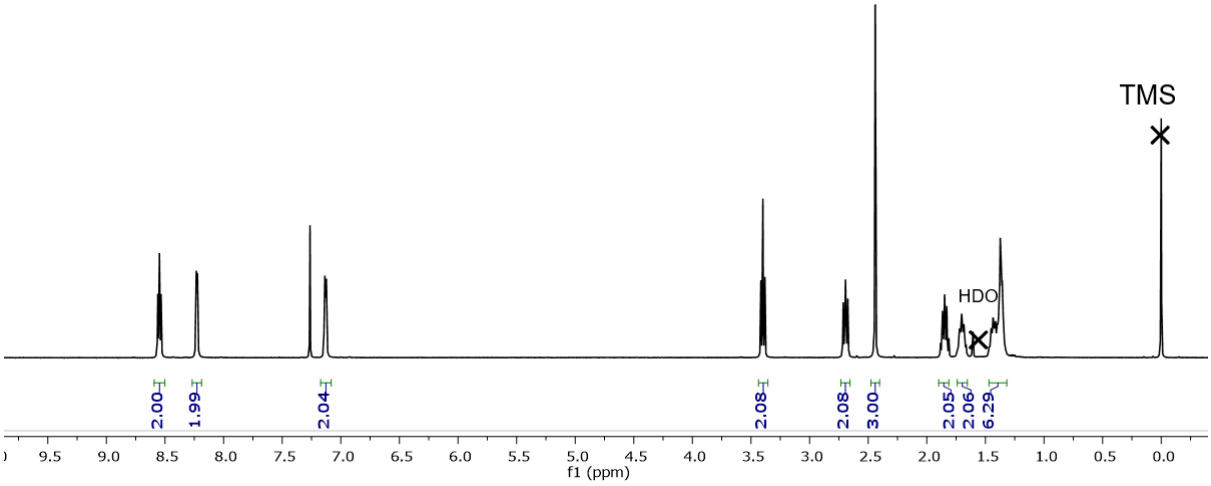
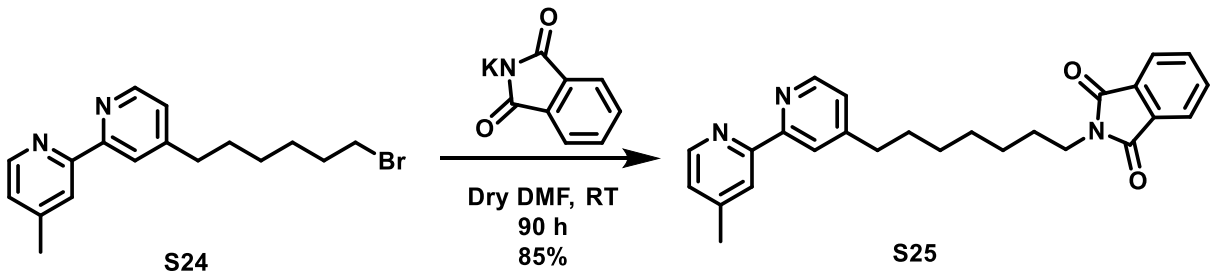


Fig. S13. ^{1}H -NMR spectrum of 4-(7-bromoheptyl)-4'-methyl-2,2'-bipyridine in $CDCl_3$

3.9 2-(7-(4'-Methyl-[2,2'-bipyridin]-4-yl)heptyl)isoindoline-1,3-dione[8]



4-(7-Bromoheptyl)-4'-methyl-2,2'-bipyridine **S24** (340 mg, 1 eq, 1 mmol) was dissolved in dry DMF (20 mL), followed by the addition of potassium phthalimide (222 mg, 1 eq, 1.2 mmol). The reaction mixture was stirred for 90 h. Water was added (20 mL) to this mixture and product was extracted using chloroform (20 mL× 3). Organic layer was washed with 0.2 M sodium hydroxide (20 mL × 1), brine (20 mL × 1) and dried over $MgSO_4$. The crude product was purified by column chromatography (Silica, DCM) to obtain white solid. Yield: 351 mg, 85%

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (m, 2H), 8.20 (m, 2H), 7.82 (m, 2H), 7.68 (m, 2H), 7.11 (m, 2H), 3.66 (t, *J* = 7.3 Hz, 2H), 2.66 (t, *J* = 7.8 Hz, 2H), 2.42 (s, 3H), 1.67 (m, 4H), 1.34 (m, 6H).

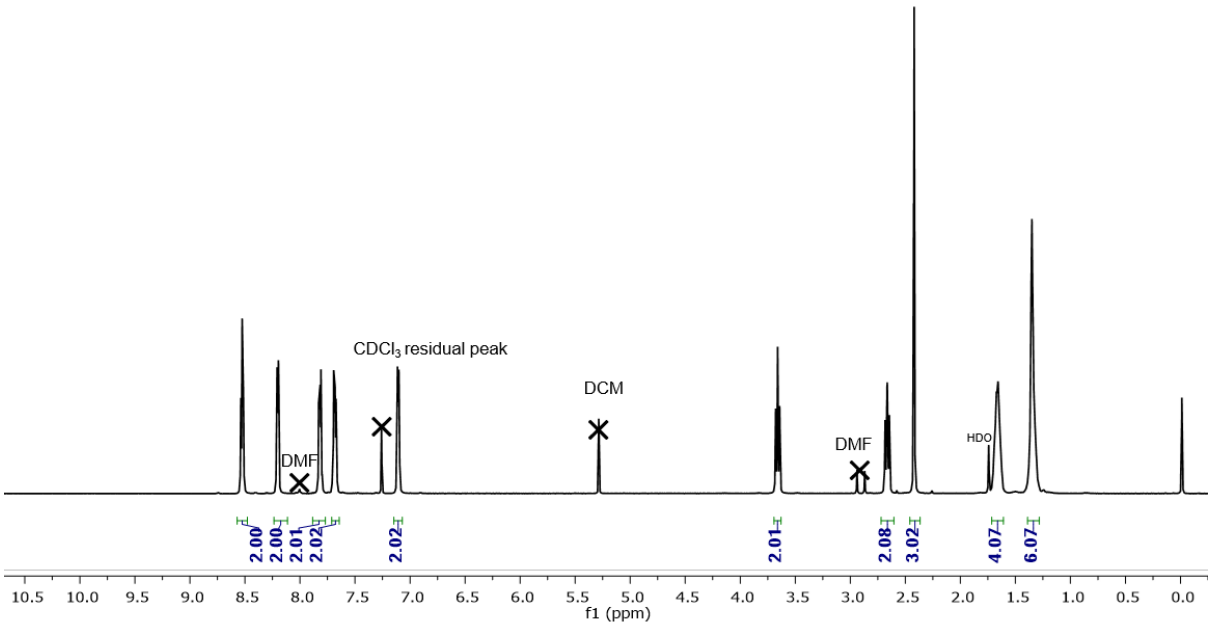
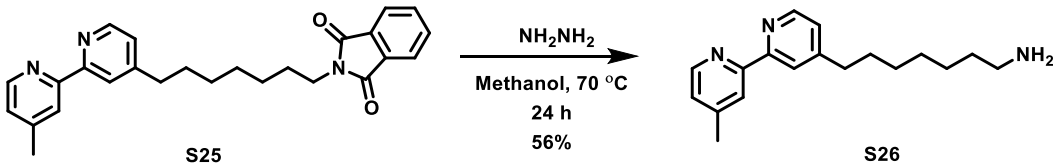


Fig. S14. ^{1}H -NMR spectrum of 2-(7-(4'-methyl-[2,2'-bipyridin]-4-yl)heptyl) isoindoline-1,3-dione in $CDCl_3$

3.10 7-(4'-Methyl-[2,2'-bipyridin]-4-yl)heptan-1-amine[8]



2-(7-(4'-Methyl-[2,2'-bipyridin]-4-yl)heptyl) isoindoline-1,3-dione **S24** (200 mg, 1 eq, 0.48 mmol) was dissolved in methanol (10 mL) and was heated to reflux in oil bath at 70 ºC followed by the addition of hydrazine hydrate (60 mg, 2.5 eq, 1.2 mmol) and was stirred for 24 h. The solvent was removed using rotary evaporator and residue was redissolved in chloroform (15 mL). This solution was washed with 6 M hydrochloric acid (10 mL × 1), water (10 mL × 1), brine (10 mL × 1) and dried over $MgSO_4$. The combined aqueous layers was basified using 5 M sodium hydroxide till pH~8 and was extracted again using chloroform (10 mL × 2). Finally, chloroform was removed using rotary evaporator and dried under vacuum to obtain product as white solid. Yield: 76 mg, 56%

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (t, *J* = 5.0 Hz, 2H), 8.23 (dd, *J* = 3.9, 1.8 Hz, 2H), 7.13 (dd, *J* = 4.9, 1.8 Hz, 2H), 2.68 (q, *J* = 7.1, 6.6 Hz, 4H), 2.44 (s, 3H), 1.70 (p, *J* = 7.6 Hz, 2H), 1.56 – 1.21 (m, 12H).

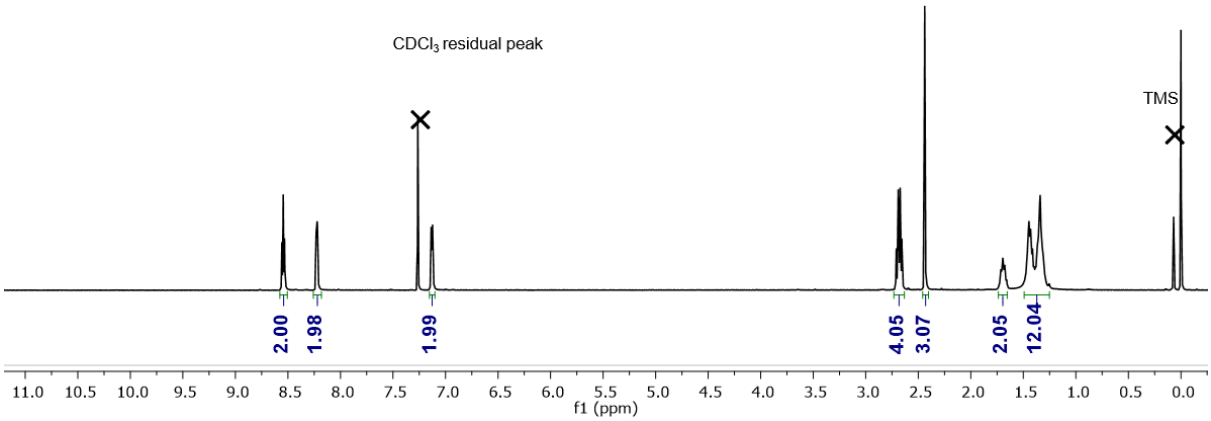
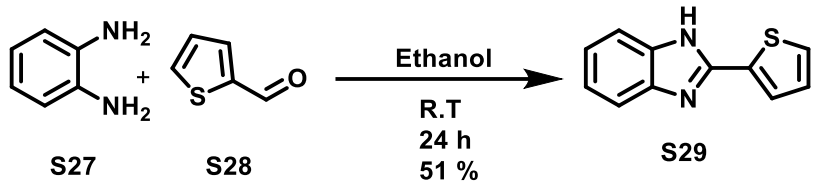


Fig. S15. ^{1}H -NMR spectrum of 7-(4'-methyl-[2,2'-bipyridin]-4-yl)heptan-1-amine in $CDCl_3$

3.11 2-(Thiophen-2-yl)-1H-benzo[d]imidazole[9]



o-Phenylenediamine **S27** (0.50 g, 1 eq, 5 mmol) was dissolved in 10 mL absolute ethanol. To this solution, 2-thiophene carboxaldehyde **S28** (0.57 g, 1 eq, 5 mmol) dissolved in absolute ethanol (20 mL) was added slowly. The reaction mixture was stirred at room temperature overnight. Completion of reaction was monitored by TLC. The crude yellow precipitate that formed was recrystallized from absolute ethanol. Yield = 500 mg, 51%

^{1}H NMR (400 MHz, DMSO-d_6) δ 12.92 (s, 1H), 7.83 (dd, J = 3.6, 1.2 Hz, 1H), 7.72 (dd, J = 5.0, 1.2 Hz, 1H), 7.60 (d, J = 7.8 Hz, 1H), 7.50 (d, J = 7.1 Hz, 1H), 7.25 – 7.14 (m, 3H).

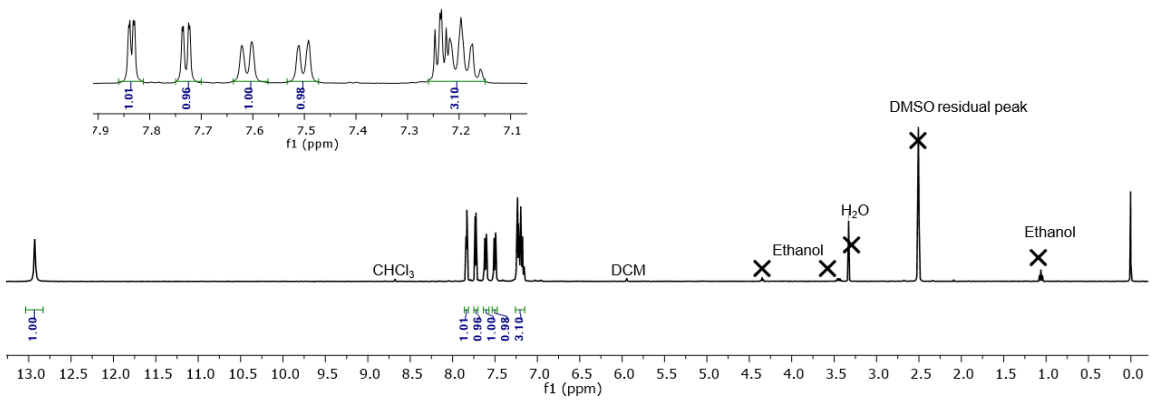
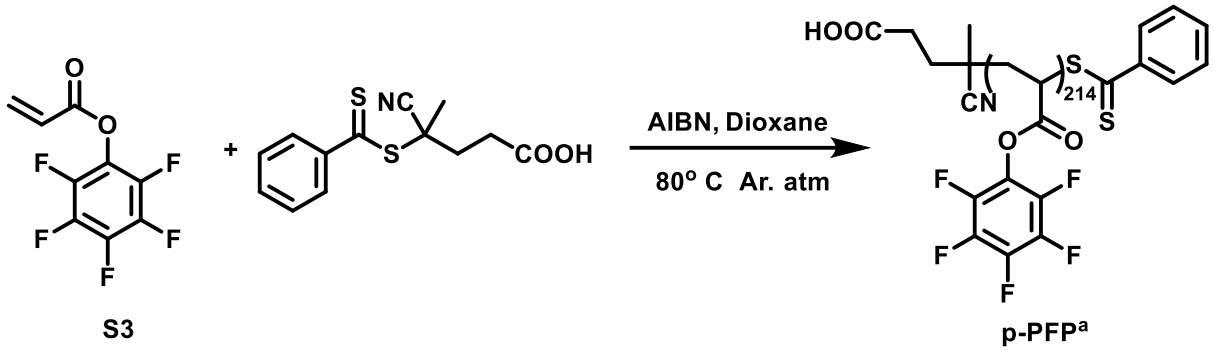


Fig. S16. ^{1}H -NMR spectrum of 2-(thiophen-2-yl)-1H-benzo[d]imidazole in DMSO-d_6

