

Supporting information

Poly(2-isopropenyl-2-oxazoline) - A Structural Analogue to Poly(vinyl azlactone) with Orthogonal Reactivity

Meike N. Leiske,^{a,†} Ayaat M. Mahmoud,^{a,†} Nicole Warne,^a Jeroen A. C. M. Goos,^{a,b} Sagrario Pascual,^c Véronique Montembault,^c Laurent Fontaine,^c Thomas P. Davis,^{a,d} Michael R. Whittaker,^a and Kristian Kempe^{a,e,}*

^aARC Centre of Excellence in Convergent Bio-Nano Science & Technology, and Drug Delivery, Disposition and Dynamics, Monash Institute of Pharmaceutical Sciences, Monash University, Parkville, VIC 3052, Australia

^bDepartments of Clinical Neuroscience, Radiopharmacy and Oncology & Pathology, Karolinska Institute, Stockholm, Sweden
MedTechLabs, Stockholm, Sweden

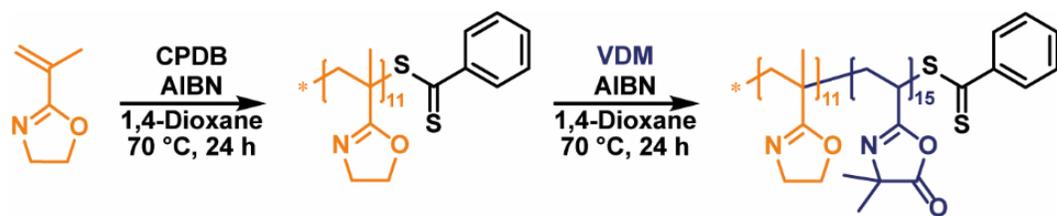
^cInstitut des Molécules et Matériaux du Mans (IMMM), UMR 6283 CNRS – Le Mans Université, Av. O. Messiaen, 72085 Le Mans Cedex 9, France

^dCentre for Advanced Imaging (CAI) and Australian Institute for Bioengineering and Nanotechnology, ARC Centre of Excellence in Convergent Bio-Nano Science and Technology and ARC Training Centre for Innovation in Biomedical Imaging Technology, The University of Queensland, St. Lucia, QLD 4072, Australia

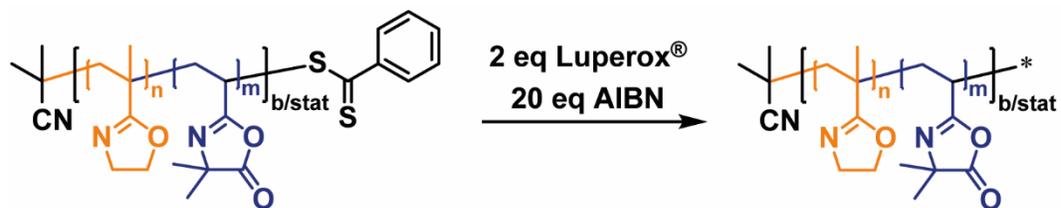
^eMaterials Science and Engineering, Monash University, Clayton, VIC 3800, Australia

†M. N. L. and A. M. M. contributed equally to this study.

*Correspondence to: kristian.kempe@monash.edu



Scheme S1. Preparation of block copolymers.



Scheme S2. Reaction conditions used for complete CTA removal. Polymers were reacted with 2 eq. Luperox[®] and 20 eq. AIBN in toluene at 80 °C for 2.5 h.

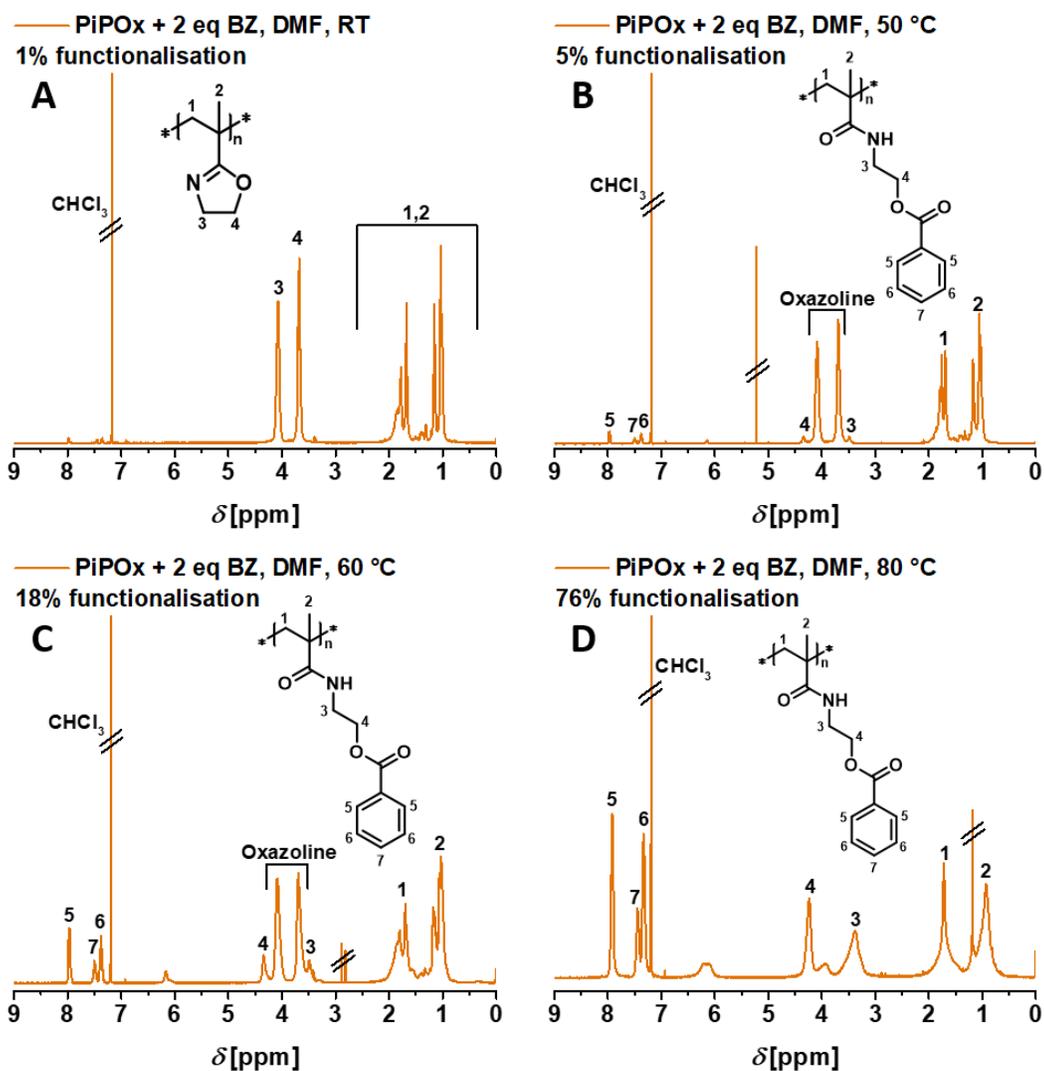


Figure S1. Characterisation of BZ-functionalised PiPOx homopolymers by ¹H NMR (400 MHz) in CDCl₃. Polymers were reacted in DMF for 24 h with 2 eq. BZ at various temperatures. (A) RT. (B) 50 °C. (C) 60 °C. (D) 80 °C.

