Aqueous asymmetric cyclopropanation reactions in polymersome membranes

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Supporting Information

Table of contents

General Information (materials/instrumentation) S2
Compound characterizations S4
Procedures S7
Figures S10
References S26
**General Information (materials/instrumentation)**

Chemicals were purchased from Sigma-Aldrich. Unless stated otherwise, chemicals were used without further purification. Reactions were carried out under an inert atmosphere of dry nitrogen or argon. Standard syringe techniques were applied for the transfer of dry solvents and air- or moisture sensitive reagents. Reactions were followed by thin layer chromatography (TLC) on silica gel-coated plates (Merck 60 F254) with the indicated solvent mixture. Detection was performed with UV-light, and/or by charring at ~150 °C after dipping into a solution of aqueous basic KMnO₄ or in a solution of ninhydrin. Column or flash chromatography was carried out using Silicycle Silicaflash P60® (40-63 µm). Fourier transform infrared spectroscopy (FT-IR) spectra were recorded on an ATI Matso Genesis Series FT-IR spectrometer fitted with an ATR cell. The vibrations (ν) are given in cm⁻¹.

Dynamic light scattering (DLS) measurements were performed on a Malvern Instrument Zetasizer Nano S (ZEN 1600), equipped with a He-Ne laser (633 nm, 4 mW) and an Avalanche photodiode detector at an angle of 173°. The DLS data were processed and analyzed with Dispersion Technology Software (Malvern Instruments).

Chiral Gas chromatography (GC) measurements were performed on a Shimadzu GC2010+, containing an Agilent CP-Chiralsil-DEX CB column (25m, 0.32 mm ID, 0.25 µm DF) using FID detection. Chiral HPLC measurements were performed on a Shimadzu LC2010C, containing a Phenomenex Lux Amylose-2 (250x4.6 mm) column, a Phenomenex Lux Cellulose-2 (250x4.6 mm) column or a Dr. Maisch Reprosil Chiral-OM (250x4.6 mm) column, using UV detection (220 nm).

NMR spectra were recorded on a Bruker DMX 300 (300 MHz), a Bruker DMX 500 (500 MHz) and a Varian 400 (400 MHz) spectrometer in CDCl₃ solutions (unless reported otherwise). ¹H NMR chemical shifts are given in ppm with respect to tetramethylsilane (TMS, δ 0.00 ppm) as internal standard, ¹³C NMR shifts are given in ppm with respect to CHCl₃ (δ 77.00 ppm). Coupling constants are reported as J-values in Hz. High resolution mass spectra were recorded on a JEOL AccuTOF (ESI).

Transmission electron microscopy (TEM) was performed on a JEOL TEM 1010 microscope with an acceleration voltage of 60 kV equipped with a charge-coupled device (CCD) camera. Sample specimens were prepared by placing a drop (6 µL) of a diluted aqueous vesicle solution on an EM science carbon-coated copper grid (200 mesh). The grid was air dried for at least 2 hours and analyzed without further treatment. Cryogenic SEM (Cryo-SEM) was performed on a JEOL 6330 Cryo Field Emission Scanning Electron Microscope (FESEM). Samples were rapidly frozen in nitrogen slush at -220 °C and freeze fractured in the cooling pre-chamber of the microscope at -120 °C. The plane of fracture was etched for 5 min via sublimation at -95 °C, and transferred to the microscope chamber where the temperature was maintained at -120 °C. EDX images were measured on a JEOL TEM 2100 microscope, equipped with a Bruker XFlash 6T|60 EDX module. Sample specimens were prepared by placing a drop (6 µL) of a diluted aqueous vesicle solution on an EM science carbon-coated nickel grid (200 mesh). The grid was air dried for at least 2 hours and analyzed without further treatment. Inductively coupled plasma-mass spectrometry (ICP-MS) measurements were performed on a Thermo Fisher Scientific Xseries I quadrupole machine using 5.0 mL samples containing 0.49 mg/L InCl₃ solutions as internal standard.
The size exclusion chromatography-multi angle laser light scattering (SEC-MALLS) experiments were conducted at room temperature using a SEC column (Dr. Maisch, GPC-PS, 300x8 mm, particle size 5 μm) in-line with a Wyatt DAWN HELEOS II light scattering detector using a laser operating at 658 nm and a Wyatt Optilab T-Rex refractive index detector. Number-averaged molecular weight calculations were performed using ASTRA 6.0.6.13, using a dn/dc value of 0.185.
Poly (ethylene glycol)-chain transfer agent PEG$_{44}$-CTA