3.12 Poly(pentafluorophenyl) acrylate[1]



Cyano-4-(phenyl-carbonothioylthio)pentanoic acid (16.9 mg, 0.0035 eq, 0.06 mmol) and azobisisobutyronitrile (0.99 mg, 0.00035 eq, 0.006 mmol) was dissolved in 4 mL dry dioxane and was transferred to a oven dried Schlenk tube containing pentafluorophenylacrylate **S3** (4.1 g, 1 eq, 17.3 mmol) under argon atmosphere. The mixture was thoroughly degassed for 1 h and was placed into a pre-heated oil bath at 80 ºC. After 3.5 h, monomer conversion was determined by ^{19}F NMR spectroscopy from an aliquot of reaction mixture and conversion was 75%. The reaction mixture was immediately quenched by placing the flask in liquid nitrogen. Later, flask was brought to room temperature and highly viscous mixture was dissolved in 5 mL DCM and precipitated into 800 mL ice-cold pentane (3 times). The precipitate was filtrated out and dried in the oven under vacuum overnight at 40 °C. After drying, 2.6 g of polymer ***p*-PFP[a]** was obtained. Yield: 2.6 g, 86%

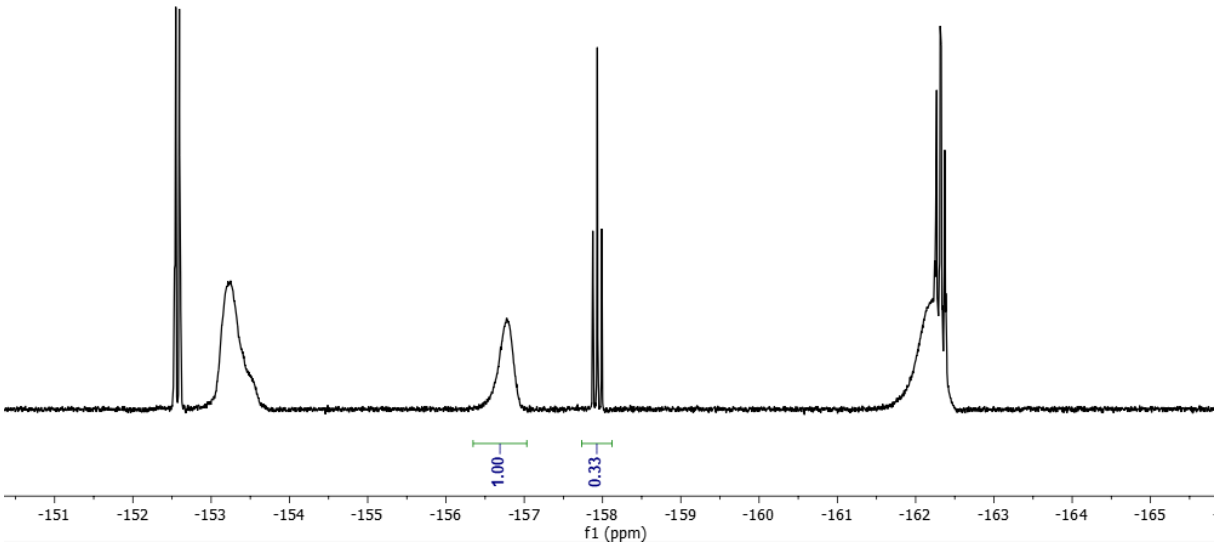
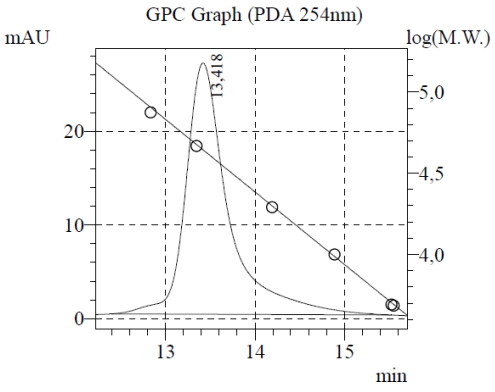


Figure S17. ^{19}F-NMR spectrum of final conversion of RAFT polymerization in $CDCl_3$



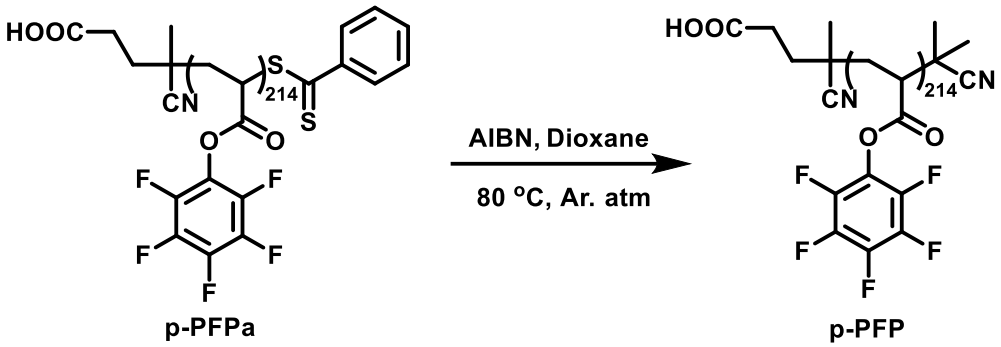
Total Average (PDA 254 nm)

Chromatogram PDA Ch1

#	Mn	Mw	Mz	Mw/Mn
1	35135	40941	45264	1.16525
	35135	40941	45264	1.16525

Figure S18. GPC-SEC chromatogram of ***p*-PFP[a]** in THF after purification

3.13 End group modification - *p*-PFP[1]



***p*-PFP[a]** (1.1 g, 21 µmol, 1 eq), azobisisobutyronitrile (68 mg, 420 µmol, 20 eq) and lauryl peroxide (16 mg, 42 µmol, 2 eq) were dissolved in dry dioxane (15 mL) and degassed for 1 h. Then the reaction mixture was heated to 80 °C under argon atmosphere for 3 h when the solution turned colourless from pink. Later, the solvent was removed, and the residue was re-dissolved in 5 mL chloroform and was precipitated in 800 mL ice-cold pentane (× 3) and dried overnight under vacuum at 40 °C. Yield: 1 g, 91%

^{1}H NMR (400 MHz, Chloroform-*d*) δ 3.08 (br), 2.49 (br), 2.14 (br).

^{19}F NMR (376 MHz, Chloroform-*d*) δ -153.23, -156.75, -162.17.

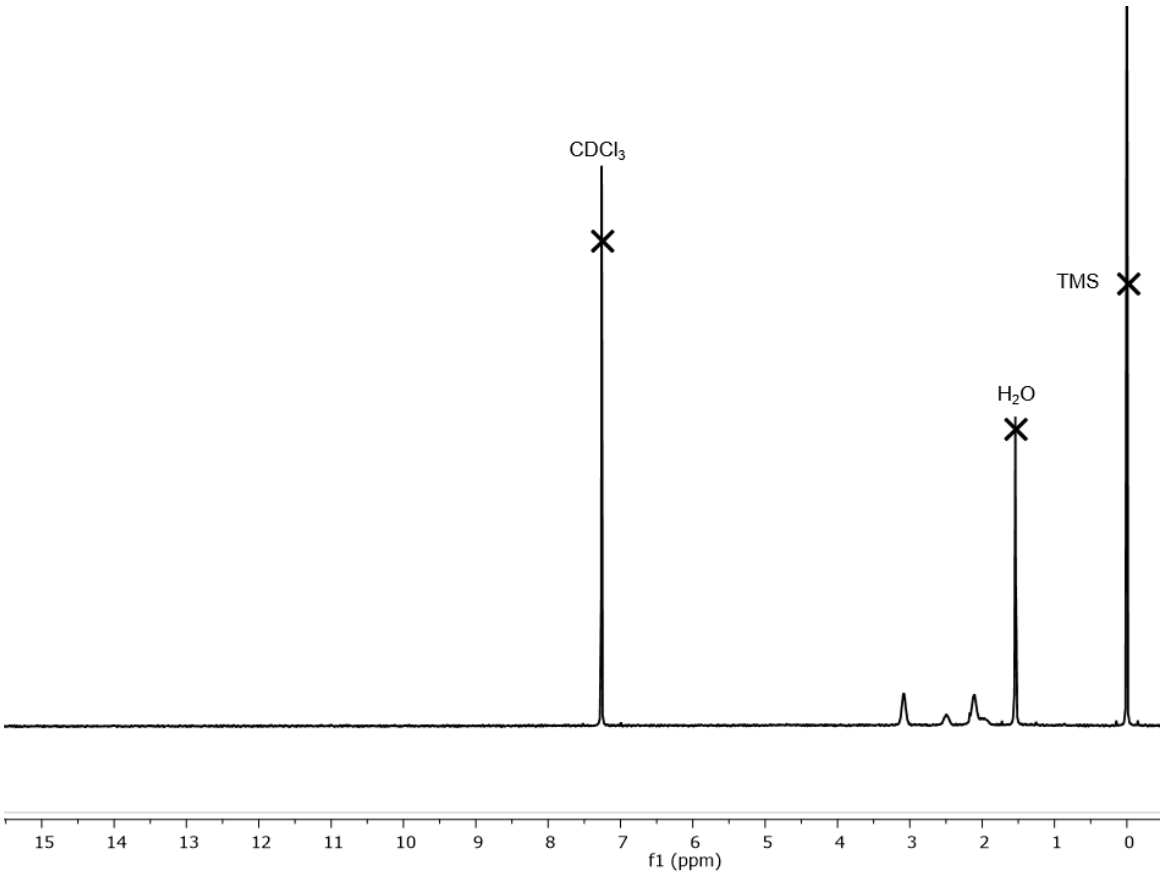


Fig. S19. ^{1}H-NMR spectrum of **p-PFP** in $CDCl_3$

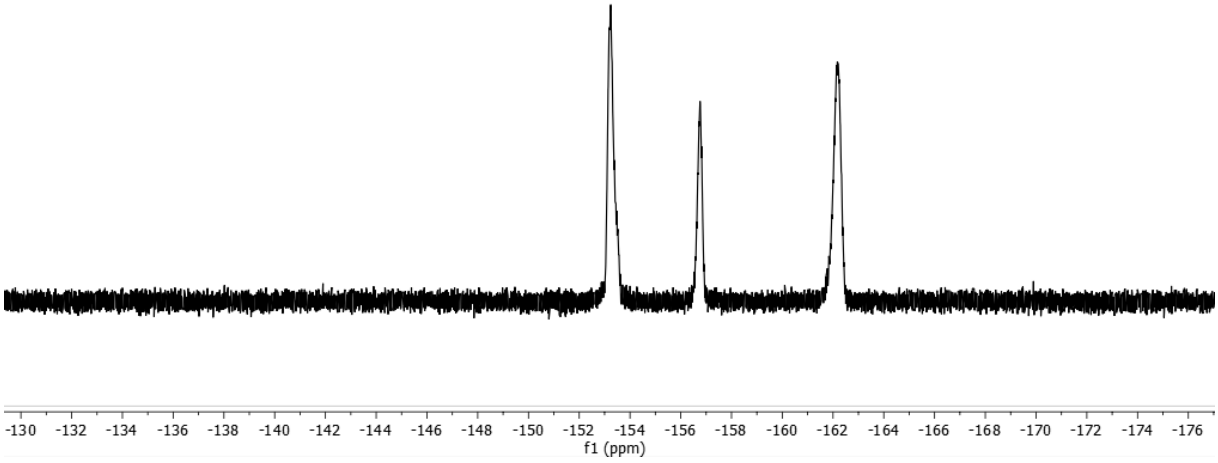
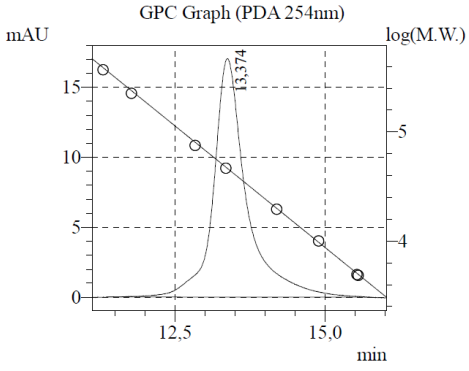


Fig. S20. ^{19}F-NMR spectrum of **p-PFP** in $CDCl_3$



Total Average (PDA 254 nm)

Chromatogram PDA Ch1

#	Mn	Mw	Mz	Mw/Mn
1	36738	45212	54100	1,23064
	36738	45212	54100	1,23064

Fig. S21. GPC chromatogram of **p-PFP** in THF after purification

3.14 Post functionalization

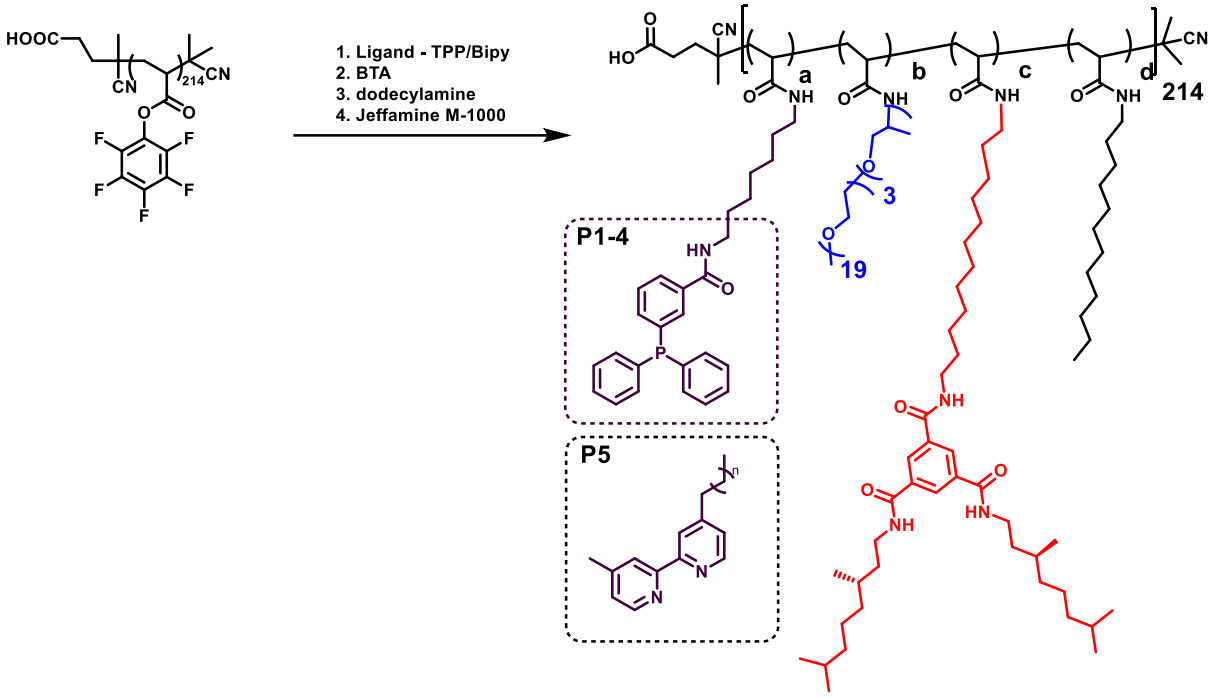


Fig S22: Post functionalization of ***p*-PFP** by sequential addition of amines

Synthesis of **P1-P6**: Polymers were synthesized by post functionalization of ***p*-PFP** according to previously reported protocols.[10]

P1: ***p*-PFP** (200 mg, 1 eq, 0,0039 mmol) was dissolved in dry and degassed DMF in a Schlenk flask kept in preheated oil bath at 50 ºC. To this solution, TPP ligand **8** (31 mg, 20 eq, 0,078 mmol) was added and stirred for 2 h. Incorporation was followed by ^{19}F NMR by comparing the peaks of free pentafluorophenol with those in the polymer backbone. Afterwards, BTA amine (51 mg, 20 eq, 0.078 eq) was added to the mixture and stirred for 2 h, and incorporation was monitored. Finally, Jeffamine (624 mg, 160 eq, 0.62 mmol) was added. The reaction

mixture was then left overnight under argon and completion of reaction was again monitored using ^{19}F NMR. Then, the reaction mixture was purified by dialysis (1 x 1 L methanol, 2 0x 1 L THF) for 3 days in a tightly closed screw capped container. Degassed solvents were used for dialysis which was refreshed as frequently as possible (> 6 h time gap) to prevent oxidation of triphenylphosphine. After dialysis, THF was reduced to ~ 3 mL using rotary evaporator and polymer was precipitated into ice cold pentane (800 mL). The polymer was dried under vacuum overnight at 50 ºC to yield a pale-yellow solid and was stored at -19 ºC. Yield: 426 mg, $M_{theoretical}$ = 183 kD, $M_{n,\ SEC\text{-}DMF}$ = 46.8 kD.