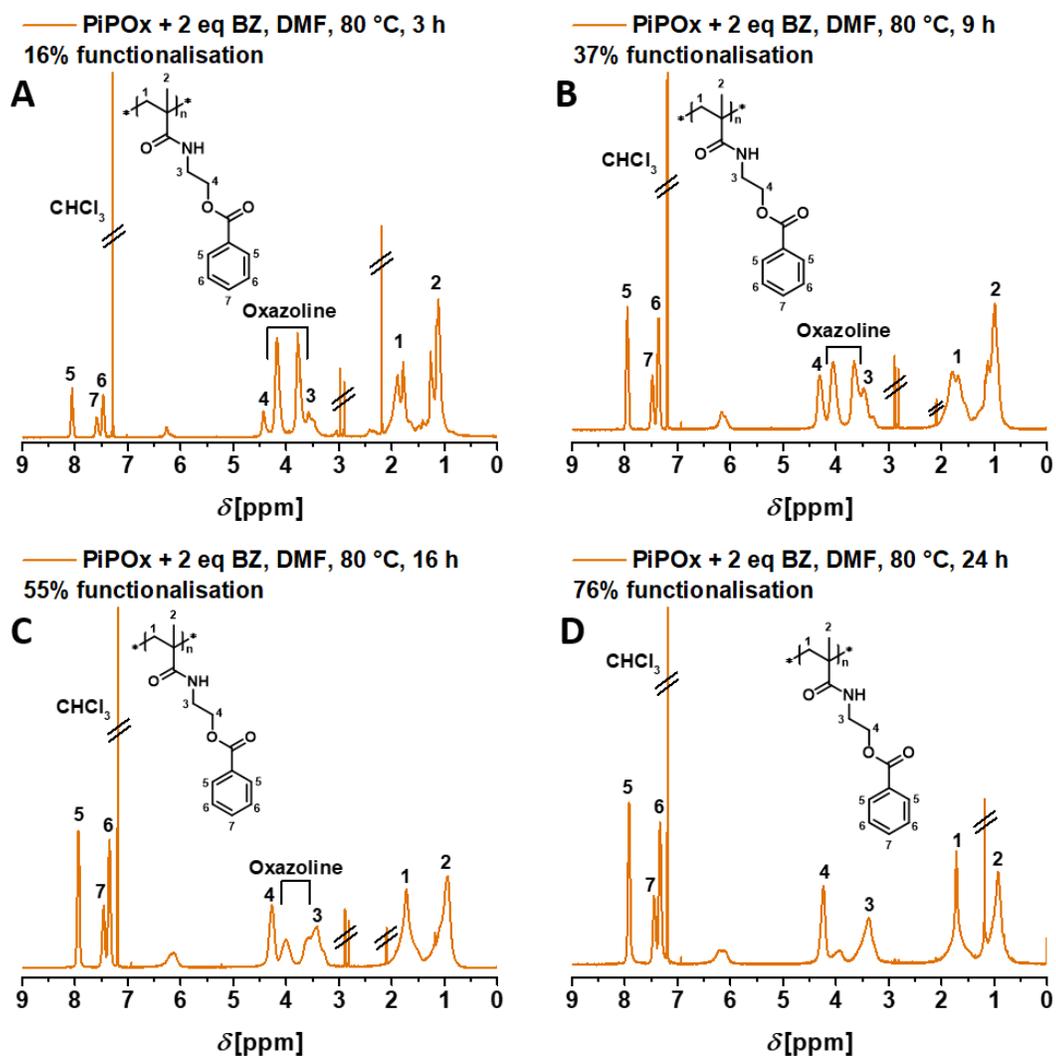


Figure S2. Characterisation of BZ-functionalised PiPOx homopolymers by ^1H NMR (400 MHz) in CDCl_3 . Polymers were reacted at 80 °C in DMF with 2 eq. BZ for indicated times. (A) 3 h. (B) 9 h. (C) 16 h. (D) 24 h.

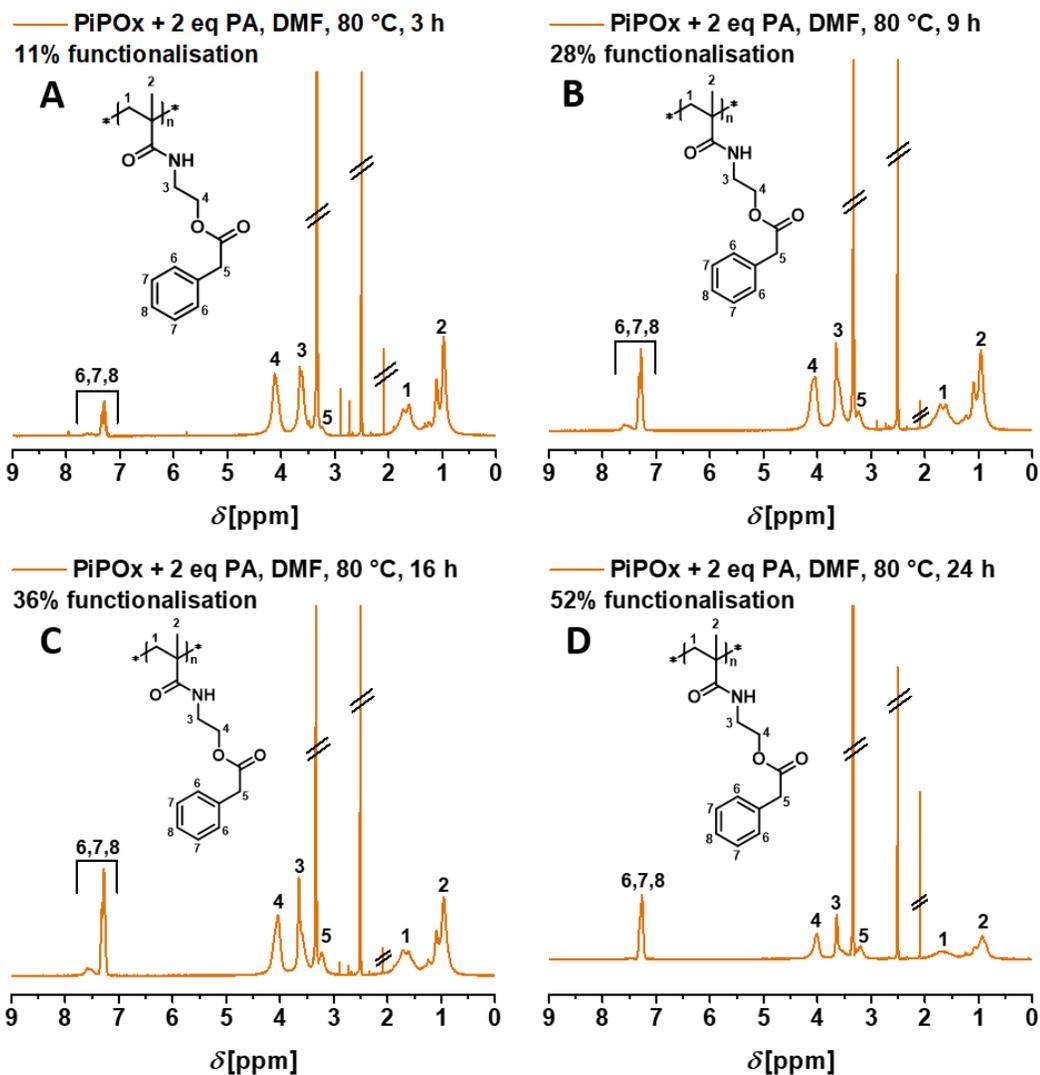


Figure S3. Characterisation of PA-functionalised PiPOx homopolymers by ^1H NMR (400 MHz) in DMSO-d_6 . Polymers were reacted at 80 °C in DMF with 2 eq. PA for indicated times. (A) 3 h. (B) 9 h. (C) 16 h. (D) 24 h.