Poly(ethylene glycol) ($M_n = 2000$ g mol$^{-1}$) chain transfer agent (PEG$_{44}$-CTA) was synthesized according to literature procedures.$^{[1]}$ $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 8.02-7.98 (m, 2H, arom. H), 7.56-7.47 (m, 3H, arom. H), 7.41-7.34 (m, 5H, arom. H), 5.73 (s, 1H, -CH=Ar), 4.42-4.24 (m, 2H, -COOCH$_2$), 3.87-3.44 (m, 174H, PEG backbone), 3.38 (s, 3H, CH$_3$OCH$_2$).

Poly(ethylene glycol)-b-poly(styrene-co-4-vinylbenzyl chloride) PEG$_{44}$-b-P(S$_{128}$-co-4-VBC$_6$) (P1a)

A flame-dried Schlenk tube equipped with a stirring bar was loaded with styrene (1.80 g, 17.3 mmol, 288 equiv), purified 4-vinylbenzyl chloride (326 mg, 1.92 mmol, 32 equiv), PEG$_{44}$-CTA (137 mg, 0.06 mmol, 1.0 equiv) and AIBN (2.0 mg, 0.012 mmol, 0.2 equiv). The mixture was degassed by three freeze-pump-thaw cycles. The Schlenk tube was then immersed in a preheated oil bath of 70 °C and the polymerization was monitored by $^1$H-NMR spectroscopy. When a 40% conversion was reached, the polymerization was terminated by removing the Schlenk tube from the oil bath. After the reaction mixture had cooled down to room temperature, it was diluted with CHCl$_3$ and transferred to a round-bottom flask. The product was precipitated by addition of cold MeOH (250 mL) and subsequently filtered over a glass filter. The latter three steps were repeated five times to remove excess monomer. The resulting pink solid was dried in vacuo to yield P1a (480 mg). $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.25-6.20 (m, arom. H), 4.60-4.35 (br. s, -CH$_2$Cl), 3.70-3.60 (br. s, PEG backbone), 2.2-1.10 (m, P(S-co-4-VBC) backbone). FT-IR (ATR): 3058, 3026, 2922, 1601, 1491, 1452, 1111, 760, 699 cm$^{-1}$. $M_n$ ($^1$H NMR) = 19.4 kDa. $M_n$ (MALLS) = 16.7 kDa. PDI = 1.06

Poly(ethylene glycol)-b-poly(styrene-co-4-vinylbenzyl chloride) PEG$_{44}$-b-P(S$_{133}$-co-4-VBC$_6$) (P2a)

Prepared as described above starting from styrene (1.90 g, 18.3 mmol, 304 equiv), 4-vinylbenzyl chloride (163 mg, 0.96 mmol, 16 equiv), PEG$_{44}$-CTA (137 mg, 0.06 mmol, 1.0 equiv) and AIBN (2.0 mg, 0.012 mmol, 0.2 equiv). Precipitation yielded P2a as a pink solid (450 mg). $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.23-6.25 (m, arom. H), 4.58-4.41 (br. s, -CH$_2$Cl), 3.67-3.60 (br. s, PEG backbone), 2.10-1.20 (m, P(S-co-4-VBC) backbone). FT-IR (ATR): 3059, 3025, 2924, 1600, 1491, 1453, 1109, 760, 699 cm$^{-1}$. $M_n$ ($^1$H NMR) = 17.4 kDa. $M_n$ (MALLS) = 15.0 kDa. PDI = 1.02.

Poly(ethylene glycol)-b-poly(styrene-co-4-vinylbenzyl chloride) PEG$_{44}$-b-P(S$_{128}$-co-4-VBC$_{64}$) (P3a)