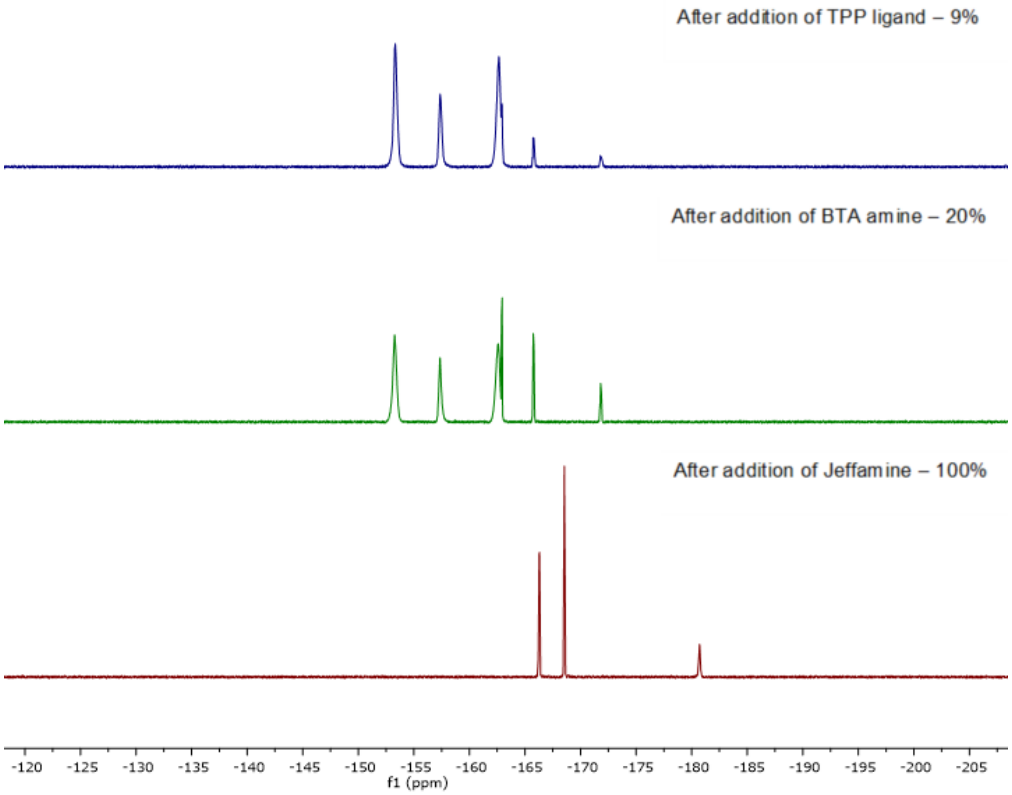


Fig. S23. ^{19}F NMR spectra (376 MHz, $CDCl_3$) after each addition step during the synthesis of polymer **P1**. The degree of functionalization was determined based on the ratio of pentafluorophenol on polymer backbone and free pentafluorophenol.

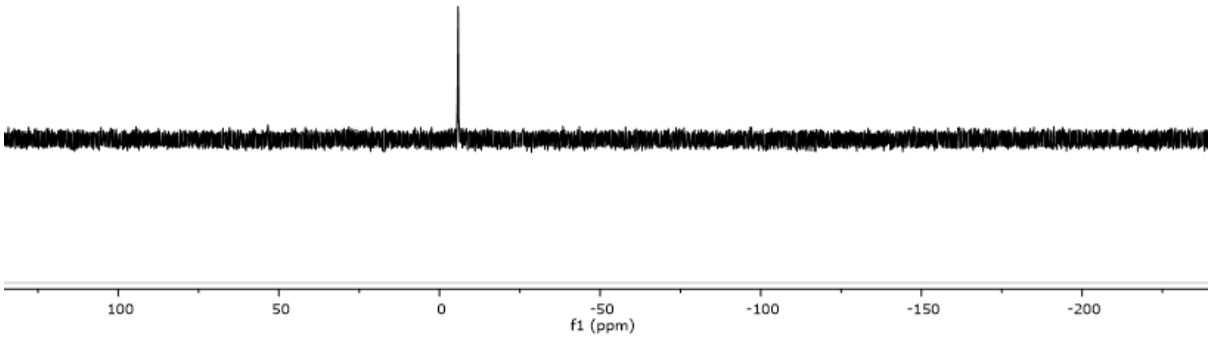


Fig. S24. ^{31}P-NMR spectrum of **P1** in $CDCl_3$

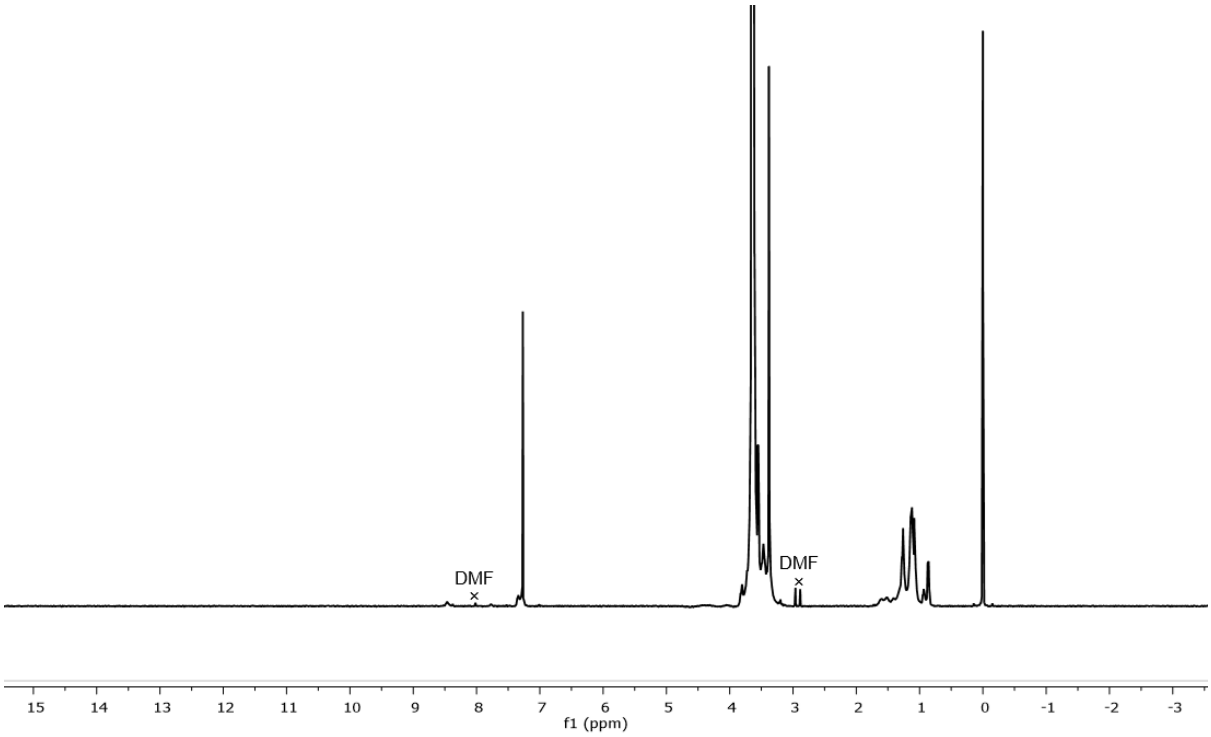
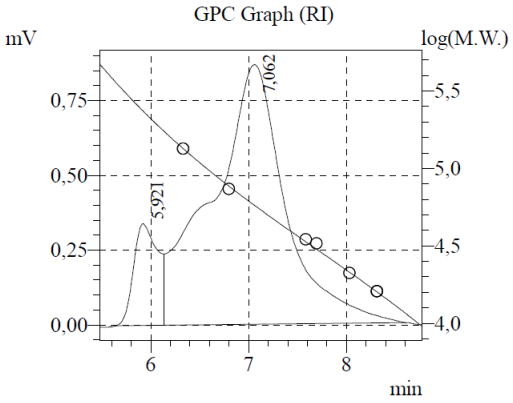


Fig. S25. ^{1}H-NMR spectrum of **P1** in $CDCl_3$



Total Average(RI)

Chromatogram Detector 2 Ch1

#	Mn	Mw	Mw/Mn
1	62047	89028	1,43485
	62047	89028	1,43485

Fig. S26. GPC-SEC chromatogram of **P1** in DMF[##]

P2 : ***p*-PFP** (100 mg, 1 eq, 0,0019 mmol) was dissolved in dry and degassed DMF in a Schlenk flask kept in preheated oil bath at 50 ºC. To this solution, TPP ligand **8** (15 mg, 20 eq, 0,038 mmol) was added and stirred for 2 h. Incorporation was followed by ^{19}F NMR by comparing the peaks of free pentafluorophenol with those in the polymer backbone. Afterwards, BTA amine (12 mg, 10 eq, 0.019 eq) was added to the mixture and stirred for 2 h, after determining the incorporation, dodecyl amine (10 mg, 30 eq, 0.057 mmol) was added. The reaction mixture was again stirred for 2 h, progress followed by ^{19}F NMR. Finally, Jeffamine (266 mg, 140 eq, 0.26 mmol) was added to the mixture. The reaction mixture was then left overnight under argon and completion of reaction was again monitored using ^{19}F NMR. Then, the reaction mixture was purified by dialysis (1 x 1 L methanol, 2 0x 1 L THF) for 3 days in a tightly closed screw capped container. Degassed solvents were used for dialysis which was refreshed frequently (> 6h time gap) to prevent oxidation of triphenylphosphine. After dialysis, THF was reduced to ~ 3 mL using rotary evaporator and polymer was precipitated into ice cold pentane (800 mL). The polymer was dried under vacuum overnight at 50 ºC to yield a pale-yellow solid and was stored at -19 ºC. Yield: 231 mg, $M_{theoretical}$ = 163 kD, $M_{n,\ SEC\text{-}DMF}$ = 42.2 kD.

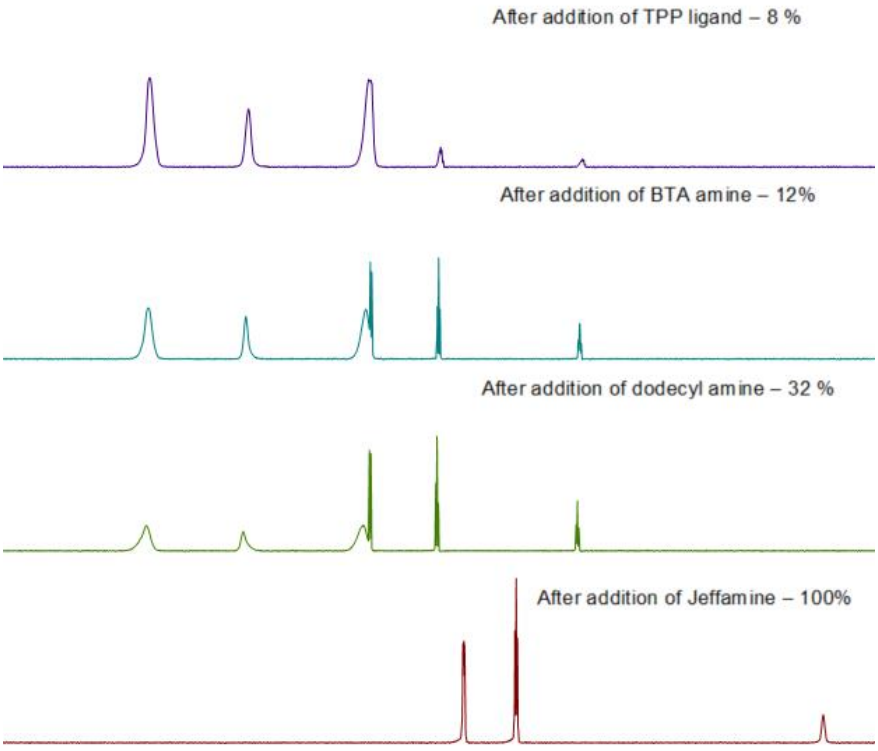


Fig. S27. ^{19}F NMR spectra (376 MHz, $CDCl_3$) after each addition step during the synthesis of polymer **P2**. The degree of functionalization was determined based on the ratio of pentafluorophenol on polymer backbone and free pentafluorophenol.