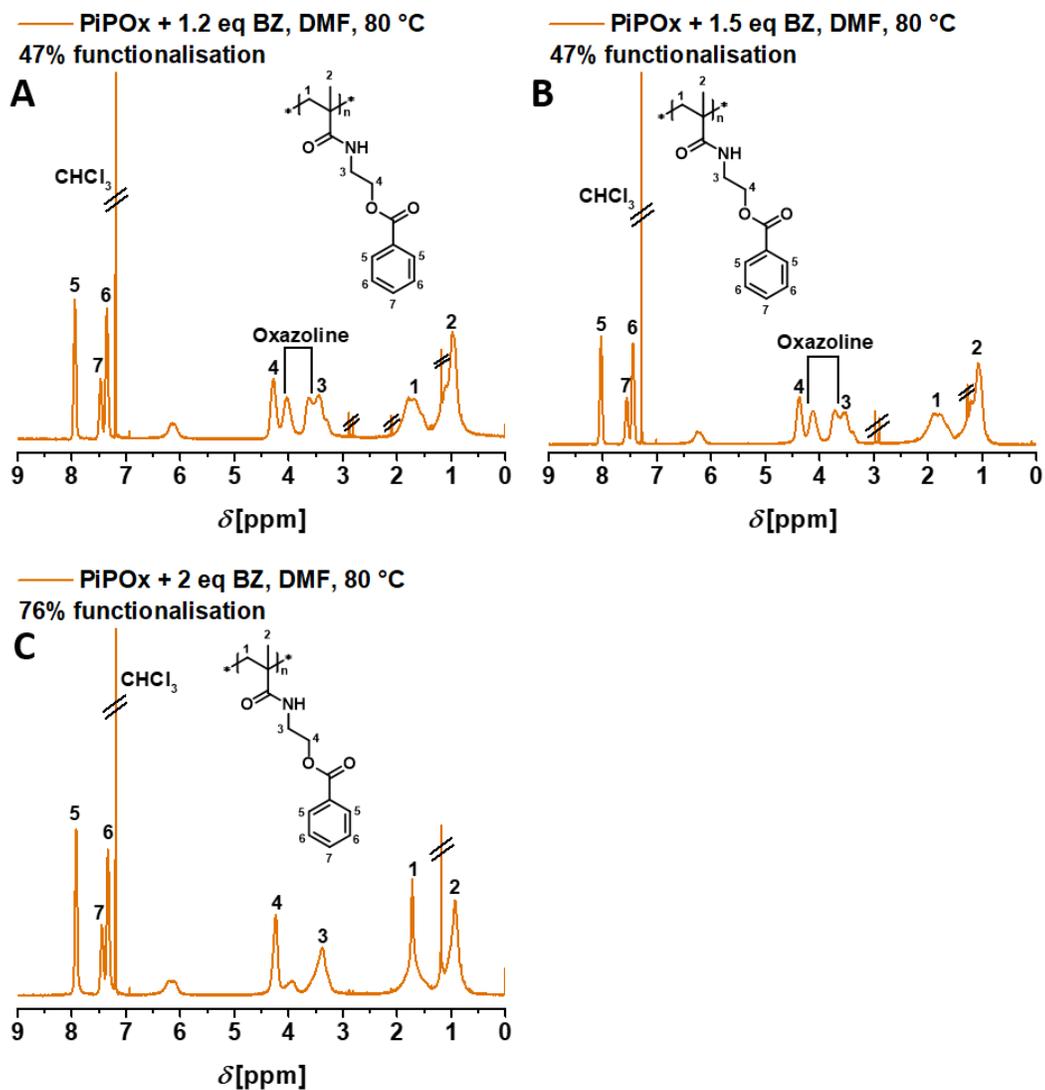


Figure S4. Characterisation of BZ-functionalised PiPOx homopolymers by ¹H NMR (400 MHz) in CDCl₃. Polymers were reacted at 80 °C in DMF for 24 h with indicated amounts of BZ. (A) 1.2 eq. (B) 1.5 eq. (C) 2.0 eq.

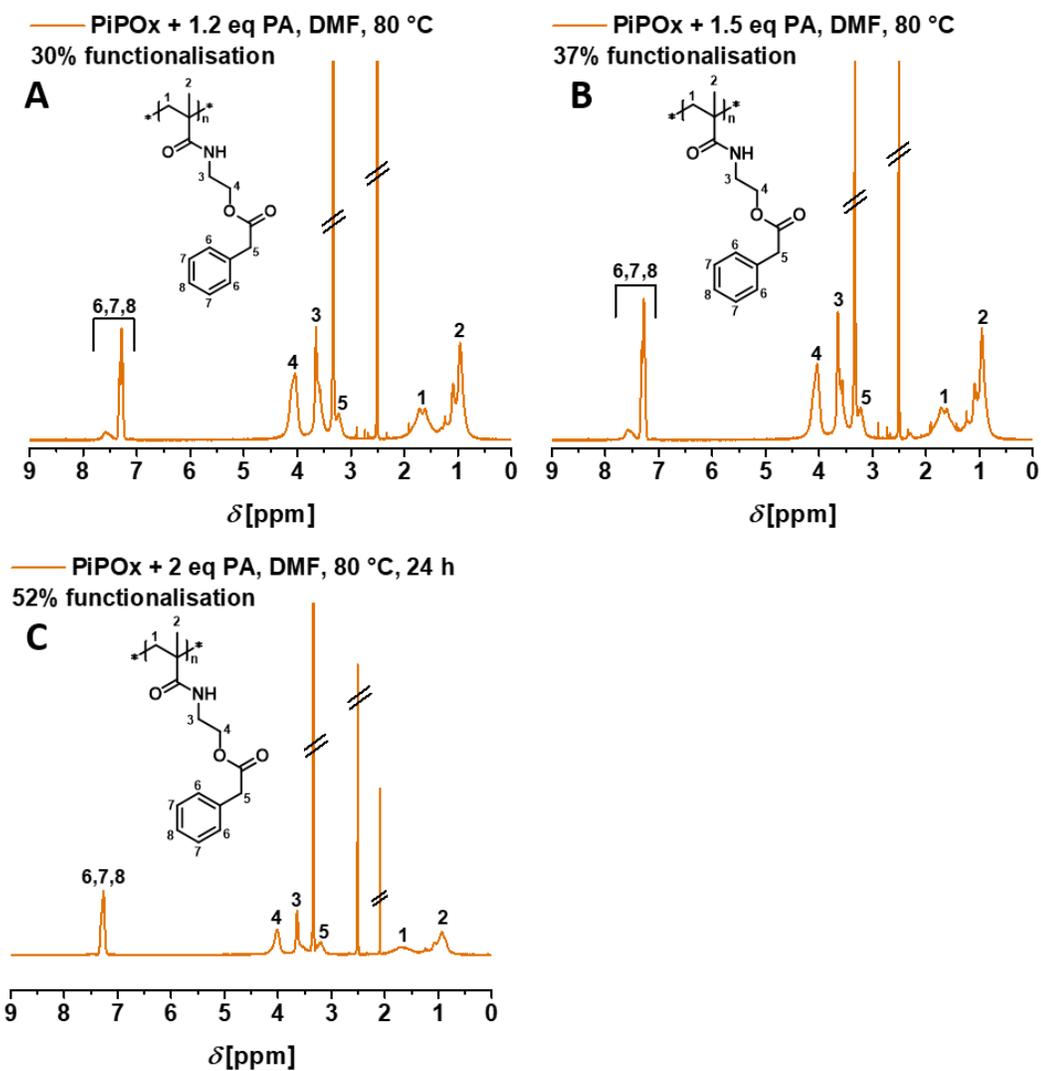


Figure S5. Characterisation of PA-functionalised PiPOx homopolymers by ^1H NMR (400 MHz) in DMSO-d_6 . Polymers were reacted at 80 °C in DMF for 24 h with indicated amounts of PA. (A) 1.2 eq. (B) 1.5 eq. (C) 2.0 eq.