Prepared as described above starting from styrene (1.60 g, 15.4 mmol, 256 equiv), 4-vinylbenzyl chloride (652 mg, 3.84 mmol, 64 equiv), PEG$_{44}$-CTA (137 mg, 0.06 mmol, 1.0 equiv) and AIBN (2.0 mg, 0.012 mmol, 0.2 equiv). Precipitation yielded P3a as a pink solid (390 mg). $^1$H NMR (CDCl$_3$, 400 MHz):
Poly(ethylene glycol)-b-poly(styrene-co-4-vinylbenzyl azide) PEG<sub>44</sub>-b-P(S<sub>138</sub>-co-4-VBA<sub>18</sub>) (P1)

\[ \text{NaN}_3 \text{ (666 mg, 10.2 mmol, 488 equiv) was added to a solution of polymer P1a (400 mg, 0.021 mmol, 1.0 equiv) in DMF (2.5 mL) in a flame-dried Schlenk tube. The mixture was stirred at room temperature for 3 days. The reaction mixture was then diluted with CHCl}_3 \text{ and transferred to a round-bottom flask. Precipitation was induced upon addition of cold MeOH and the resulting white solid P1 was filtered and dried in vacuo. Yield (420 mg).} \]

$^1$H NMR (CDCl<sub>3</sub>, 400 MHz): δ 7.25-6.56 (m, arom. H), 4.30-4.10 (br. s, -CH<sub>3</sub>N<sub>3</sub>), 3.65-3.60 (br. s, PEG backbone), 2.00-1.20 (m, P(S-co-4-VBA) backbone). FT-IR (ATR): 3058, 2923, 1601, 1493, 1453, 1110, 760, 700 cm<sup>-1</sup>. $M_n$ ($^1$H NMR) = 19.5 kDa. $M_n$ (MALLS) = 26.1 kDa. PDI = 1.31 (Fig S4).

Poly(ethylene glycol)-b-poly(styrene-co-4-vinylbenzyl azide) PEG<sub>44</sub>-b-P(S<sub>133</sub>-co-4-VBA<sub>8</sub>) (P2)

Prepared as described above starting from polymer P2a (400 mg, 0.023 mmol, 1.0 equiv) and NaN<sub>3</sub> (342 mg, 5.26 mmol, 229 equiv) to yield a white solid (410 mg) $^1$H NMR (CDCl<sub>3</sub>, 400 MHz): δ 7.23-6.54 (m, arom. H), 4.30-4.10 (br. s, -CH<sub>3</sub>N<sub>3</sub>), 3.65-3.59 (br. s, PEG backbone), 2.10-1.15 (m, P(S-co-4-VBA) backbone). FT-IR (ATR): 3059, 3026, 2922, 2095, 1601, 1493, 1453, 1110, 760, 709, 699 cm<sup>-1</sup>. $M_n$ ($^1$H NMR) = 17.4 kDa. $M_n$ (MALLS) = 24.0 kDa. PDI = 1.26 (Fig S4).

Poly(ethylene glycol)-b-poly(styrene-co-4-vinylbenzyl azide) PEG<sub>44</sub>-b-P(S<sub>128</sub>-co-4-VBA<sub>34</sub>) (P3)

Prepared as described above starting from P3a (400 mg, 0.019 mmol, 1.0 equiv) and Na<sub>2</sub>N<sub>3</sub> (1.22 g, 18.8 mmol, 980 equiv) to yield a white solid (320 mg) $^1$H NMR (CDCl<sub>3</sub>, 400 MHz): δ 7.25-6.56 (m, arom. H), 4.30-4.10 (br. s, -CH<sub>3</sub>N<sub>3</sub>), 3.66-3.60 (br. s, PEG backbone), 2.00-1.20 (m, P(S-co-4-VBA) backbone). FT-IR (ATR): 3059, 3027, 2922, 2096, 1601, 1492, 1452, 1111, 762, 699 cm<sup>-1</sup>. $M_n$ ($^1$H NMR) = 21.0 kDa. $M_n$ (MALLS) = 26.9 kDa. PDI = 1.32 (Fig S4).
(4S,4’S)-2,2’-(hepta-1,6-diyne-4,4-diyil)bis(4-phenyl-4,5-dihydrooxazole) (C1a)