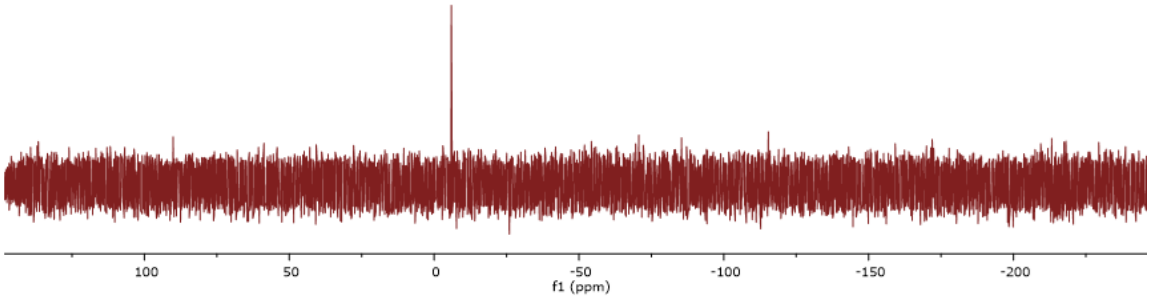


Fig. S28. ^{31}P-NMR spectrum of **P2** in $CDCl_3$

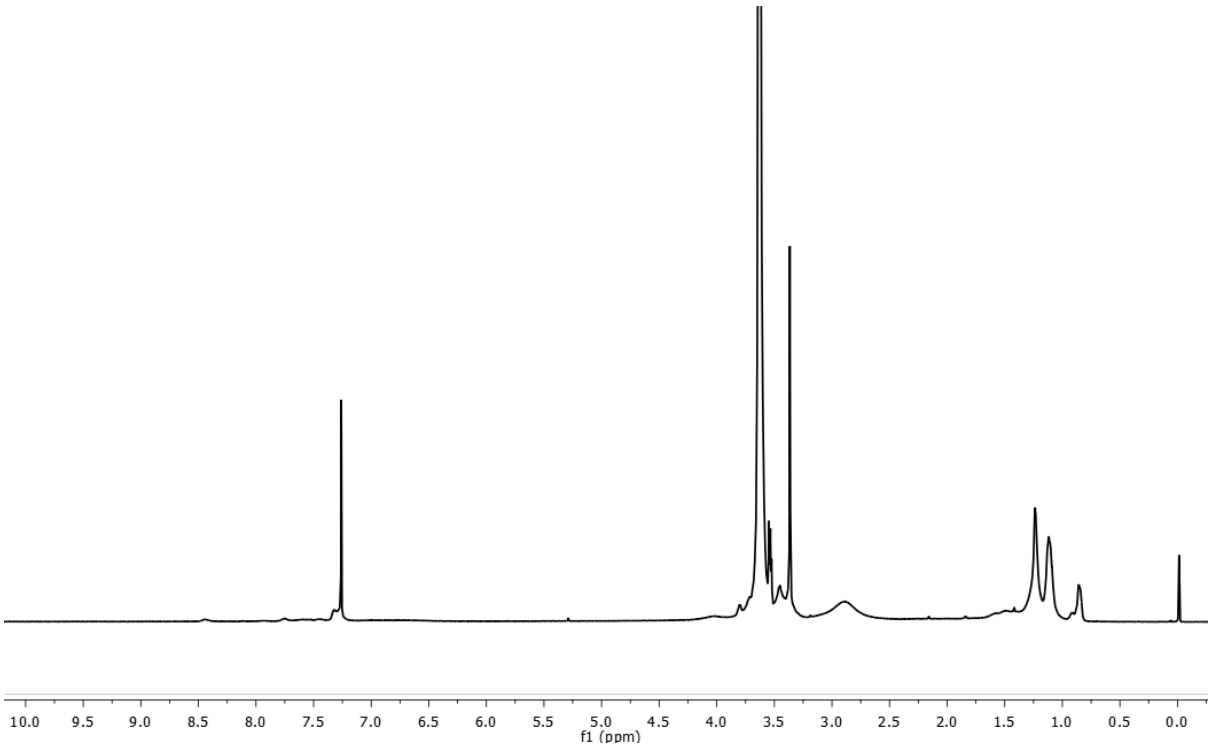
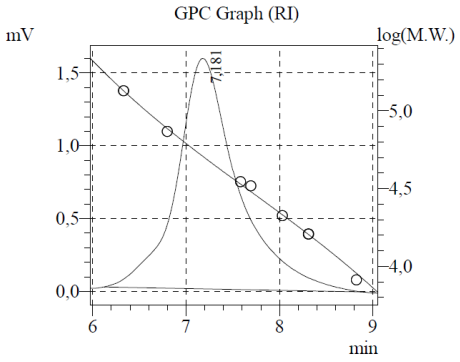


Fig. S29. ^{1}H-NMR spectrum of **P2** in $CDCl_3$



Total Average(RI)

Chromatogram Detector 2 Ch1

#	Mn	Mw	Mw/Mn
1	42218	50220	1,18954
	42218	50220	1,18954

Fig. S30. GPC-SEC chromatogram of **P2** in DMF

P3: ***p*-PFP** (150 mg, 1 eq, 0,0029 mmol) was dissolved in dry and degassed DMF in a Schlenk flask kept in preheated oil bath at 50 ºC. To this solution, TPP ligand **8** (23 mg, 20 eq, 0,058 mmol) was added and stirred for 2 h. Incorporation was followed by ^{19}F NMR by comparing the peaks of free pentafluorophenol with those in the polymer backbone. Afterwards, dodecyl amine (21 mg, 40 eq, 0.116 eq) was added to the mixture and stirred for 2 h and incorporation was determined. Finally, Jeffamine (400 mg, 140 eq, 0.40 mmol) was added to the mixture and left overnight under argon. Then, the reaction mixture was purified by dialysis (1 x 1 L

methanol, 2 x 1 L THF) for 3 days in a tightly closed screw capped container. Degassed solvents were used for dialysis which was refreshed frequently (> 6 h time gap) to prevent oxidation of triphenylphosphine. After dialysis, THF was reduced to ~3 mL using rotary evaporator and polymer was precipitated into ice cold pentane (800 mL). The polymer was dried under vacuum overnight at 50 ºC to yield a colourless solid and was stored at -19 ºC. Yield: 316 mg, $M_{theoretical}$ = 158 kD, $M_{n,\ SEC\text{-}DMF}$ = 62 kD.

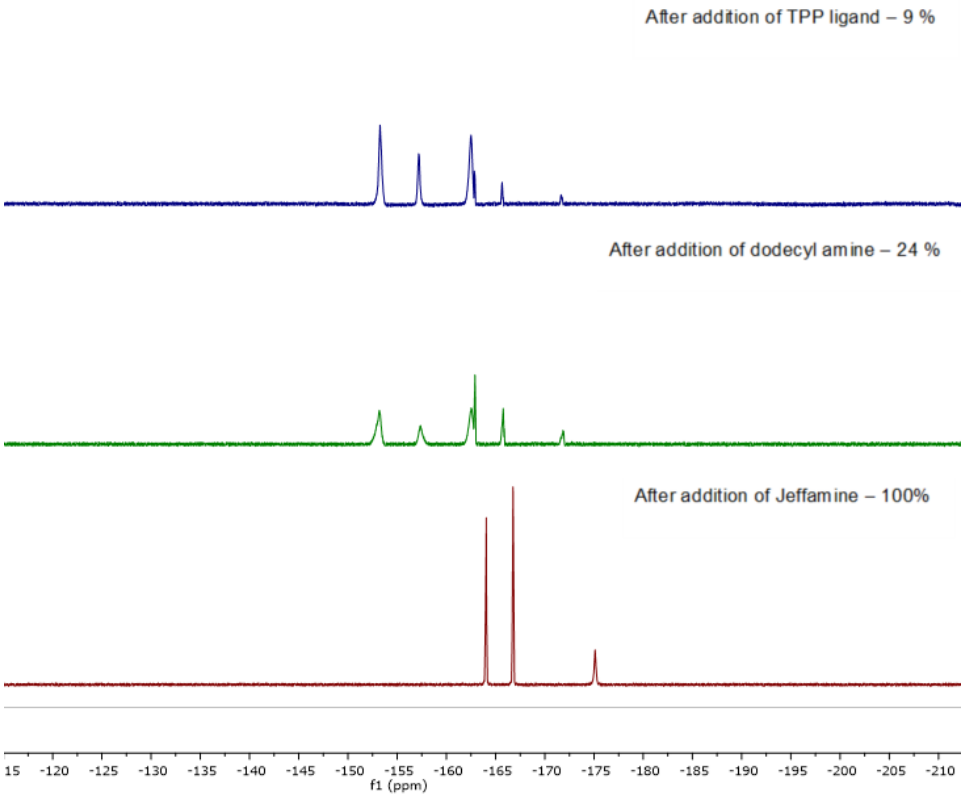


Fig. S31. ^{19}F NMR spectra (376 MHz, $CDCl_3$) after each addition step during the synthesis of polymer **P3**. The degree of functionalization was determined based on the ratio of pentafluorophenol on polymer backbone and free pentafluorophenol.

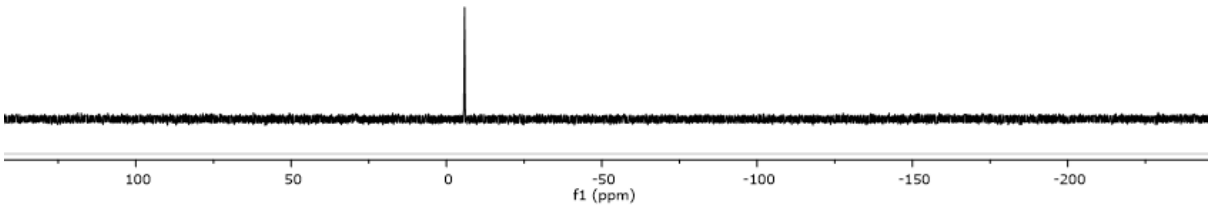


Fig. S32. ^{31}P-NMR spectrum of **P3** in $CDCl_3$

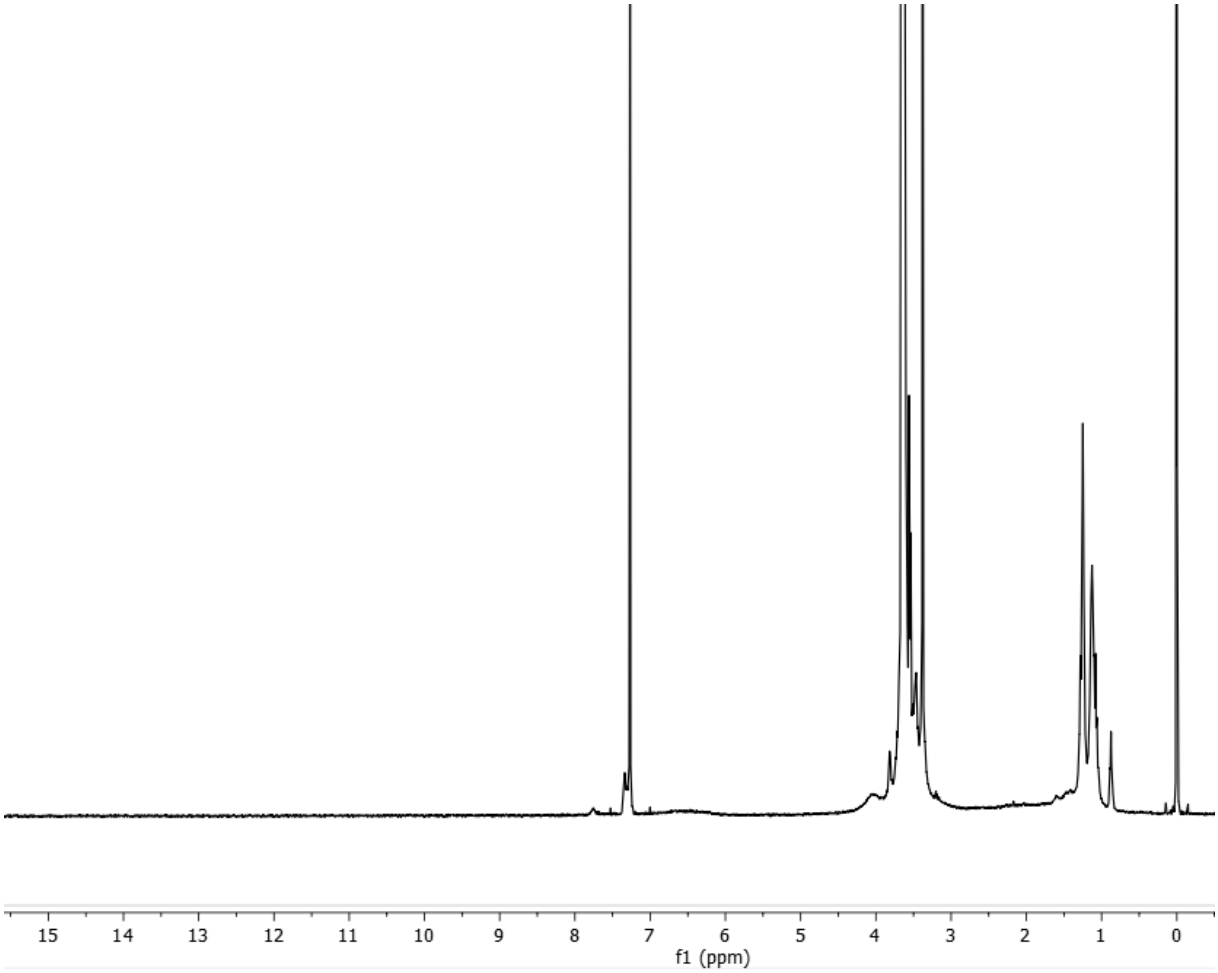
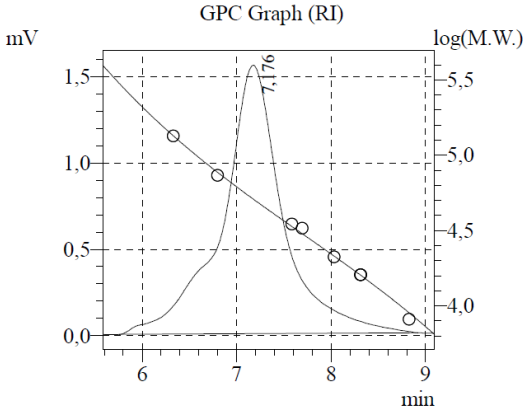


Fig. S33. ^{1}H-NMR spectrum of **P3** in $CDCl_3$



Total Average(RI)

Chromatogram Detector 2 Ch1

#	Mn	Mw	Mw/Mn
1	46818	58743	1,25472
	46818	58743	1,25472

Fig. S34. GPC-SEC chromatogram of **P3** in DMF

P4: ***p*-PFP** (100 mg, 1 eq, 0,0019 mmol) was dissolved in dry and degassed DMF in a Schlenk flask kept in preheated oil bath at 50 ºC. To this solution, TPP ligand **8** (30 mg, 40 eq, 0,076 mmol) was added and stirred for 2 h. Incorporation was followed by ^{19}F NMR by comparing the peaks of free pentafluorophenol with those in the polymer backbone. Afterwards, Jeffamine (300 mg, 160 eq, 0.30 mmol) was added to the mixture. The reaction mixture was then left overnight under argon and completion of reaction was again monitored using ^{19}F NMR. After completion of the reaction, the reaction mixture was purified by dialysis (1 x 1 L methanol, 2 x 1 L THF) for 3 days in a tightly closed screw capped container. Degassed solvents were used for dialysis and was refreshed frequently (> 6 h time gap). After dialysis, THF was reduced to ~ 3 mL using rotary evaporator and polymer was precipitated into ice-cold pentane (800 mL). The polymer was dried under vacuum overnight at 50 ºC to yield a colourless solid and was stored at −19 ºC. Yield: 223 mg, $M_{theoretical}$ = 178 kD, $M_{n,\ SEC\text{-}DMF}$ = 55.4 kD.