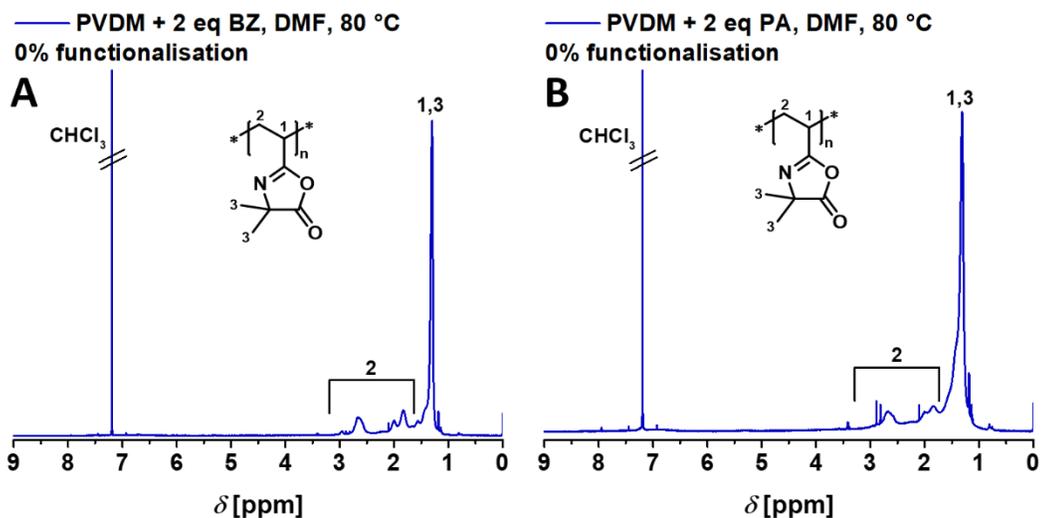


Figure S6. Characterisation of the reaction of PVDM homopolymers with BZ by ^1H NMR (400 MHz) in CDCl_3 . Polymers were reacted in DMF for 24 h with 2 eq. BZ (A) or PA (B) at 80 °C.

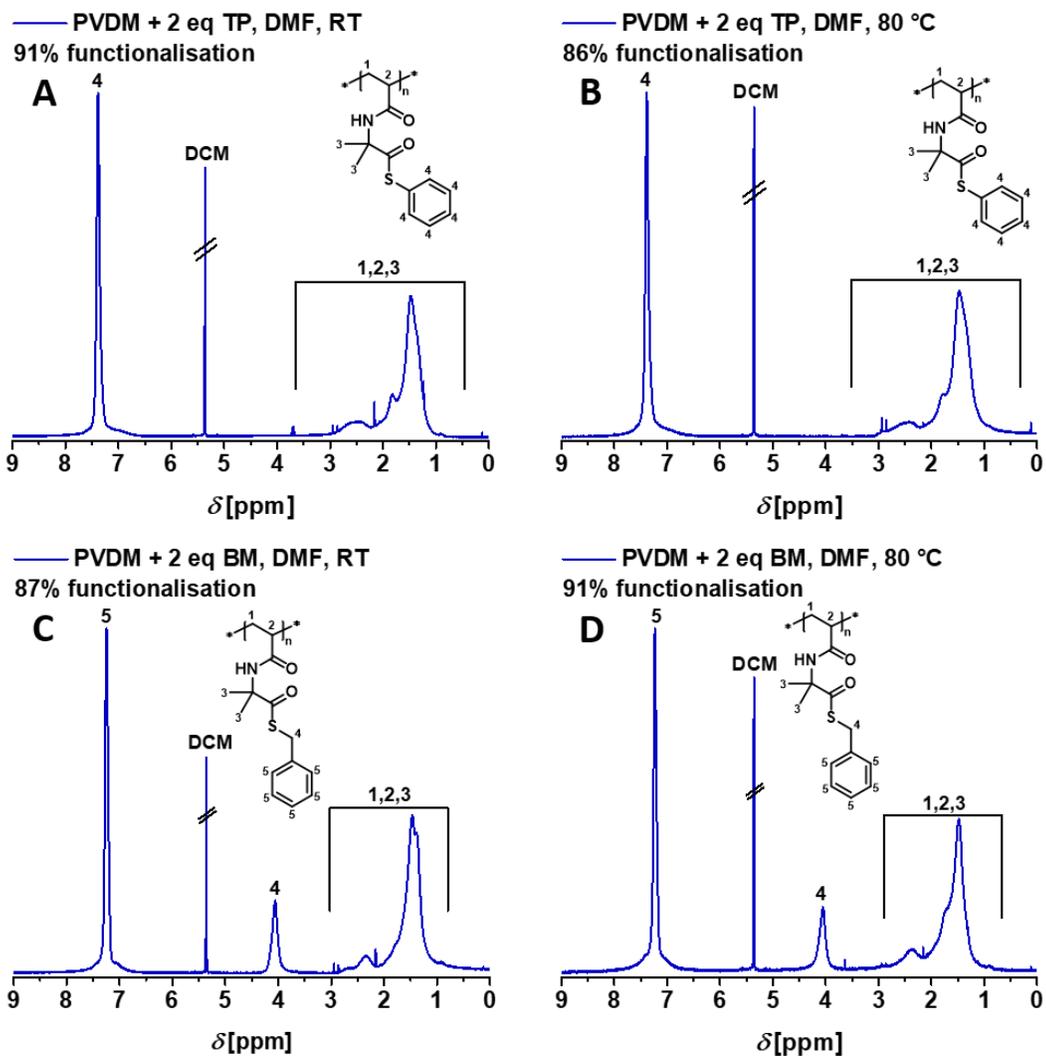


Figure S7. Characterisation of BM- and TP-functionalised PVDM homopolymers by ^1H NMR (400 MHz) in CD_2Cl_2 . Polymers were reacted in DMF for 24 h with 2 eq. BM or TP at indicated temperature. (A) TP, RT. (B) TP, 80 °C. (C) BM, RT. (D) BM, 80 °C.

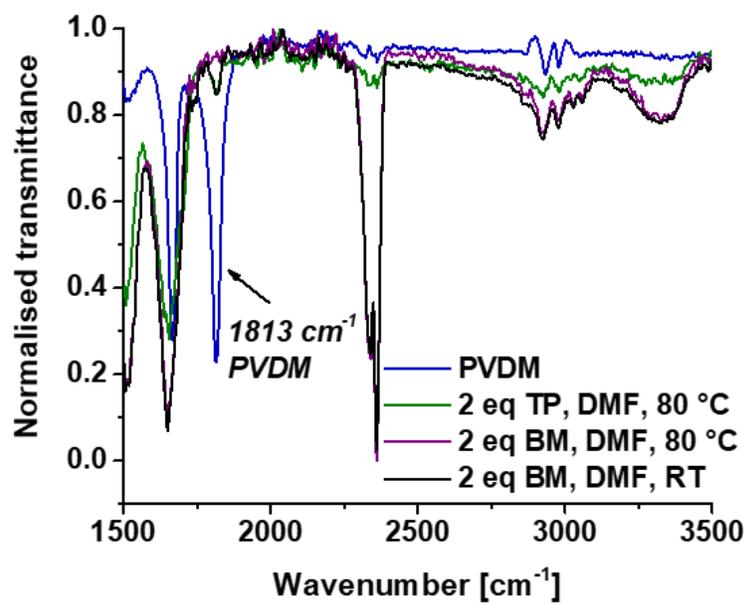


Figure S8. Characterisation of the reaction of PVDM homopolymers with the thiolated aromatic compounds TP and BM by FT-IR. Polymers were reacted in DMF for 24 h with 2 eq. BM or TP at indicated temperatures.