A solution of 2,2’-methylenebis[(4S)-4-phenyl-2-oxazoline] (400 mg, 1.31 mmol, 1.0 equiv) in dry THF (13 mL) was cooled to -55 °C. n-Butyllithium (1.80 mL of a 1.6 M solution in hexanes, 2.88 mmol, 2.2 equiv) was added dropwise. The reaction mixture was stirred for 1h, after which propargyl bromide (428 mg of a 80% solution in toluene, 2.88 mmol, 2.2 equiv) was added. The reaction mixture was subsequently stirred for 3h at -10 °C. After the reaction was quenched with saturated aqueous NH₄Cl, the product was extracted with Et₂O (5 × 30 mL). The resulting organic fraction was dried (Na₂SO₄) and concentrated in vacuo. Column chromatography (EtOAc/heptane, 1:10→1:3) yielded compound C1a (352 mg, 70%) as a yellow oil. Rf 0.56 (EtOAc/heptane, 1:1). [α]D²⁰ -121.5 (c 1.00, CHCl₃). FT-IR (ATR): 3291, 2922, 1657, 1189, 1031, 974, 700 cm⁻¹. ¹H NMR (CDCl₃, 400 MHz): δ 7.33-7.25 (m, 10H), 5.26 (dd, J = 10.2, 8.1 Hz, 2H), 4.70 (dd, J = 10.2, 8.4 Hz, 2H), 4.16 (t, J = 8.3 Hz, 2H), 3.27 (dd, J = 5.4, 2.7 Hz, 4H), 2.10 (t, J = 2.6 Hz, 2H). ¹³C NMR (CDCl₃, 126 MHz): δ 166.1, 141.8, 128.7, 127.7, 126.9, 79.2, 75.9, 71.6, 69.9, 45.1, 23.7. HRMS (ESI) m/z calcd for C₂₃H₂₅N₂O₂ (M+H)+: 383.1760, found: 383.1780.

(4S,4’S)-2,2’-(hepta-1,6-diyne-4,4-diyil)bis(4-tert-butyl-4,5-dihydrooxazole) (C2a)

Prepared as described above starting from 2,2’-isopropylidenebis[(4S)-4-tert-butyl-2-oxazoline] (300 mg, 1.13 mmol, 1.0 equiv). Column chromatography (EtOAc/heptane, 1:10→1:3) yielded compound C2a (270 mg, 70%) as a yellow oil. Rf 0.69 (EtOAc/heptane, 1:1). [α]D²⁰ -101.5 (c 1.00, CH₂Cl₂). FT-IR (ATR): 3294, 2954, 1644, 1479, 1365, 1194, 1050, 969, 645 cm⁻¹. ¹H NMR (CDCl₃, 400 MHz): δ 4.19 (dd, J = 10.1, 8.6 Hz, 2H), 4.08 (dd, J = 8.6, 7.6 Hz, 2H), 3.89 (dd, J = 10.1, 7.6 Hz, 2H), 3.23-3.01 (m, 4H), 1.97 (t, J = 2.6 Hz, 2H), 0.88 (s, 18H). ¹³C NMR (CDCl₃, 126 MHz): δ 164.3, 79.5, 75.6, 70.9, 69.3, 44.9, 33.7, 25.8, 23.3. HRMS (ESI) m/z calcd for C₂₁H₂₃N₂O₂ (M+H)+: 343.2386, found: 343.2371.

(4R,4’R,5S,5’S)-2,2’-(hepta-1,6-diyne-4,4-diyil)bis(4,5-diphenyl-4,5-dihydrooxazole) (C3a)

Prepared as described above starting from 2,2’-methylenebis[(4R,5S)-4,5-diphenyl-2-oxazoline] (400 mg, 0.87 mmol, 1.0 equiv). Column chromatography (EtOAc/heptane, 1:10→1:3) yielded compound C3a (335 mg, 72%) as a bright yellow solid. Rf 0.49 (EtOAc/heptane, 1:1). [α]D²⁰ +306.5 (c 1.00, CH₂Cl₂). FT-IR (ATR): 3294, 3030, 1659, 1497, 1454, 1188, 1049, 964, 697 cm⁻¹. ¹H NMR (CDCl₃, 400 MHz): δ 7.04-6.95 (m, 20H), 6.00 (d, J = 10.3 Hz, 2H), 5.64 (d, J = 10.3 Hz, 2H), 3.64-3.37 (m, 4H), 2.25 (t, J = 2.7 Hz, 2H). ¹³C NMR (CDCl₃, 126 MHz): δ 166.1, 137.0, 135.9, 128.0, 127.7, 127.6, 127.1, 126.6, 86.7, 79.4, 73.9, 72.0, 45.9, 23.9. HRMS (ESI) m/z calcd for C₃₇H₃₁N₂O₂ (M+H)+: 535.2386, found: 535.2391.