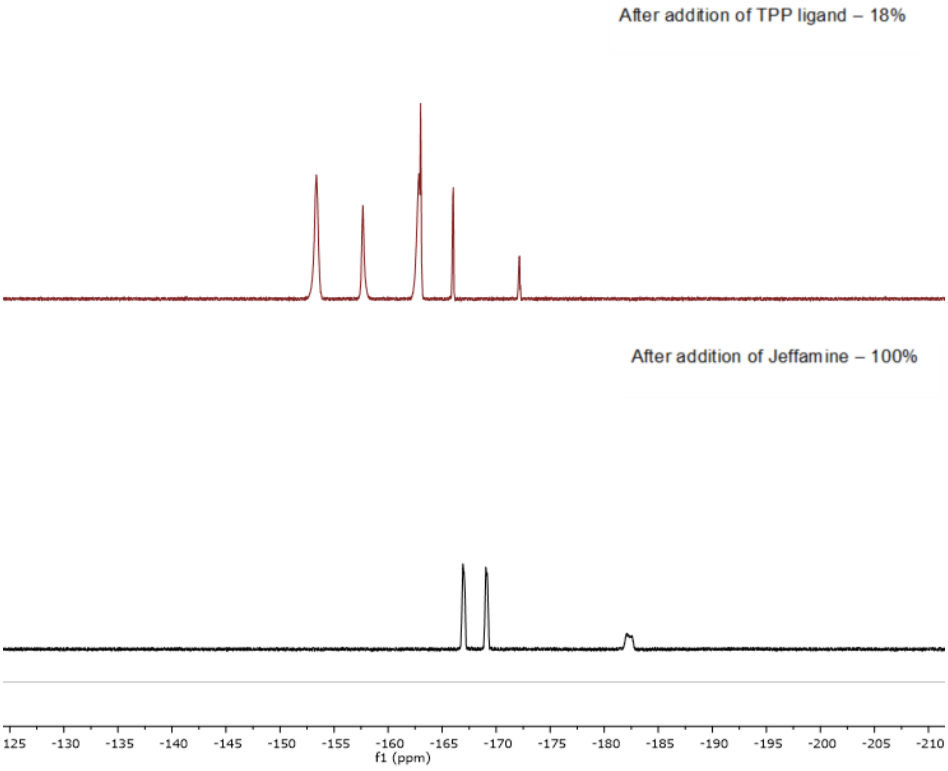


Fig. S35. ^{19}F NMR spectra (376 MHz, $CDCl_3$) after each addition step during the synthesis of polymer **P4**. The degree of functionalization was determined based on the ratio of pentafluorophenol on polymer backbone and free pentafluorophenol.

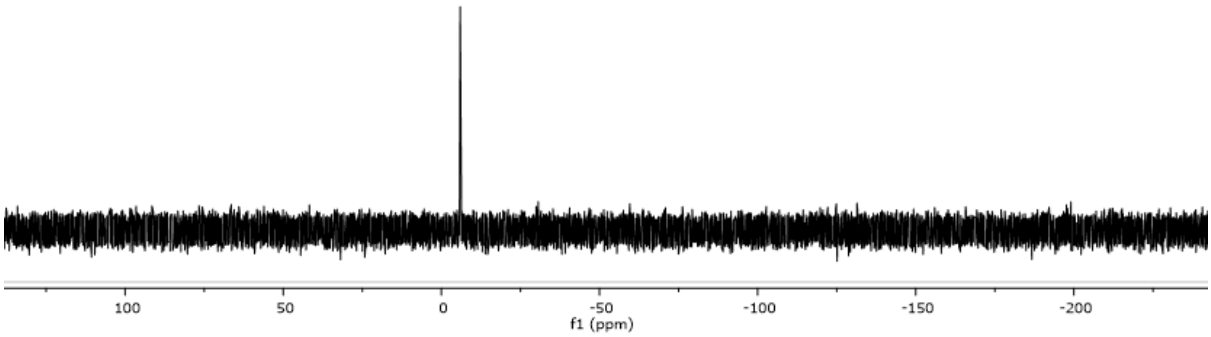


Fig. S36. ^{31}P-NMR spectrum of **P4** in $CDCl_3$

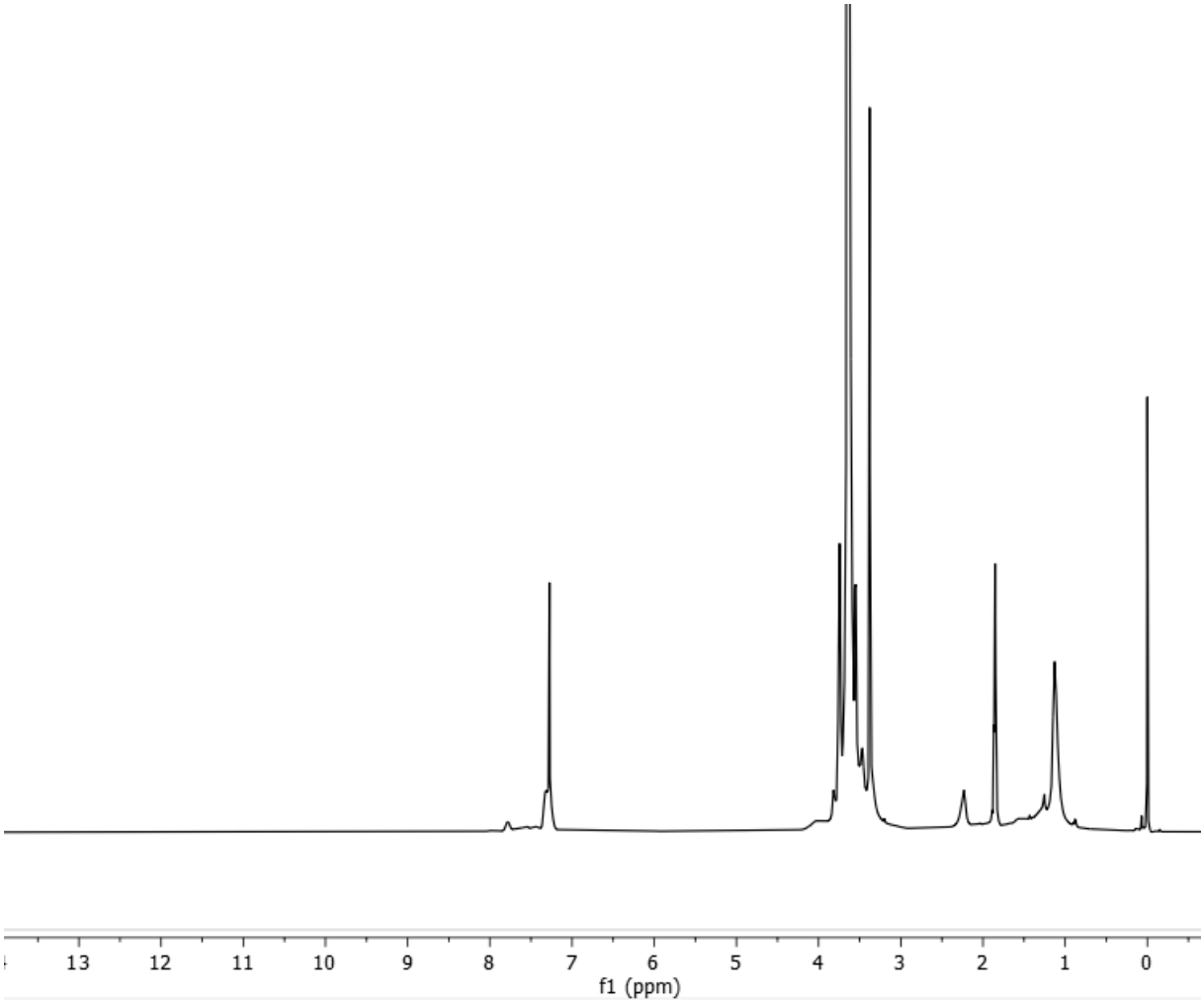
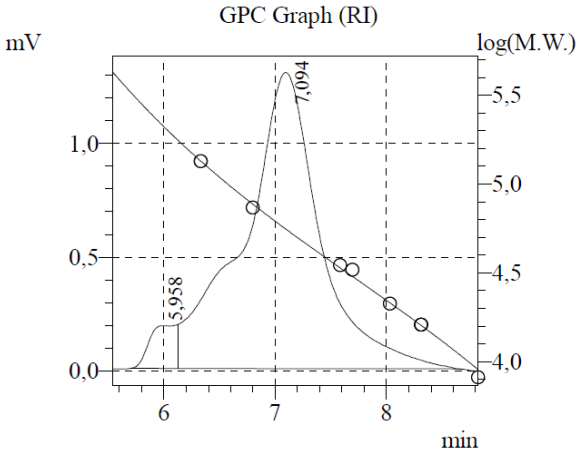


Fig. S37. ^{1}H-NMR spectrum of **P4** in $CDCl_3$



Total Average(RI)

Chromatogram Detector 2 Ch1

#	Mn	Mw	Mw/Mn
1	55405	73202	1,32120
	55405	73202	1,32120

Fig. S38. GPC-SEC chromatogram of **P4** in DMF[##]

P5: ***p*-PFP** (100 mg, 1 eq, 0,0019 mmol) was dissolved in dry and degassed DMF in a Schlenk flask kept in preheated oil bath at 50 ºC. To this solution, bipy ligand **26** (10 mg, 20 eq, 0,038 mmol) was added and stirred for 2 h. Incorporation was followed by ^{19}F NMR by comparing the peaks of free pentafluorophenol with those in the polymer backbone. Afterwards, BTA amine (12 mg, 10 eq, 0.019 eq) was added to the mixture and stirred for 2 h, after determining the incorporation, dodecyl amine (10 mg, 30 eq, 0.057 mmol) was added. The reaction mixture was again stirred for 2 h, progress followed by ^{19}F NMR. Finally, Jeffamine (266 mg, 140 eq, 0.26 mmol) was added to the mixture. The reaction mixture was then left overnight under argon and completion of reaction was again monitored using ^{19}F NMR. After completion of the reaction, the reaction mixture was purified by dialysis (1 x 1 L methanol, 2 x 1 L THF) for 3 days. After dialysis, THF was reduced to ~ 3 mL using rotary evaporator and polymer was precipitated into ice-cold pentane (800 mL). The polymer was dried under vacuum overnight at 50 ºC to yield a colourless solid and was stored at –19 ºC. Yield: 170 mg, $M_{theoretical}$ = 179 kD, $M_{n,\ SEC\text{-}DMF}$ = 46.9 kD.

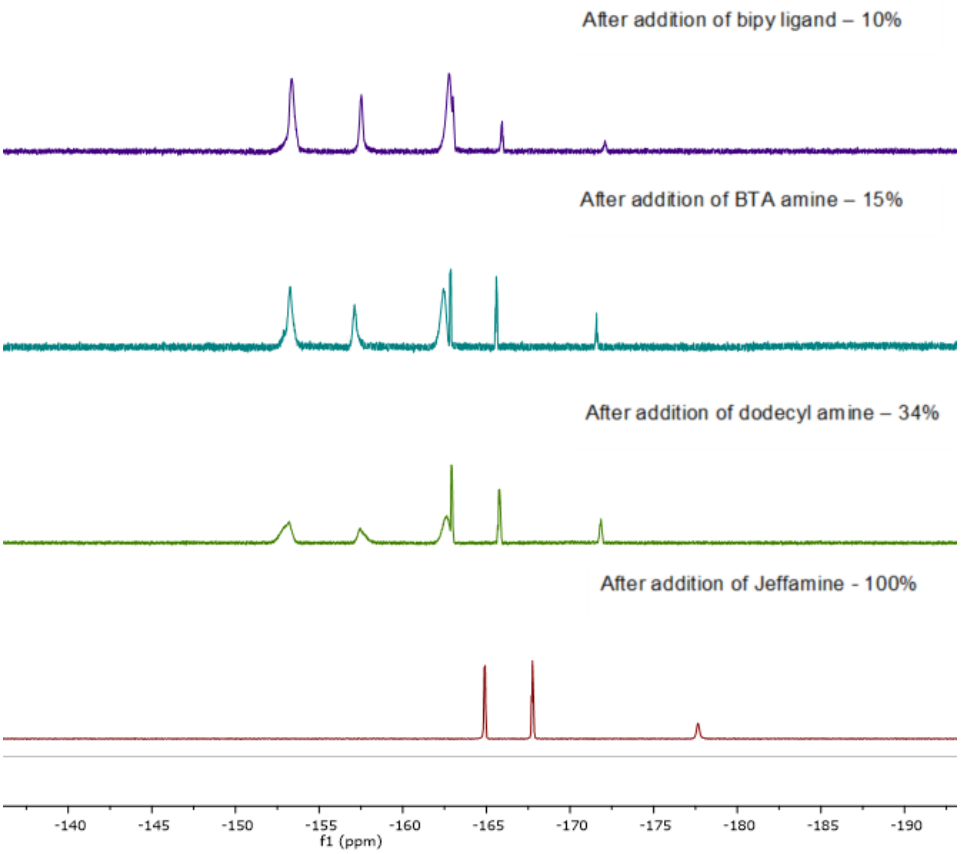


Fig S39: ^{19}F NMR spectra (376 MHz, $CDCl_3$) after each addition step during the synthesis of polymer **P5**. The degree of functionalization was determined based on the ratio of pentafluorophenol on polymer backbone and free pentafluorophenol.

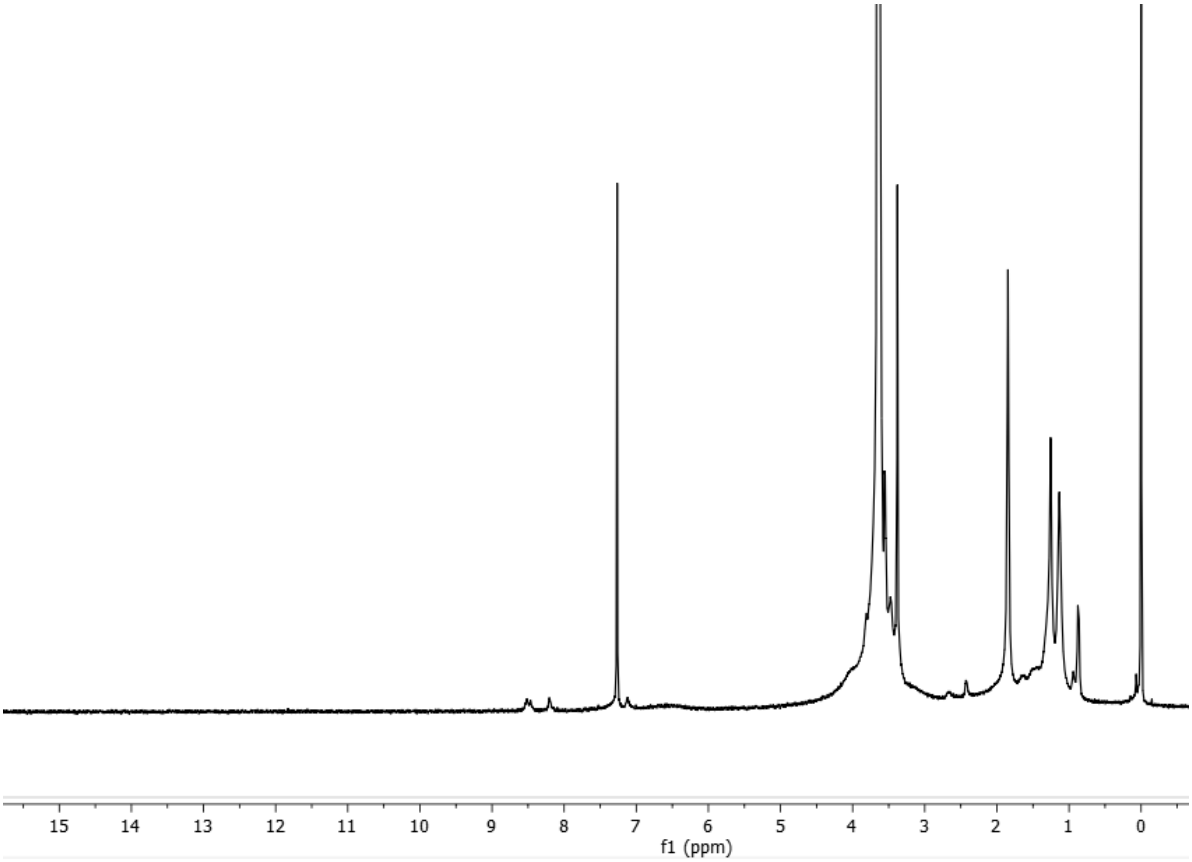
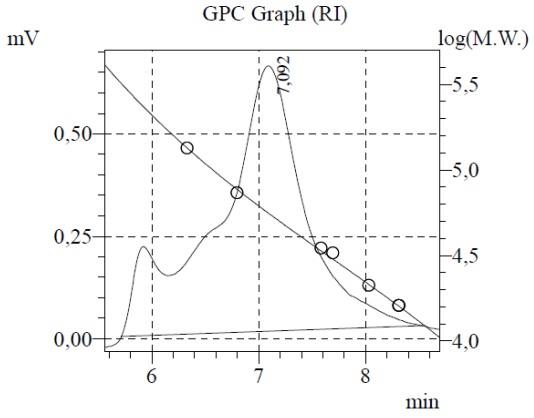


Fig. S40. ^{1}H-NMR spectrum of **P5** in $CDCl_3$



Total Average(RI)

Chromatogram Detector 2 Ch1

#	Mn	Mw	Mw/Mn
1	57880	82632	1,42766
	57880	82632	1,42766

Fig. S41. GPC-SEC chromatogram of **P5** in DMF[##]

P6: ***p*-PFP** (100 mg, 1 eq, 0,0019 mmol) was dissolved in dry and degassed DMF in a Schlenk flask kept in preheated oil bath at 50 ºC. To this solution, dodecyl amine (21 mg, 40 eq, 0.116 eq) was added and stirred for 2 h. Incorporation was followed by ^{19}F NMR by comparing the peaks of free pentafluorophenol with those in the polymer backbone. Afterwards, Jeffamine (300 mg, 160 eq, 0.30 mmol) was added to the mixture. The reaction mixture was then left overnight under argon and completion of the reaction was again monitored using ^{19}F NMR.