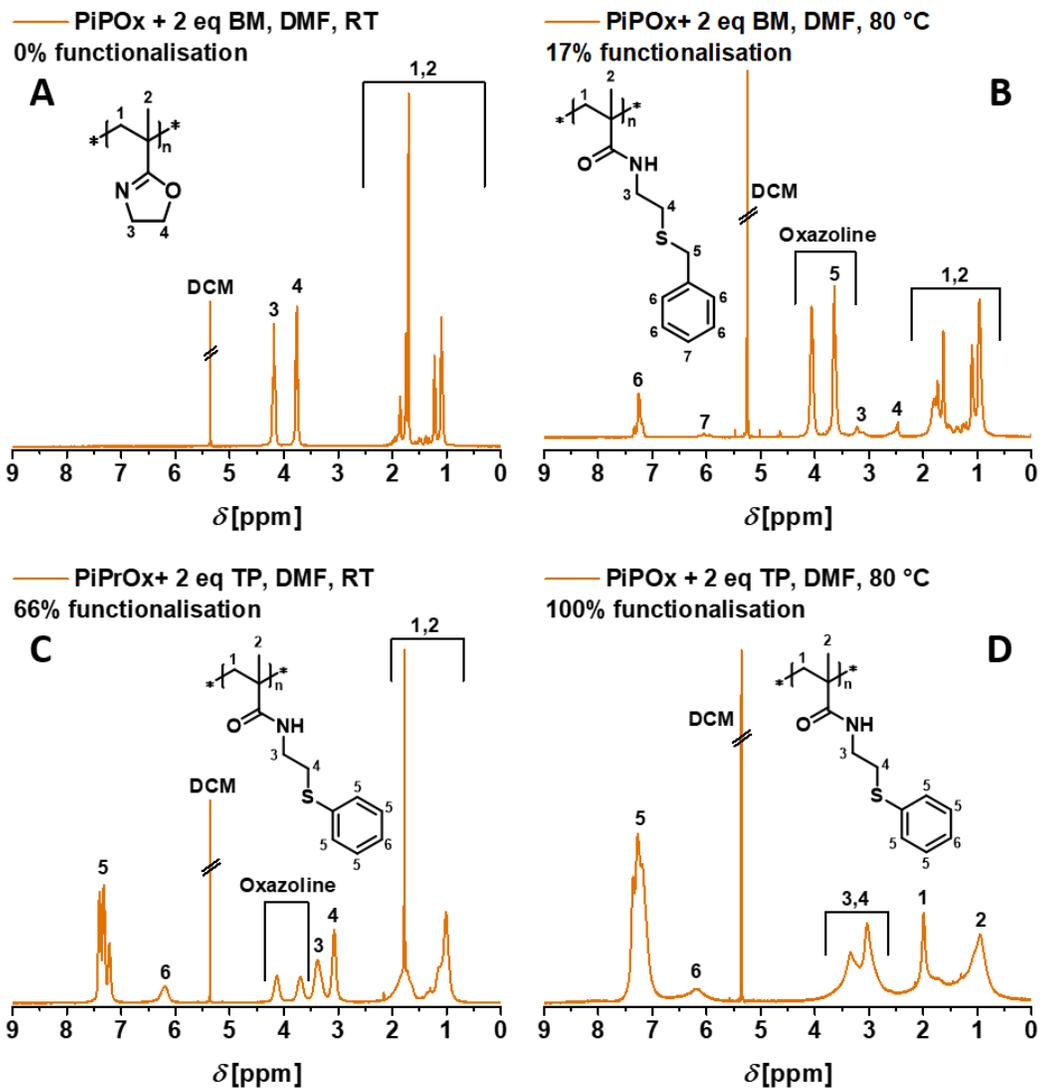


Figure S9. Characterisation of BM- and TP-functionalised PiPOx homopolymers by ^1H NMR (400 MHz) in CD_2Cl_2 . Polymers were reacted in DMF for 24 h with 2 eq. BM or TP at indicated temperature. (A) BM, RT. (B) BM, 80 °C. (C) TP, RT. (D) TP, 80 °C.

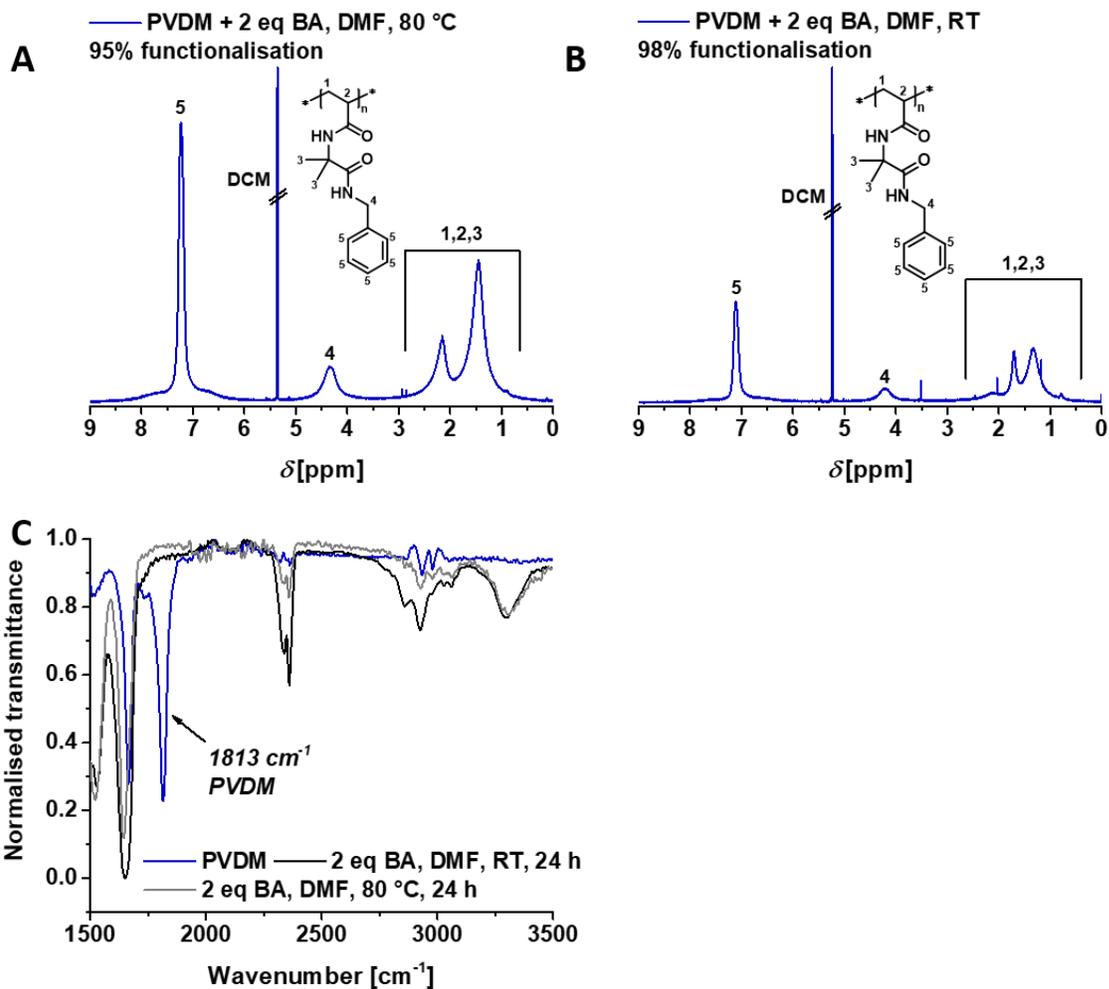


Figure S10. Characterisation of BA-functionalised PVDM homopolymers. Polymers were reacted in DMF for 24 h with 2 eq. BA at indicated temperatures. (A) and (B) ¹H NMR (400 MHz) in CD₂Cl₂. (C) FT-IR.

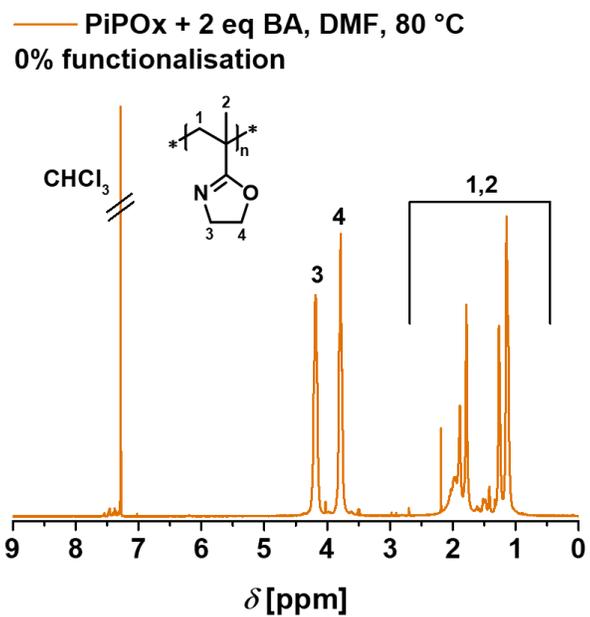


Figure S11. Characterisation of the reaction of PiPOx homopolymers with BA by ¹H NMR (400 MHz) in CDCl₃. Polymers were reacted in DMF for 24 h with 2 eq. BA at 80 °C.