[(4S,4’S)-2,2’-(hepta-1,6-diyne-4,4-diyil)bis(4-phenyl-4,5-dihydrooxazole)]-copper(II) triflate (C1)

C1a (50.0 mg, 0.13 mmol, 1.0 equiv) was added to a solution of Cu(OTf)₂ (47.3 mg, 0.13 mmol, 1.0 equiv) in anhydrous MeOH (1.5 mL). After stirring for 24 h, the resulting product was separated by filtration, washed with MeOH and dried under vacuum to afford C1 (89 mg, 92%) as a green solid.
[(4S,4'S)-2,2'-(hepta-1,6-diyne-4,4-diyl)bis(4-tert-butyl-4,5-dihydrooxazole)]-copper(II) triflate (C2)
Prepared as described above starting from C2a (35.0 mg, 0.10 mmol, 1.0 equiv).
Product C2 (67.6 mg, 94%) was afforded as a blue solid.

[(4R,4'R,5S,5'S)-2,2'-(hepta-1,6-diyne-4,4-diyl)bis(4,5-diphenyl-4,5-dihydrooxazole)]-copper(II) triflate (C3)
Prepared as described above starting from C3a (50.0 mg, 0.094 mmol, 1.0 equiv).
Product C3 (77.1 mg, 92%) was afforded as a green solid.

Catalytic polymersomes preparation
Block copolymer P1 (20.0 mg, 0.0010 mmol, 0.019 mmol of azides, 1.0 equiv) was dissolved in THF (1.0 mL) in a scintillation vial. 1.0 mL of ultrapure water (Milli-Q, 18.2 MΩ) was added dropwise within 1 hour while stirring the solution at 700 rpm. The polymersomes were allowed to self-assemble for 30 min. Then, catalyst C1 (8.1 mg, 0.011 mmol, 0.6 equiv) was added, followed by a solution of CuSO₄·5H₂O (2.7 mg, 0.011 mmol, 0.6 equiv), bathophenanthroline, sulfonated sodium salt (5.6 mg, 0.011 mmol, 0.6 equiv) and sodium ascorbate (4.3 mg, 0.022 mmol, 1.2 equiv) in Milli-Q (100 µL). The dispersion was stirred for 3 days after which the polymersomes were transferred to a dialysis membrane (MWCO 30 kDa). The polymersomes were subsequently dialyzed against Milli-Q for 72 hours to remove THF and the excess of catalyst. The final volume was adjusted to 3.0 mL with Milli-Q.

Polymersomes functionalized with catalyst C2 and C3 were prepared as described above starting from C2 (7.7 mg, 0.011 mmol, 0.6 equiv) and C3 (9.8 mg, 0.011 mmol, 0.6 equiv) respectively.

Polymersomes consisting of block copolymers P2 and P3 were prepared as described above starting from P2 (40.0 mg, 0.0023 mmol, 0.018 mmol of azides, 1.0 equiv) and P3 (11.0 mg, 0.00052 mmol, 0.020 mmol of azides, 1.0 equiv.)

General procedures asymmetric cyclopropanation reaction

Procedure A: Catalyst C1, C2 or C3 (0.0095 mmol, 10 mol%) was dissolved in dry CH₂Cl₂ (3 mL) in a scintillation vial. Styrene (49.5 mg, 0.475 mmol, 5.0 equiv) was added, followed by ethyl diazoacetate (10.8 mg, 11.8 µL of 85% solution in CH₂Cl₂, 0.095 mmol, 1.0 equiv). The reaction mixture was stirred at room temperature for 10 min or 2 h, after which the solvent was evaporated. Conversion was determined by ¹H NMR, using triethylene glycol dimethyl ether as internal standard.
Procedure B: Same conditions as above but instead of dry CH₂Cl₂, ultrapure water (Milli-Q, 18.2 MΩ) was used as a solvent. The reaction mixture was stirred for 10 min after which the product was extracted with CH₂Cl₂ (5 x 8 mL). The resulting organic fraction was dried (Na₂SO₄) and concentrated in vacuo. Conversion was determined by ¹H NMR, using triethylene glycol dimethyl ether as internal standard.

Procedure C: Catalytic polymersomes, prepared as described above, were transferred to a scintillation vial charged with a stirring bar. Styrene (49.5 mg, 0.475 mmol, 5.0 equiv) was added, followed by ethyl diazoacetate (10.8 mg, 11.8 µL of 85% solution in CH₂Cl₂, 0.095 mmol, 1.0 equiv). The reaction mixture was stirred for 10 min after which the product was extracted with CH₂Cl₂ (5 x 8 mL). The resulting organic fraction was dried (Na₂SO₄) and concentrated in vacuo. Conversion was determined by ¹H NMR, using triethylene glycol dimethyl ether as internal standard.