After completion of the reaction, the reaction mixture was purified by dialysis (1 x 1 L methanol, 2 x 1 L THF) for 3 days. After dialysis, THF was reduced to ~ 3 mL using rotary evaporator and polymer was precipitated into ice-cold pentane (800 mL). The polymer was dried under vacuum overnight at 50 ºC to yield a pale-yellow solid and was stored at −19 ºC. Yield: 186 mg, $M_{theoretical}$ = 172 kD, $M_{n,\ SEC\text{-}DMF}$ = 49.8 kD.

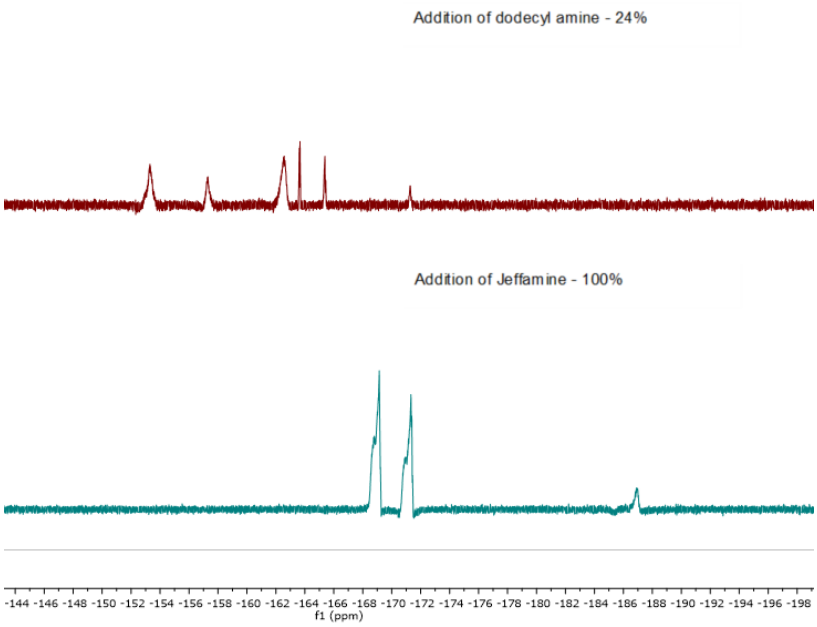


Fig. S42. ^{19}F NMR spectra (376 MHz, $CDCl_3$) after each addition step during the synthesis of polymer **P6**. The degree of functionalization was determined based on the ratio of pentafluorophenol on polymer backbone and free pentafluorophenol.

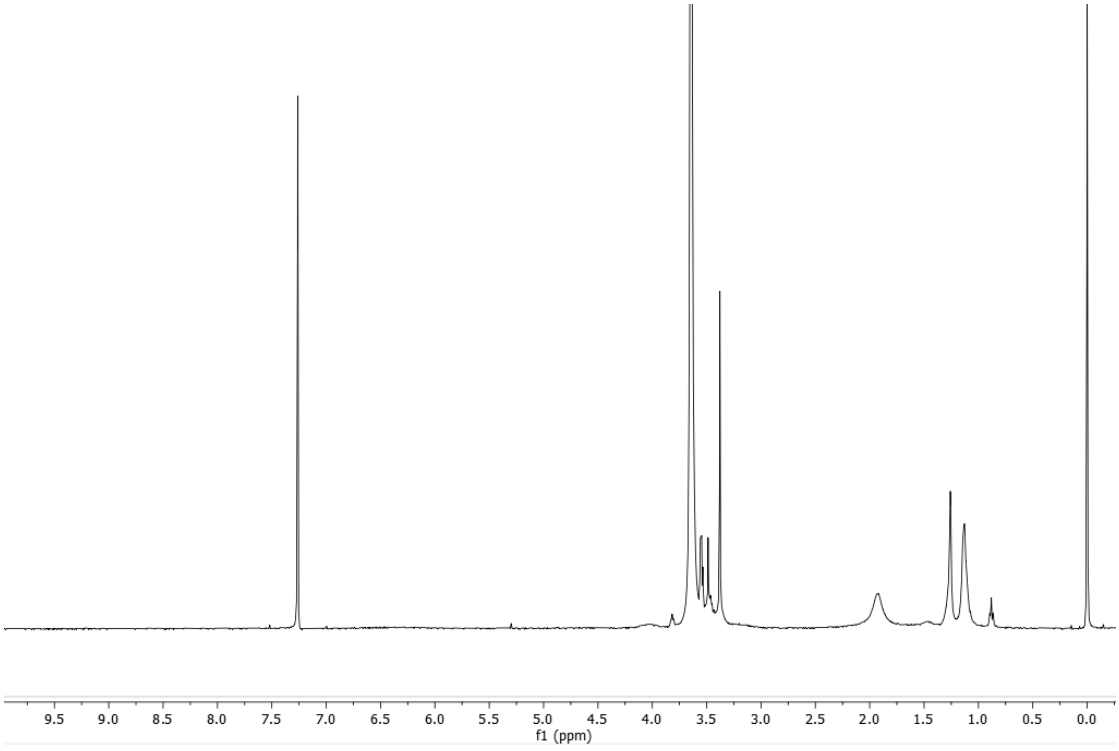
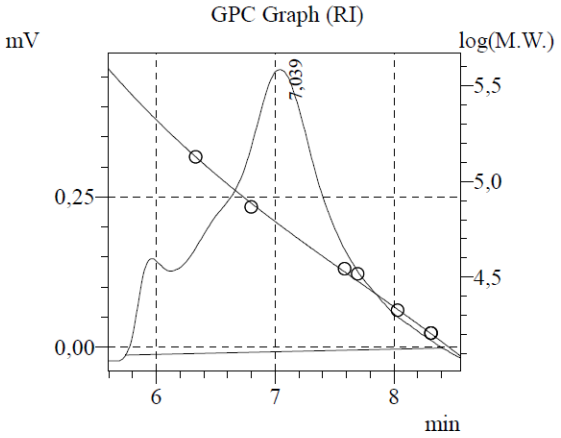


Fig. S43. ^{1}H-NMR spectrum of **P6** in $CDCl_3$



Total Average(RI)

Chromatogram Detector 2 Ch1

#	Mn	Mw	Mw/Mn
1	57640	81405	1,41230
	57640	81405	1,41230

Fig. S44. GPC-SEC chromatogram of **P6** in DMF[##]

4. Complexation of polymers with Pd (II)

4.1 Complexation with Pd(II) of polymers P1-P4[11]:

Dry chloroform was thoroughly degassed by 6 freeze-pump thaw cycles to remove any trace of oxygen in the solvent and all additions were performed under argon using cannula without atmospheric contamination. Degassed solvent (25 mL) was transferred to 50 mg TPP-functionalized polymers **P1-P4** kept in an oven-dried Schlenk tube via cannula (dried in oven overnight). Degassed solvent (25 mL) was also transferred in the same way into another flask containing 3 mg of **$PdCODCl_2$** (3 eq. with respect to TPP ligand). After that, the polymer solution was transferred dropwise into the $PdCODCl_2$ solution over 20 min while stirring. This reaction mixture was stirred overnight under argon and concentrated in vacuum and dialyzed for 3 days (3 × 1 L $CHCl_3$) to remove most of the unbound $PdCODCl_2$. Complexation was also performed at 2:1 ratio of TPP ligand: Pd(II), however, it resulted in the oxidation of TPP due to highly diluted conditions. Therefore, this protocol was followed to obtain **P1-P4@Pd(II)** that form nanoparticles with small size when dissolved in water with minimal aggregates. Complexation was monitored by ^{31}P NMR (Figure S45). After complexation, there is a possibility of both cis and trans complexes, where trans isomers are more predominantly reported in the case of macromolecules,[11,12] and cis isomers in few small molecule complexes.[13–15] From ^{31}P NMR, however, it is difficult to establish the stereochemistry of the Pd complex formed due to the possible presence of hydrogen-bonding interactions of the complex with both BTA and the polymer backbone. MP-AES was performed to obtain the final concentration of Pd(II) in the sample which revealed the presence of unbound $PdCODCl_2$ which was not removed during dialysis

as they are trapped inside polymers. This was also taken into consideration during catalysis studies.

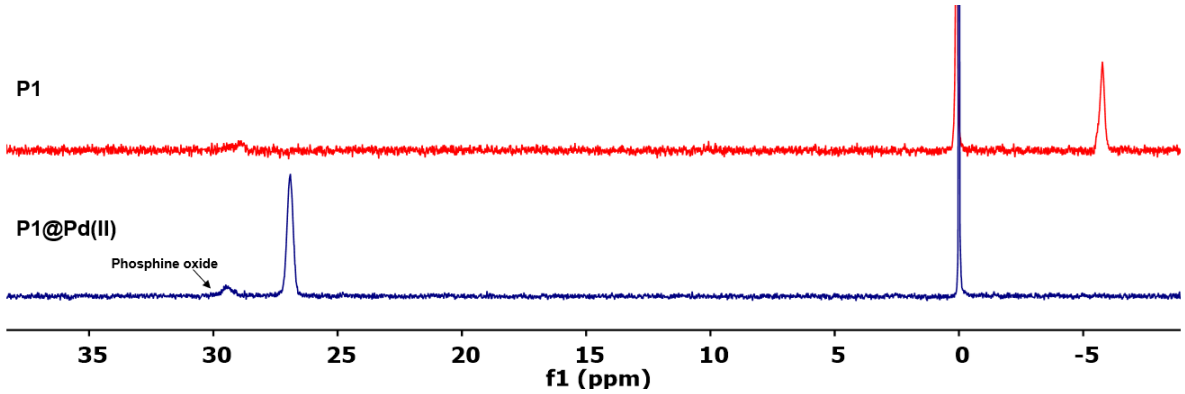


Fig. S45. ^{31}P NMR of palladium complexation of **P1** red) before complexation blue) after complexation.

4.2 Complexation with Pd(II) of polymer P5[16]:

1 mg/mL of **P5** was dissolved in Milli-Q water followed by sonication for 30 min and was allowed to equilibrate for 1 h. To this 10 µL of 10 mM Na_2PdCl_4 solution was added and was stirred for 15 min. Complexation was monitored by UV-Vis Spectroscopy[16].

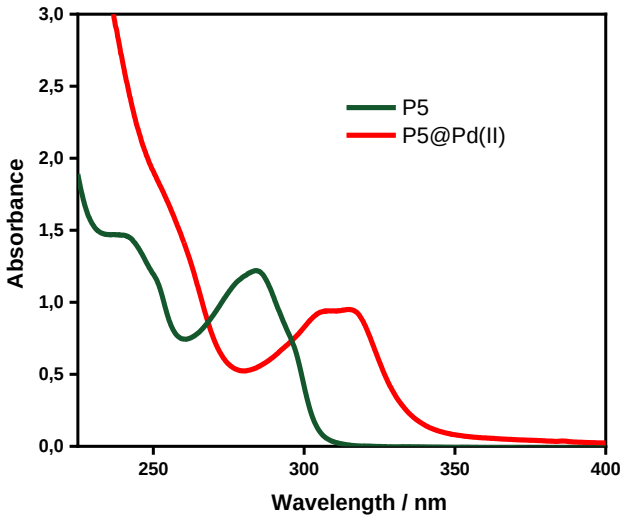


Fig. S46. Complexation of **P5** with Pd(II) monitored using UV-Vis Spectroscopy in water. [**P5**] = 1 mg/mL, [Pd(II)] = 100 µM at RT

5. Dynamic light scattering (DLS) measurements

All polymers **P1-P5** and **P1-P5@Pd(II)** were dissolved in water at 1 mg/mL concentrations in water by sonication for 30 min followed by equilibration of 1 h. Then samples were taken to perform DLS studies.