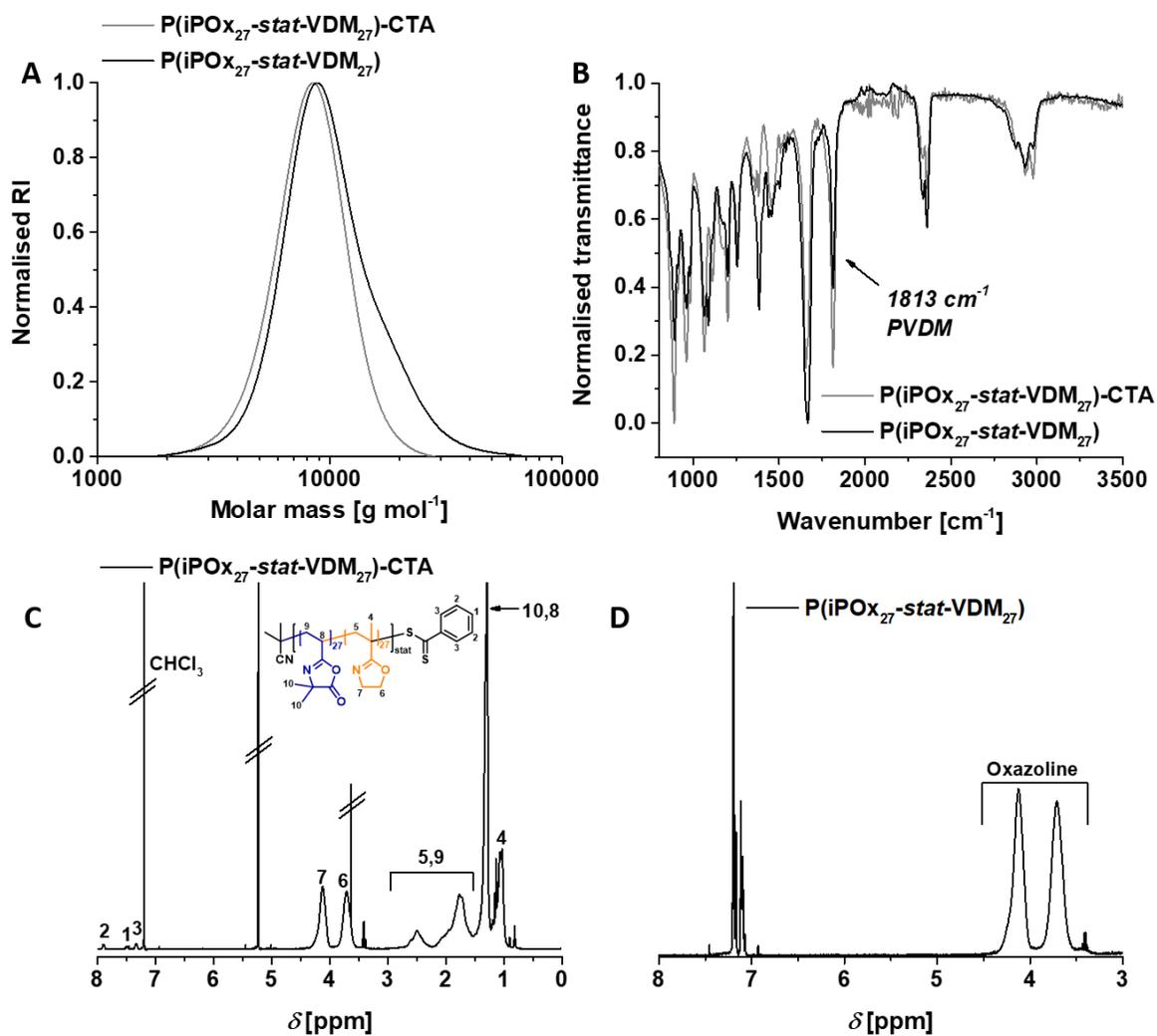


Figure S12. Characterisation of P(iPO_{x27}-stat-VDM₂₇) before and after end-group removal. (A) SEC (DMAc, PS-cal.). (B) FT-IR. (C) and (D) ¹H NMR (400 MHz) in CDCl₃.

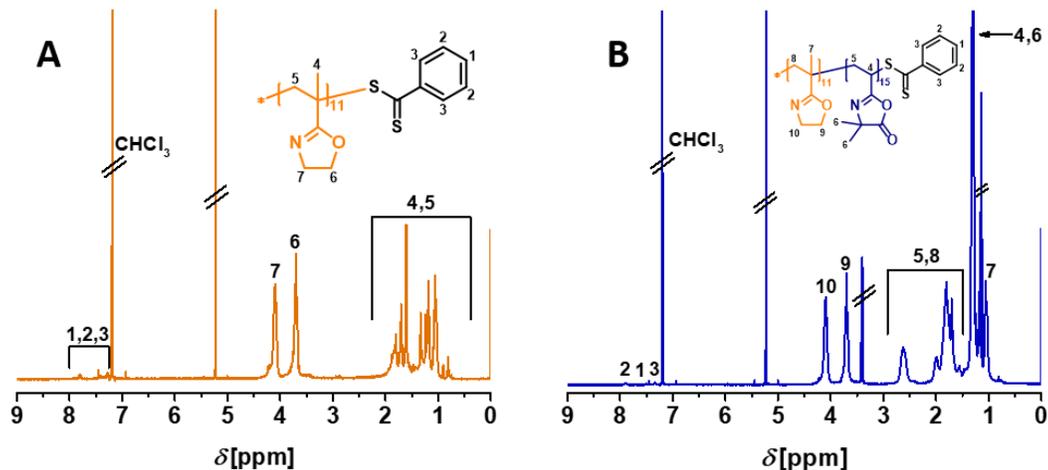


Figure S13. Characterisation of block copolymer synthesis by ^1H NMR (400 MHz) in CDCl_3 . (A) PiPOx_{11} -CTA. (B) $\text{P}(\text{iPOx}_{11}\text{-}b\text{-VDM}_{15})$ -CTA.