(R)-ethyl 2-phenylcyclopropanecarboxylate (1)

Prepared as described in procedure C, starting from styrene (49.5 mg, 0.475 mmol, 5.0 equiv). The catalytic polymersomes consisted of P1 block copolymers and were functionalized with catalyst C2. Column chromatography (EtOAc/heptane, 1:20) yielded 1 as a mixture of trans and cis isomers (7.3 mg, 42%) as colorless oil. Cis isomer: e.e = 72% (Chiral-sil GC column). ¹H NMR (CDCl₃, 400 MHz): δ 7.28-7.05 (m, 5H), 3.87 (q, J = 7.1 Hz, 2H), 2.58 (dt, J = 9.0, 7.6 Hz, 1H), 2.06 (ddd, J = 9.3, 7.8, 5.6 Hz, 1H), 1.71 (ddt, J = 7.5, 5.6, 5.1 Hz, 1H), 1.33-1.28 (m, 1H), 0.95 (t, J = 7.1 Hz, 3H). Trans isomer: e.e = 84% (Chiral-sil GC column). ¹H NMR (CDCl₃, 400 MHz): δ 7.30-7.07 (m, 5H), 4.17 (q, J = 7.2 Hz, 2H), 2.52 (ddd, J = 9.2, 6.5, 4.2 Hz, 1H), 1.90 (ddd, J = 8.4, 5.3, 4.2 Hz, 1H), 1.60 (ddd, J = 9.2, 5.3, 4.5 Hz, 1H), 1.34-1.30 (m, 1H), 1.28 (t, J = 7.2 Hz, 3H). Spectral data are in accordance with literature.[²]

(R)-ethyl 2-(4-methoxyphenyl)cyclopropanecarboxylate (2)

Prepared as described in procedure C, starting from 4-methoxystyrene (63.8 mg, 0.475 mmol, 5.0 equiv). The catalytic polymersomes consisted of P1 block copolymers and were functionalized with catalyst C2. Column chromatography (EtOAc/heptane, 1:20) yielded 2 as a mixture of trans and cis isomers (19.0 mg, 93%) as an amorphous solid. Cis isomer: e.e = 53% (HPLC eluent heptane:isopropanol = 97:3, flow 0.5 mL/min, oDH column). ¹H NMR (CDCl₃, 400 MHz): δ 7.21-7.00 (m, 2H), 6.82-6.77 (m, 2H), 3.87 (s, 3H), 2.58-2.47 (m, 1H), 2.03 (ddd, J = 9.2, 7.8, 5.6 Hz, 1H), 1.65 (dt, J = 7.5, 5.3 Hz, 1H), 1.33-1.29 (m, 1H), 1.01 (t, J = 7.1 Hz, 3H). Trans isomer: e.e = 59% (HPLC eluent heptane:isopropanol = 97:3, flow 0.5 mL/min, oDH column). ¹H NMR (CDCl₃, 400 MHz): δ 7.07-7.00 (m, 2H), 6.85-6.79 (m, 2H), 4.16 (q, J = 7.1 Hz, 2H), 3.78 (s, 3H), 2.48 (ddd, J = 9.2, 6.5, 4.2 Hz, 1H), 1.82 (ddd, J = 8.4, 5.2, 4.2 Hz, 1H), 1.58-1.52 (m, 1H), 1.28 (t, J = 7.1 Hz, 3H), 1.26-1.22 (m, 1H). Spectral data are in accordance with literature.[²]
(R)-ethyl 2-(4-chlorophenyl)cyclopropanecarboxylate (3)