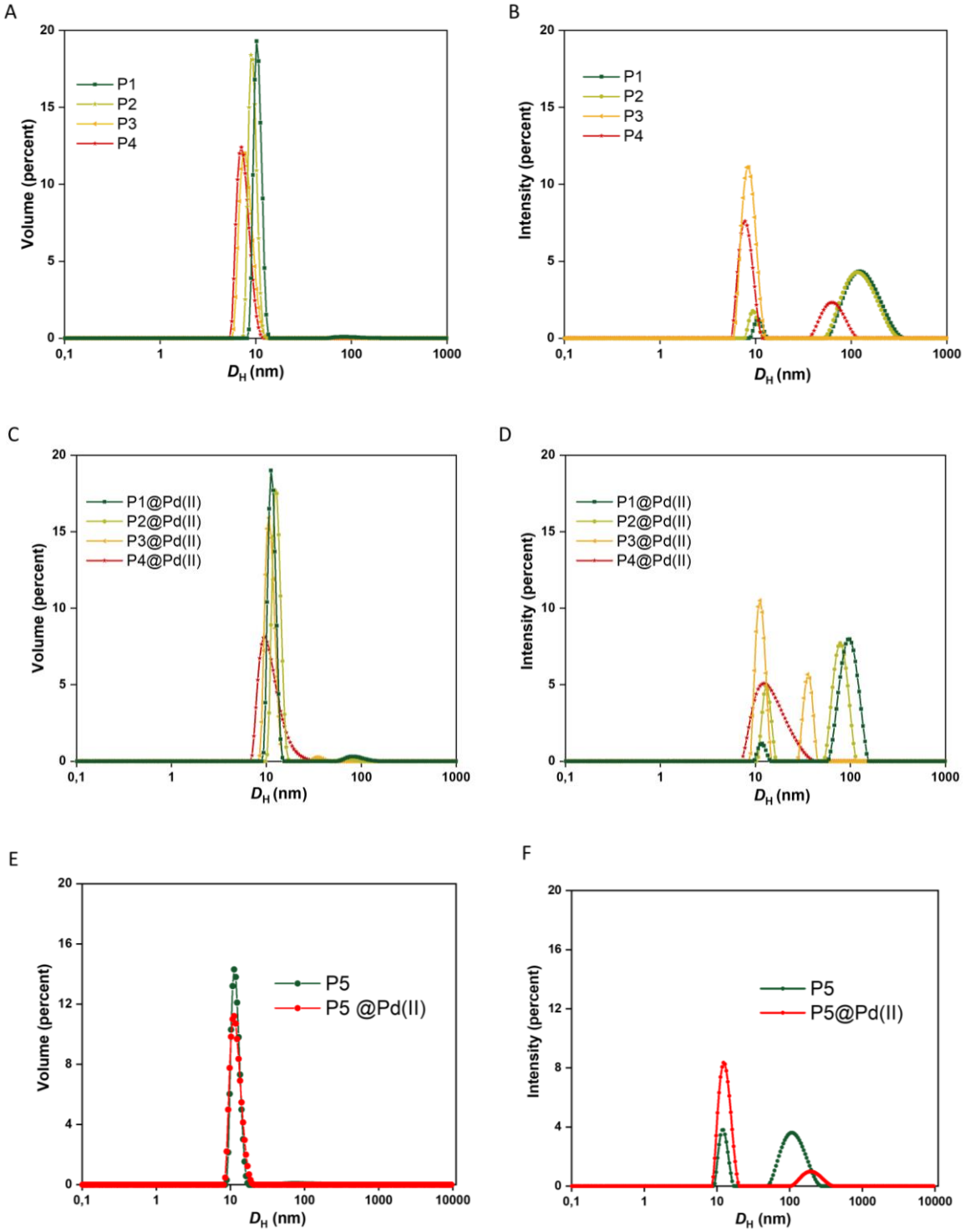


Fig. S47. Dynamic light scattering studies of **P1-P5** before and after complexation [**P1-P5**] = 1 mg/mL, [**P1-P5@Pd(II)**] = 1 mg/mL in water at RT.

Polymer	R_H (nm) Volume	Polymer@Pd(II)	R_H (nm) Volume
P1	5.2	P1@Pd(II)	5.7
P2	4.6	P2@Pd(II)	6.4
P3	3.7	P3@Pd(II)	5.4
P4	5.9	P4@Pd(II)	5.6
P5	5.7	P5@Pd(II)	5.8

Fig. S48. Hydrodynamic Radii of **P1-P5** before and after complexation in water

6. Circular dichroism (CD) measurements

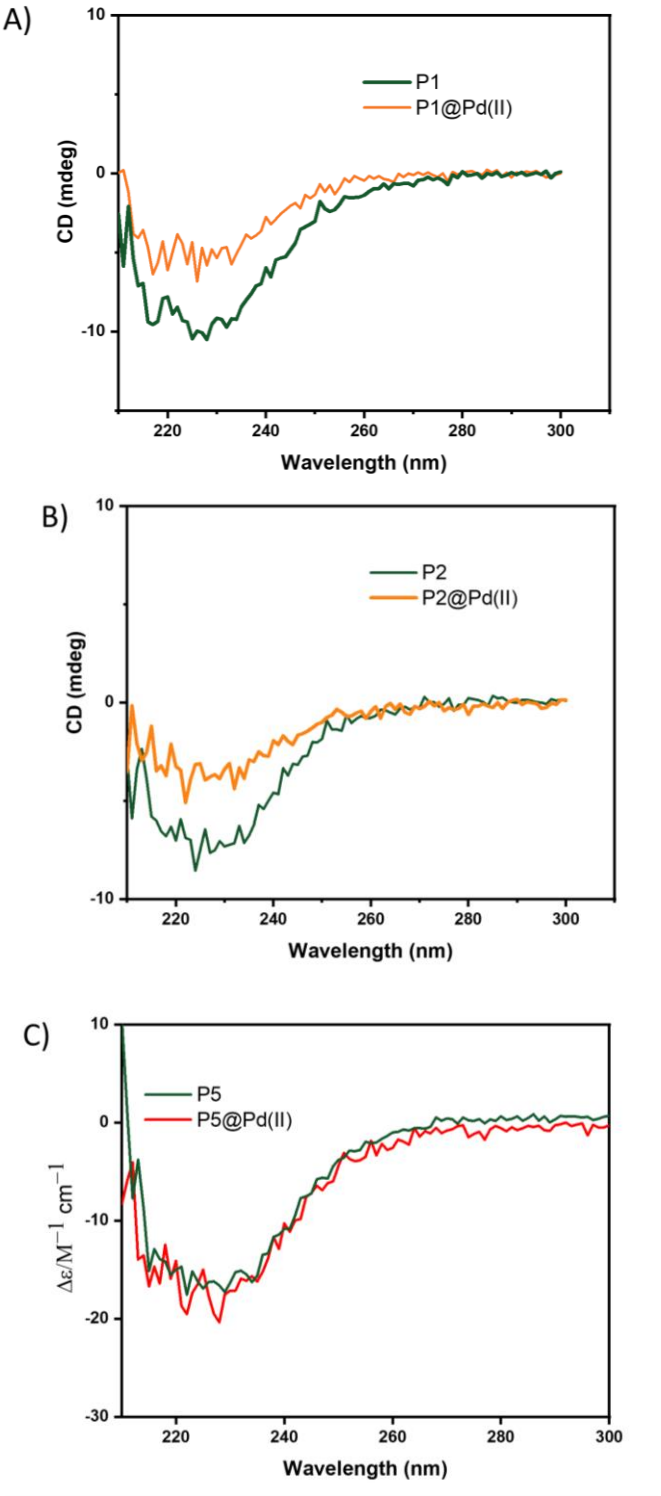


Fig. S49. CD spectra of polymers **P1**, **P2** and **P5** before and after complexation with Pd(II). ([**P1**] = 0.4 mg/mL,[**P2**] = 0.5 mg/mL, [**P5**] = 1 mg/mL, [**P5@Pd(II)**] = 0.5 mg/mL. All measurements were done in a 0.5 cm cuvette) at RT.

7. Determining concentration of Pd(II) with MP-AES

The concentration of palladium in complexed polymers was analyzed using MP-AES spectroscopy. The results suggest that Pd(II) precursor is trapped inside the hydrophobic environment of polymers even after dialysis. For catalysis measurements total Pd(II) concentration was kept constant including unbound $PdCODCl_2$.

Table S1: Determination of Pd(II) concentration using MP-AES

Polymer	Pd concentration	Pd concentration (1 mg/mL polymer in water)	Approximate Pd(II) ions per particle ([Pd(II)]/[P])
P1@Pd(II) (0.18 mg/mL polymer in water)	2.6 mg/L	135 μM	25
P2@Pd(II) (0.167 mg/mL polymer in water)	4.62 mg/L	259 μM	43
P3@Pd(II) (0.16 mg/mL polymer in water)	5.45 mg/L	306 μM	48
P4@Pd(II) (0.167 mg/mL polymer in water)	7.65 mg/L	429 μM	76

8. Log P value of substrates and products

Pro-dyes/drugs	Log P	Dyes/drugs	Log P
Pro-paclitaxel (10)	4.1	Paclitaxel (12)	3.2
Pro-5FU (8)	0.4	5FU (9)	-0.1
Pro-Dox (13)	1.2	Dox (14)	0.5
Pro-DNP (1)	1.9	DNP (4)	1.6
Pro-coumarin (2)	2.0	Coumarin (5)	1.1
Pro-rhodamine (3)	3.4	Rhodamine (6)	2.4

Fig. S50 Log P values of substrates and products

*Obtained from ChemAxon Marvinsketch 19.0

9. Catalysis measurements

9.1 Prodye activation

General procedure :

Pro-dye activation **1-3** in water/PBS/DMEM:

P1-P4@Pd(II) stock solutions were prepared in water by dissolving 10 mg polymer in 1 mL (10 mg/mL) water by sonication for 30 min. **P5@Pd(II)** stock solution was prepared by dissolving 10 mg **P5** in 900 μL water water by sonication for 30 min followed by the addition of 100 μL Na_2PdCl_4 stock solution (10 mM in water). This solution (10 mg/mL) was stirred for 15 min before use. Pro-dye stock solutions (**1-3**) were prepared in DMSO at 50 mM concentration. Stock solution of control $PdCODCl_2$ was prepared in DMSO at 30/50 mM concentration. Depending on each experiment, all stock solutions were diluted in 3 mL water/PBS in 10 mm fluorescence ((pro-cou (**2**)),(pro-rho (**3**))/absorbance cuvette (pro-dnp (**1**)) to a reach final concentration of Pd(II) = 30 μM; [**1-3**] = 100 μM. Final concentration of DMSO in aqueous solution is 0.2-0.3 v/v%. For DMEM, all additions were done as mentioned above except that 30 mg/mL polymer stock solution in water was prepared. Depending on each experiment, all stock solutions were diluted in 2900 μL DMEM in 10 mm fluorescence cuvette to reach a final concentration of Pd(II) = 30 μM/ Pd(II) = 100 μM (as specified); [**1-3**] = 100 μM. The amount of water added from stock solutions was compensated to 100 μL in all samples. Cuvettes were then transferred to UV-Vis/Fluorescence spectrophotometer at 37 °C with stirring and the reaction progress was monitored in real-time. Aliquots from the sample were taken at specified intervals and diluted with 50% ACN by volume which was then analyzed using HPLC-UV/MS.

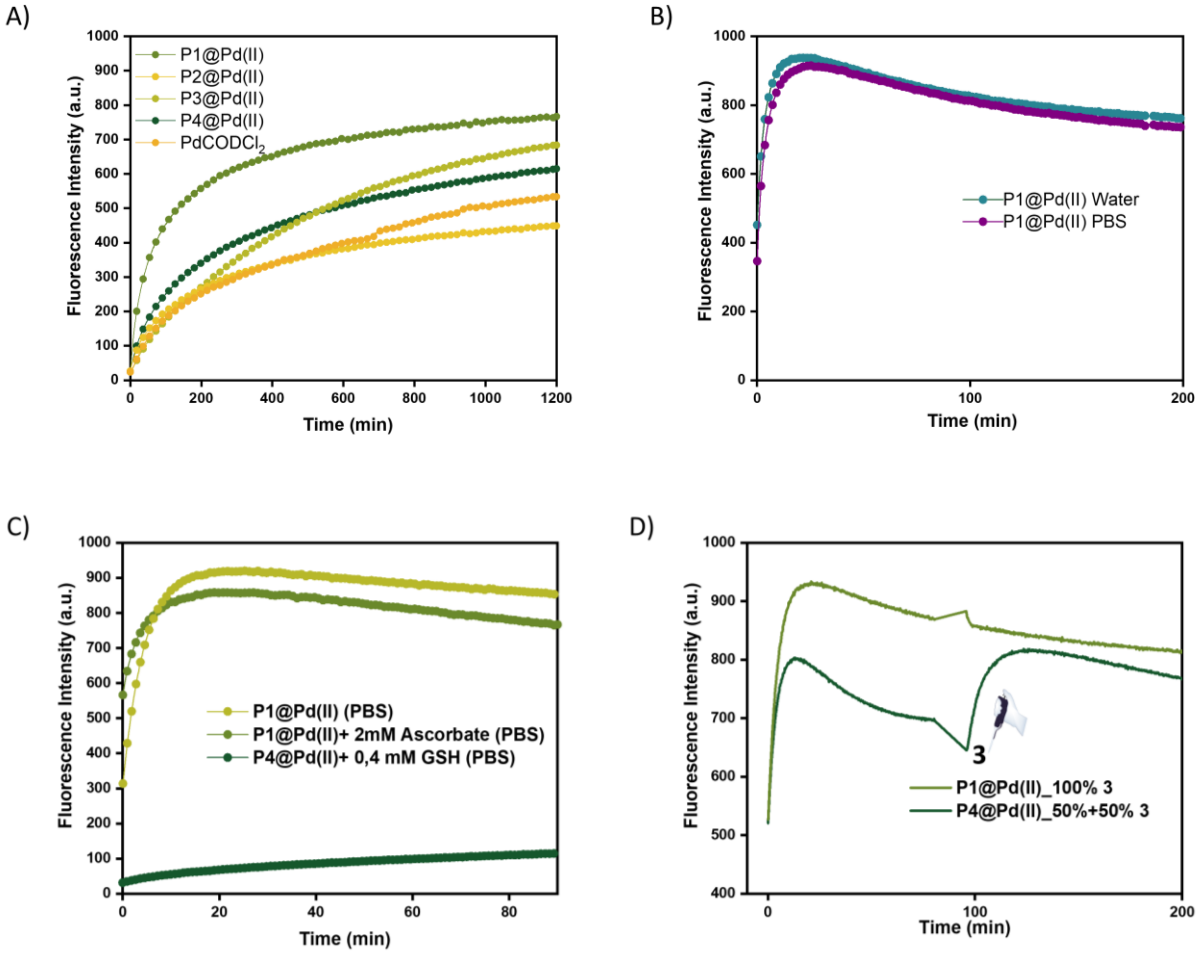


Fig. S51 A) Activation of pro-cou **2** (100 μM) to cou **5** monitored by fluorescence spectroscopy over time λ_{ex}= 370 nm and λ_{em} = 420 nm in PBS using **P1-P4@Pd(II)** and **PdCODCl$_2$** B) Comparison of activation of pro-rho **3** (100 μM) to rho **6** in water and PBS, **P1@Pd(II)** C) Activation of pro-rho **3** (100 μM) to rho **6** in the presence of additives using **P1@Pd(II)**, monitored by fluorescence spectroscopy over time λ_{ex}= 485 nm and λ_{em} = 520 nm in PBS D) Catalyst deactivation check during pro-rho **3** (100 μM) activation using **P1@Pd(II),** substrate was added portion wise. All reactions were performed at 37 ºC, in all cases [Pd(II)] = 30 μM.

10. Pd(II) leaching tests

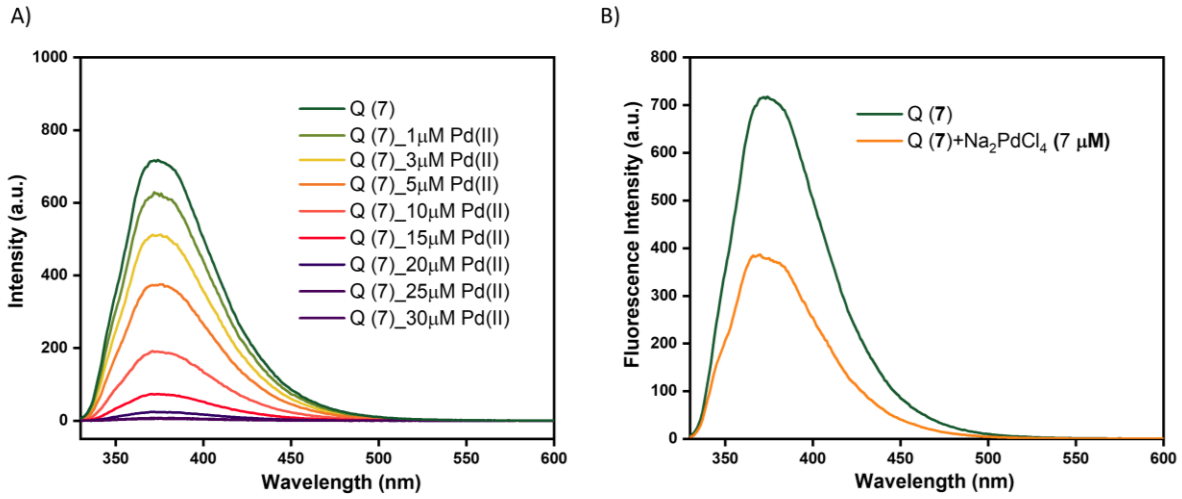


Fig. S52 A) Quenching of Q(**7**) with increasing $PdCODCl_2$ concentration B) with Na_2PdCl_4 (7 μM), monitored using fluorescence spectroscopy at λ_{ex} = 320 nm. Amount of DMSO (stock solution) added is kept constant for all measurements by increasing concentration of stock solution with each measurement (0.13 v/v%), T = 20 ºC, H_2O.