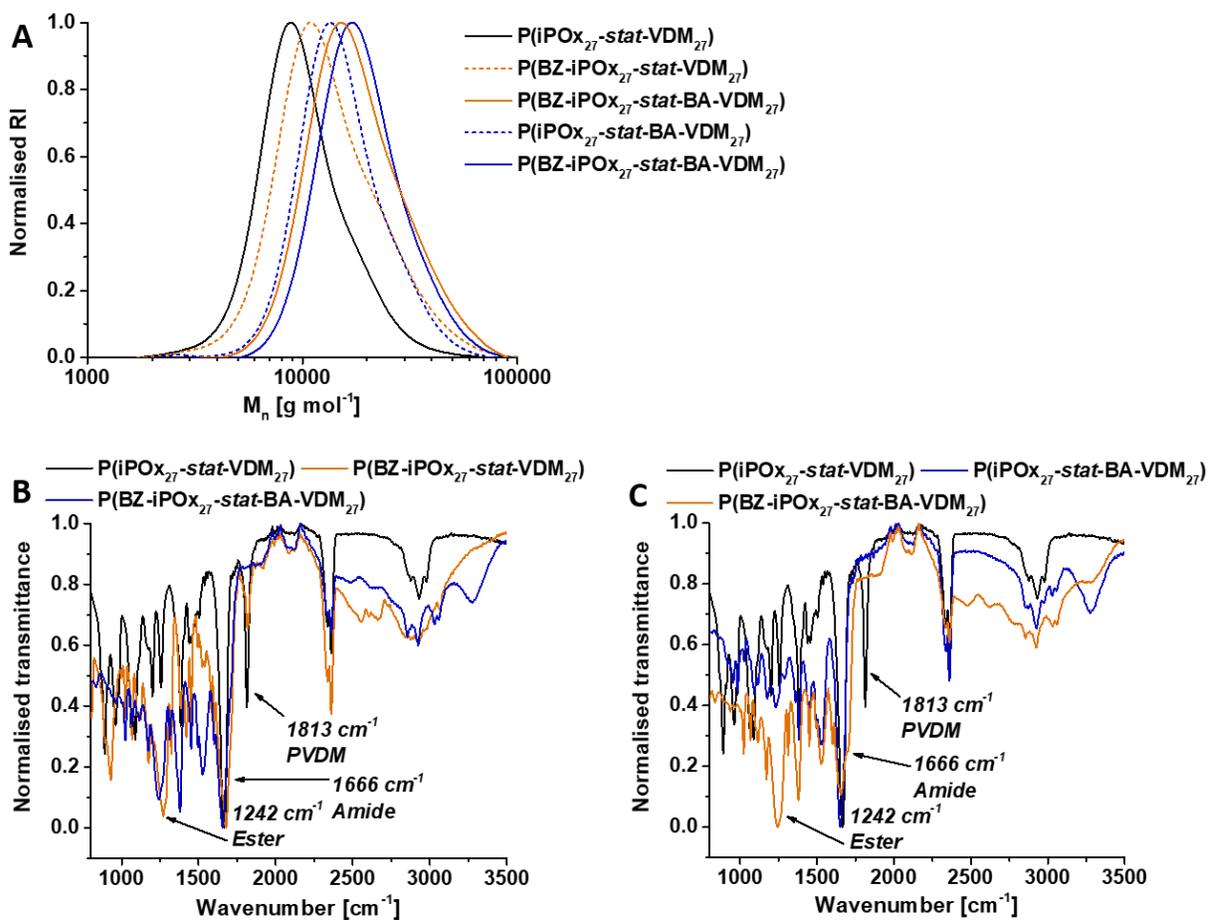


Figure S14. Characterisation of the PPM of $\text{P}(\text{iPOx}_{27}\text{-stat-VDM}_{27})$ with BA and BZ. Polymers were modified in a two-step reaction and not purified in-between. Samples were taken for characterisation by SEC to show the evolution of the molar mass and FT-IR to prove the integrity

of the VDM group. (A) SEC in DMAc (PS-cal.). First reaction depicted in dashed lines, second reaction shown in solid lines. (B) and (C) FT-IR. (B) P(iPOx₂₇-stat-VDM₂₇) was modified with BZ in a first reaction and with BA in a second reaction. (C) P(iPOx₂₇-stat-VDM₂₇) was modified with BA in a first reaction and with BZ in a second reaction.

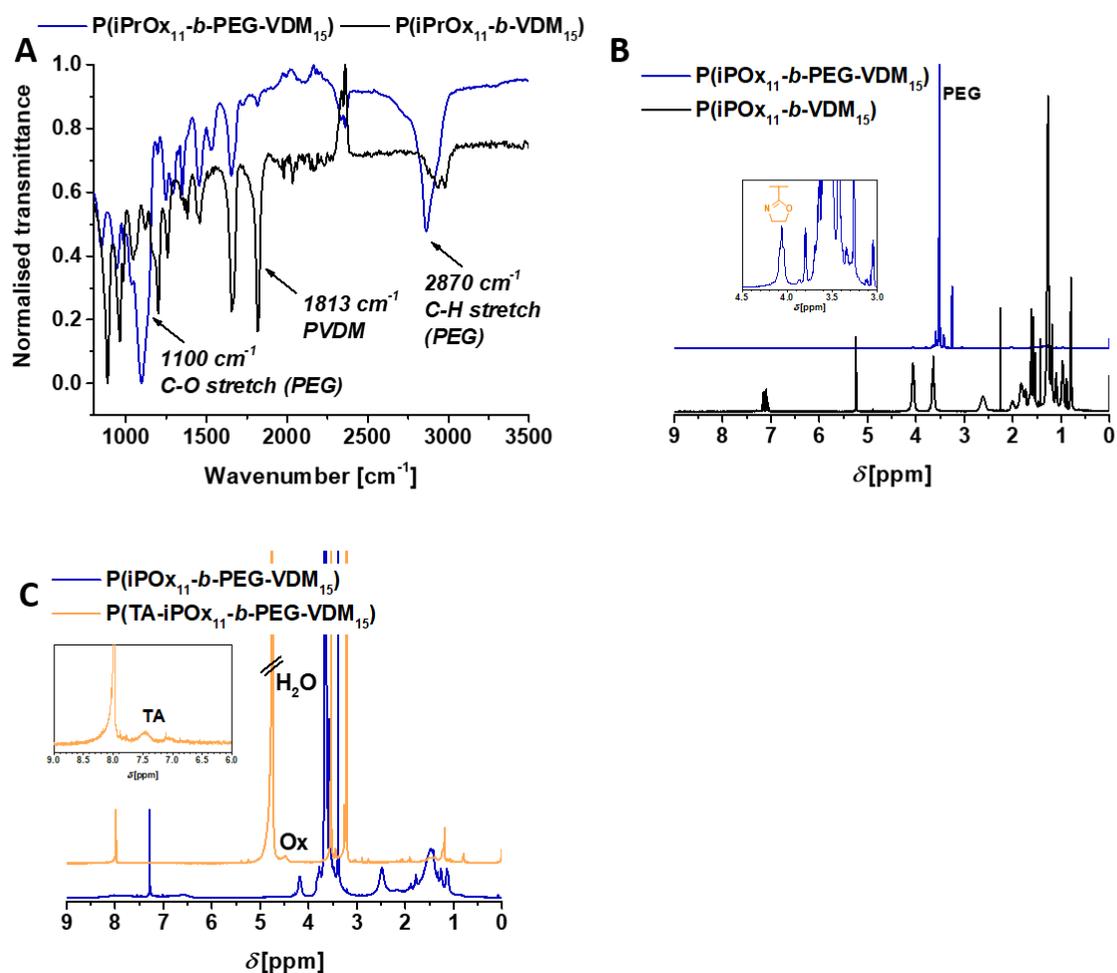


Figure S15. Characterisation of the two-step PPM of block copolymers with PEG and TA. Polymers were reacted in DMF at 80 °C for 24 h with 2 eq. PEG-NH₂ and TA per repeating unit. Polymers were purified in-between steps. (A) FT-IR. (B) ¹H NMR (400 MHz) in CDCl₃ (top) and CD₂Cl₂ (bottom). (C) ¹H NMR (400 MHz) in MeOD (top) and CDCl₃ (bottom).



Amount of cross-linker

Figure S16. Reaction of PiPOx with different amounts of TA. (A) 2 eq (4 eq). (B) 1 eq (2eq). (C) 0.5 eq (1 eq). Numbers in brackets correspond to the molar ratio of carboxylic acid to iPOx applied during the reaction.

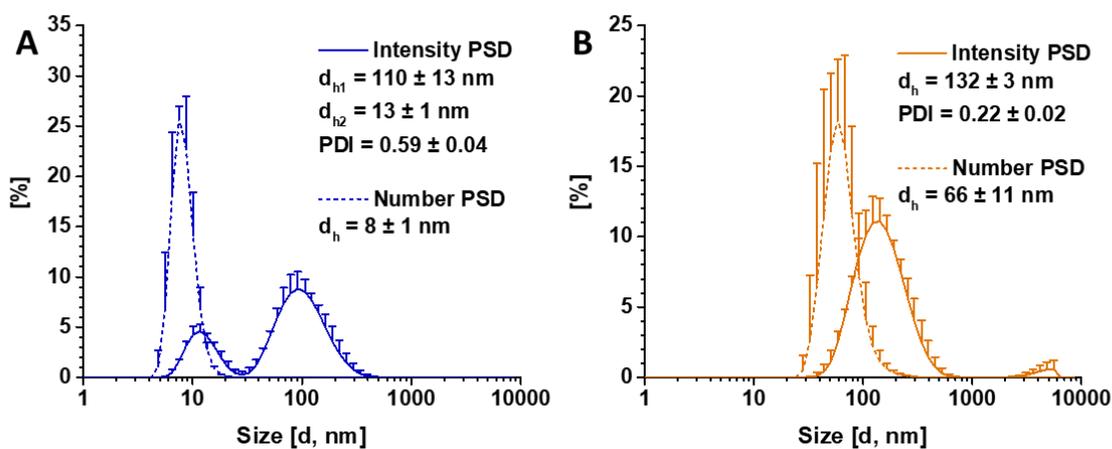


Figure S17. Characterisation of block copolymer derived nanostructures in PBS by DLS. 5 measurements with 3 runs each. Values represent the mean and SD. (A) P(iPOX₁₁-*b*-PEG-VDM₁₅). (B) P(TA-iPOX₁₁-*b*-PEG-VDM₁₅).

Table S1. Reactants used for the PPM of PiPOx and PVDM homopolymers with 2.0 eq functionalisation agent. For other molar ratios, the amount of functionalisation agent was varied, while the polymer mass and the solvent volume were kept constant. Reactions were performed at indicated temperatures for the described times as reported in the figures.

| Polymer | | | | Functionalisation agent | | | | DMF | | |
|--------------|-----|-----------------|---------------|-------------------------|-----|-----------------|---------------|---------------------|---------------|------|
| Name | Eq | <i>n</i> [mmol] | <i>m</i> [mg] | Name | Eq | <i>n</i> [mmol] | <i>m</i> [mg] | <i>V</i> [μ L] | <i>V</i> [mL] | |
| PiPOx | 1.0 | 0.225 | 25.0 | BZ | 2.0 | 0.45 | 55.0 | 49.0 | 0.75 | |
| | | | | PA | | | 61.3 | | 0.75 | |
| | | | | BA | | | 48.2 | | 0.75 | |
| | | | | BM | | | 55.9 | | 53.0 | 0.75 |
| | | | | TP | | | 49.6 | | 49.9 | 0.75 |
| PVDM | 1.0 | 0.179 | 25.0 | BZ | 2.0 | 0.359 | 43.9 | 39.0 | 0.75 | |
| | | | | PA | | | 48.9 | | 0.75 | |
| | | | | BA | | | 38.5 | | 0.75 | |
| | | | | BM | | | 44.7 | | 42.2 | 0.75 |
| | | | | TP | | | 39.6 | | 36.7 | 0.75 |

BA: Benzylamine. BM: Benzyl mercaptan. BZ: Benzoic acid. PA: Phenylacetic acid. TP: Thiophenol.

Table S2. Characterisation of purified copolymers prepared by RAFT polymerisation. ^aSEC in DMAc (PS-cal.). ^b¹H NMR (400 MHz) in CDCl₃. ^cDegree of polymerisation (DP) was calculated from monomer conversion as determined by ¹H NMR from reaction mixture. ^d*M_n* was calculated from DP.

| Polymer name | SEC ^a | | | ¹ H NMR ^b | |
|--------------------------------------------------------------|---------------------------------------------|---------------------------------------------|----------|---------------------------------|----------------------------------------------------------|
| | <i>M_n</i> [g mol ⁻¹] | <i>M_w</i> [g mol ⁻¹] | <i>D</i> | <i>DP</i> ^c | <i>M_n</i> [g mol ⁻¹] ^d |
| P(iPOx)₁₁-CTA | 2,000 | 2,500 | 1.25 | 11 | 1,400 |
| P(iPOx₁₁-<i>b</i>-VDM₁₅)-CTA | 14,800 | 19,100 | 1.29 | 26 | 3,500 |
| P(iPOx₁₁-<i>b</i>-VDM₁₅) | 15,600 | 20,400 | 1.31 | 26 | 3,300 |
| P(iPOx₂₇-<i>stat</i>-VDM₂₇)-CTA | 7,600 | 8,700 | 1.15 | 54 | 7,000 |
| P(iPOx₂₇-<i>stat</i>-VDM₂₇) | 8,900 | 11,100 | 1.25 | 54 | 6,800 |

Table S3. Characterisation of functionalised copolymers. ^aSEC in DMAc (PS-cal.). ^b¹H NMR (400 MHz) in CD₂Cl₂. ^cReactions were conducted in a “one-pot” approach, reacting the functionalisation agents consecutively, however, omitting the purification of the crude products. n. d. not determinable due to peak overlap. n. a. not available.

| Run | Polymer name | Functionalisation order | SEC ^a | | | ¹ H NMR ^b | |
|-----|------------------------------------------------------|-------------------------|---------------------------------------------|---------------------------------------------|----------|---------------------------------|-------|
| | | | <i>M_n</i> [g mol ⁻¹] | <i>M_w</i> [g mol ⁻¹] | <i>D</i> | % BA | % BZ |
| 1a | P(iPOX ₂₇ -stat-VDM ₂₇) | BA ^c | 13,500 | 16,700 | 1.23 | n. d. | n. d. |
| 1b | | BZ ^c | 16,900 | 20,600 | 1.22 | n. d. | n. d. |
| 2a | P(iPOX ₂₇ -stat-VDM ₂₇) | BZ ^c | 11,300 | 15,300 | 1.35 | n. d. | n. d. |
| 2b | | BA ^c | 15,700 | 20,100 | 1.28 | n. d. | n. d. |
| 3a | P(iPOX ₂₇ -stat-VDM ₂₇) | BA | 12,300 | 15,000 | 1.22 | 100 | n. a. |
| 3b | | BZ | 16,300 | 22,000 | 1.35 | 100 | 100 |
| 4 | P(iPOX ₂₇ -stat-VDM ₂₇) | BZ | 12,600 | 23,000 | 1.83 | n. a. | n. d. |
| 5a | P(iPOX ₁₁ - <i>b</i> -VDM ₁₅) | BA | 22,800 | 30,200 | 1.32 | 100 | n. a. |
| 5b | | BZ | 24,900 | 31,900 | 1.28 | 100 | 60 |
| 6a | P(iPOX ₁₁ - <i>b</i> -VDM ₁₅) | BZ | 16,500 | 27,100 | 1.64 | n. a. | 28 |
| 6b | | BA | 20,400 | 33,200 | 1.63 | 100 | 28 |

BA: Benzylamine. BZ: Benzoic acid.

Table S4. Characterisation of functionalised copolymers. ^aSEC in DMAc (PS-cal.). ^b¹H NMR (400 MHz) in CD₂Cl₂. n. d. not determinable due to peak overlap. n. a. not available.

| Run | Polymer name | Functionalisation order | SEC ^a | | | ¹ H NMR ^b | |
|-----|------------------------------------------------------|-------------------------|---------------------------------------------|---------------------------------------------|----------|---------------------------------|---------------|
| | | | <i>M_n</i> [g mol ⁻¹] | <i>M_w</i> [g mol ⁻¹] | <i>D</i> | % BA | % BZ |
| 7a | P(iPOX ₁₁ - <i>b</i> -VDM ₁₅) | PEG-NH ₂ | 39,800 | 47,400 | 1.19 | 100 (PEG) | n. a. (TA) |
| 7b | | TA | 42,400 | 52,000 | 1.23 | 100 (PEG) | n. d. (TA) |

PEG: Poly(ethylene glycol). TA: Terephthalic acid.