11. HPLC-UV/MS

11.1 Calibration curves of products from HPLC-UV

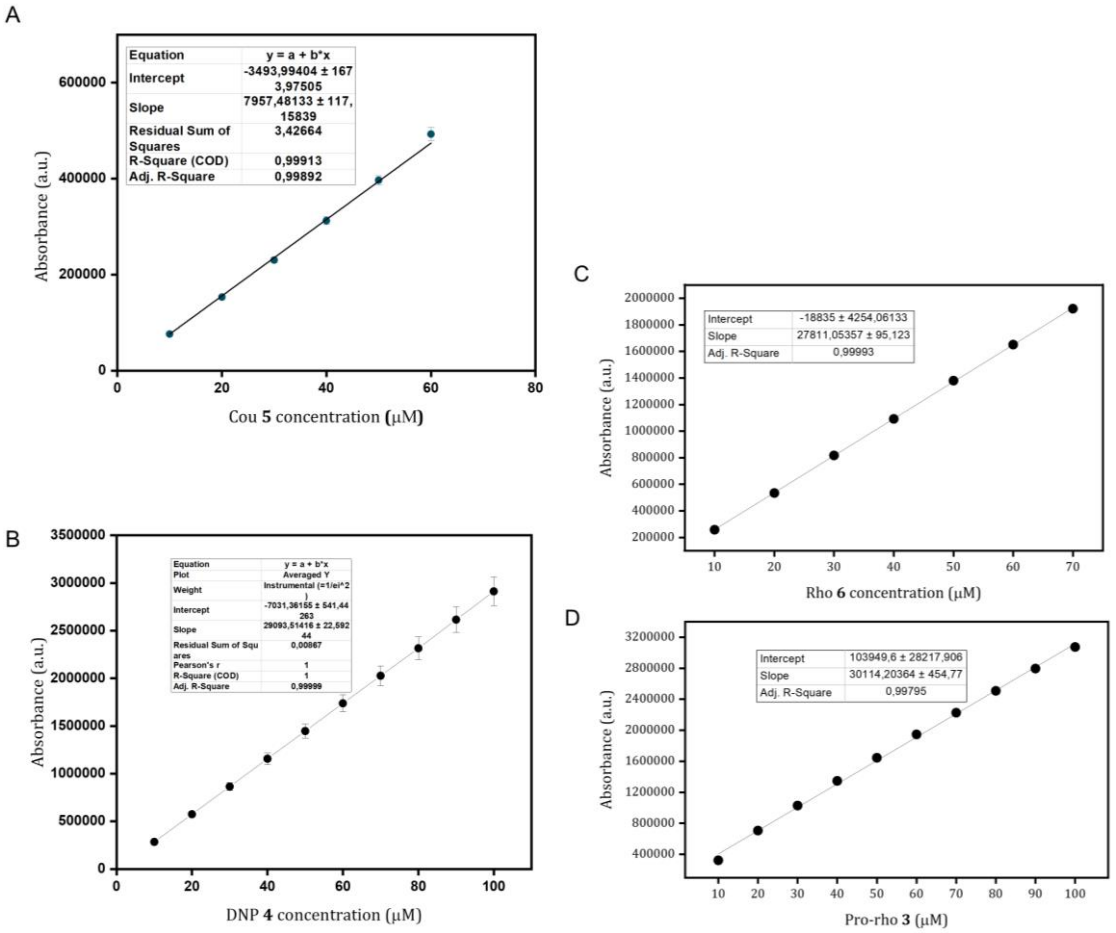


Figure S53. A) Calibration curve of DNP **4** (10-100 μM) B) Calibration curve of cou **5** (10-60 μM) C) Calibration curve of rho **6** (10-70 μM) D) Calibration curve of pro-rho **3** (10-100 μM).

The conversion of pro-dyes to corresponding dyes was quantified using HPLC-UV. The presence of polymers was a hindrance for proper analysis. Removing polymers from reaction mixture using filters was tested, however the hydrophobic substrates and products get trapped in the polymer, which ended up getting stuck to filters. Therefore, we opted for directly injecting the reaction mixture to HPLC after diluting with ACN, which can reduce the lifetime of column. The conversions are therefore approximate values as the presence of polymers affect accurate analysis. Proper monitoring of column pressure and repeated blank runs are necessary between each measurement. In case of pro-rho **3,** formed product rho **6** had problems with proper elution which required subsequent washing steps to remove the product from the column. In this case, the quantification was done from the calibration curve of pro-rho **3** as there are no side products in this reaction. Despite the challenges in quantification, reactions were monitored in real-time using UV-Vis/fluorescence spectroscopy together with qualitative analysis of chromatogram.

11.2 HPLC-MS – Activation of pro-rho 3 to rho 6 in water and DMEM

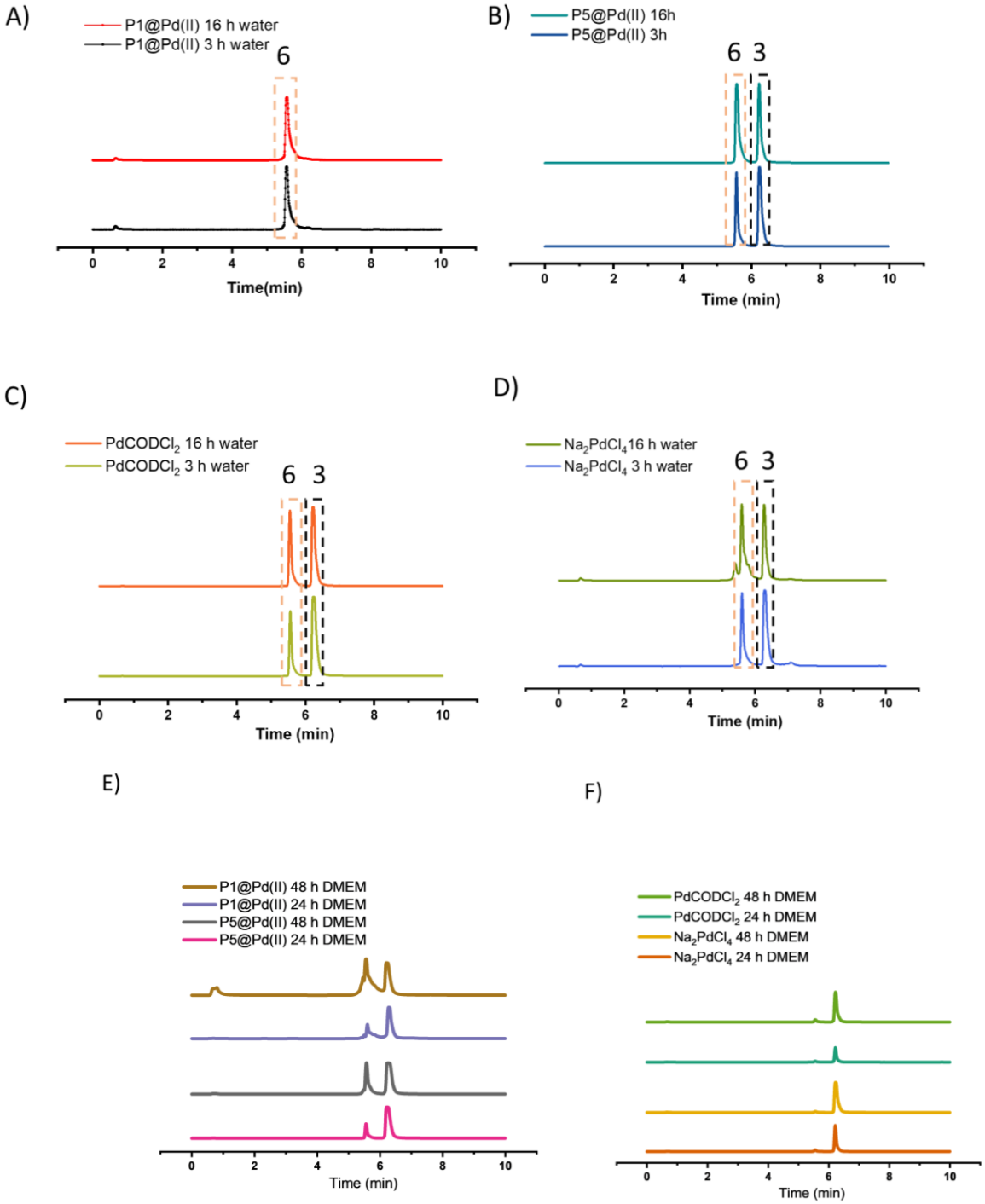


Fig. S54. Activation of pro-rhodamine (100 μM) by **P1@Pd(II), P5@Pd(II),Na_2PdCl_4** and **$PdCODCl_2$**, [Pd(II)] = 30 μM in water and [Pd(II)] = 100 μM in DMEM monitored by HPLC-MS, reaction performed at 37 °C.

12. Pro-drug activation

Pro-drug activation in water/PBS/DMEM:

P1@Pd(II) stock solutions were prepared in water by dissolving 10 mg of polymer **P1@Pd(II)** in 1 mL (10 mg/mL) water by sonication for 30 min. Pro-drug stock solutions (**8,10,13** and **15**) were prepared in DMSO at 50 mM concentration. The stock solution of control $PdCODCl_2$ was prepared in DMSO at 30/50 mM concentration. Depending on each experiment, all stock solutions were diluted in 3 mL water/PBS in glass vials to reach a final concentration of Pd(II) = 30 μM; [pro-drugs] = 100 μM. Final concentration of DMSO in aqueous solution is 0.2-0.3 v/v%. For DMEM, all additions were done as mentioned above except that 30 mg/mL polymer stock solution in water was prepared. Depending on each experiment, all stock solutions were diluted in 2900 μL DMEM in glass vial to reach a final concentration of Pd(II) = 30 μM/ Pd(II) = 100 μM (as specified); [pro-drugs] = 100 μM. The amount of water added from stock solutions was compensated to 100 μL in all samples. Then the reaction mixture was stirred at 37 °C. Aliquots from the sample were taken at specified intervals and diluted with ACN (50% v/v) for pro-pac **15** or with water (50% v/v) for pro-5FU **8** and pro-dox **13, 15** which was then analyzed using HPLC-MS.

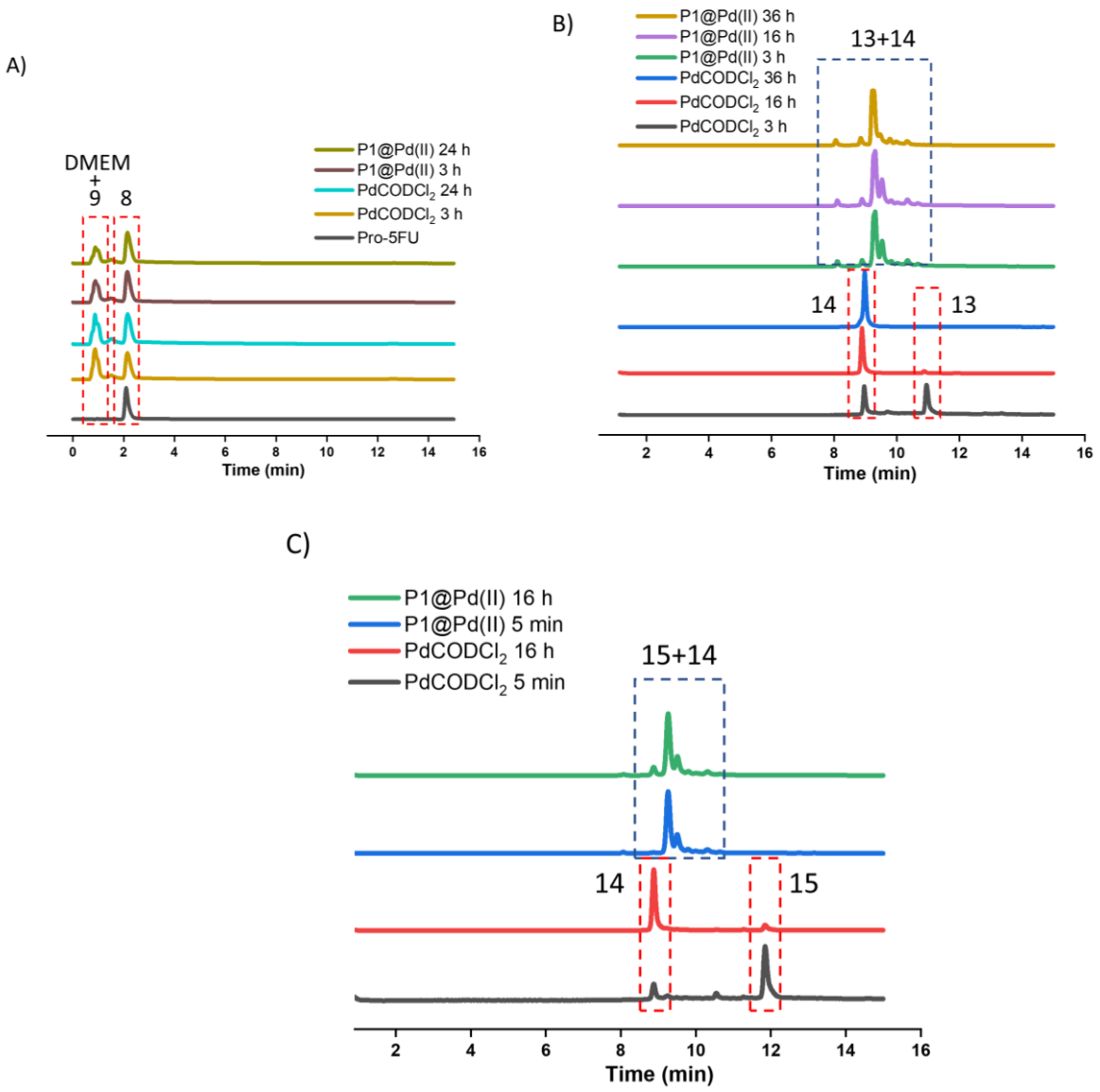


Figure S55: Activation of A) Pro-5FU **8** in DMEM medium [Pd(II)] = 100 μM, [**8**] = 100 μM B) pro-*poc*-doxorubicin in PBS [Pd(II)] = 30 μM, [**13**] = 100 μM C) pro-*pob*-doxorubicin [Pd(II)] = 30 μM, [**15**] = 100 μM by **PdCODCl₂** and **P1@Pd(II)** monitored by HPLC-MS, reaction performed at 37 °C.

13. Notes and References

Shoulder peaks observed can be due to the aggregation of polymers when dissolved in DMF.

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