Prepared as described in procedure C starting from 4-chlorostyrene (65.8 mg, 0.475 mmol, 5.0 equiv). The catalytic polymersomes consisted of P1 block copolymers and were functionalized with catalyst C2. Column chromatography (EtOAc/heptane, 1:20) yielded 3 as a mixture of trans and cis isomers (6.6 mg, 32%) as colorless oil. Cis isomer: e.e = 35% (HPLC eluent heptane:isopropanol = 95:5, flow 0.5 mL/min, amylose column). 1H NMR (CDCl$_3$, 400 MHz): δ 7.23-7.18 (m, 4H), 3.90 (q, $J = 7.2$ Hz, 2H), 2.50-2.45 (m, 1H), 2.08 (ddd, $J = 9.2, 7.9, 5.6$ Hz, 1H), 1.70-1.64 (m, 1H), 1.38-1.32 (m, 1H), 1.02 (t, $J = 7.1$ Hz, 3H). Trans isomer: e.e = 53% (HPLC eluent heptane:isopropanol = 95:5, flow 0.5 mL/min, amylose column). 1H NMR (CDCl$_3$, 400 MHz): δ 7.26-7.22 (m, 2H), 7.05-7.00 (m, 2H), 4.17 (q, $J = 7.1$ Hz, 2H), 2.56-2.50 (m, 1H), 1.86 (ddd, $J = 8.4, 5.3, 4.2$ Hz, 1H), 1.64-1.57 (m, 1H), 1.32-1.24 (m, 1H), 1.28 (t, $J = 7.1$ Hz, 3H). Spectral data are in accordance with literature.\[3\]

(R)-ethyl 2-(4-(tert-butyl)phenyl)cyclopropanecarboxylate (4)

Prepared as described in procedure C starting from 4-tert-butylstyrene (76.1 mg, 0.475 mmol, 5.0 equiv). The catalytic polymersomes consisted of P1 block copolymers and were functionalized with catalyst C2. Column chromatography (EtOAc/heptane, 1:20) yielded 4 as a mixture of trans and cis isomers (15.0 mg, 67%) as colorless oil. Cis isomer: 62% (HPLC eluent heptane:isopropanol = 99:1, flow 0.3 mL/min, cellulose-2 column). 1H NMR (CDCl$_3$, 400 MHz): δ 7.30-7.26 (m, 2H), 7.21-7.17 (m, 2H), 2.51-2.46 (m, 1H), 2.05 (ddd, $J = 9.3, 7.8, 5.6$ Hz, 1H), 1.72-1.66 (m, 1H), 1.34-1.28 (m, 1H), 1.29 (s, 9H), 0.92 (t, $J = 7.1$ Hz, 3H). Trans isomer: e.e = 71% (Chiral-sil GC column). 1H NMR (CDCl$_3$, 400 MHz): δ 7.33-7.29 (m, 2H), 7.06-7.02 (m, 2H), 4.16 (q, $J = 7.2$ Hz, 2H), 2.58-2.51 (m, 1H), 1.88 (ddd, $J = 8.4, 5.3, 4.1$ Hz, 1H), 1.61-1.55 (m, 1H), 1.34-1.28 (m, 1H), 1.30 (s, 9H), 1.29-1.25 (m, 3H). Spectral data are in accordance with literature.\[2\]
Figure S1. $^1$H NMR spectra of P1a and P1
Figure S2. $^1$H NMR spectra of P2a and P2
Figure S3. $^1$H NMR spectra of P3a and P3
Figure S4. Multiangle Laser Light Scattering (MALLS) spectra of block copolymers P1a (a), P1 (b), P2a (c), P2 (d), P3a (e) and P3 (f). The appearance of a shoulder on the left side of the spectra in (b), (d) and (f) can be explained with a partial crosslinking process between two polymers. During postmodification of the chloride-functionalized block copolymer with NaN₃ the RAFT moiety can be converted into a reactive thiolate which can subsequently carry out a nucleophilic attack on a benzyl chloride group of a pendant polymer. The degradation of the RAFT group via an addition-elimination reaction with a nucleophile has been described before[4] and is also evidenced by the disappearance of the pink colour during the reaction.

a)  

b)  

c)  

d)  

e)  

f)  

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Figure S5. $^1$H NMR and $^{13}$C NMR spectra of C1a
Figure S6. $^1$H NMR and $^{13}$C NMR spectra of C2a
Figure S7. $^1$H NMR and $^{13}$C NMR spectra of C3a
Figure S8. FT-IR (ATR) spectra of polymersomes before and after functionalization. The disappearance of the azide signal at 2095 cm$^{-1}$ shows that the CuAAC reaction was complete.

Figure S9. Dynamic Light Scattering (DLS) spectra of polymersomes consisting of P1 block copolymers before and after functionalization with catalyst C1 a) Number distribution spectrum b) Intensity distribution spectrum c) Correlogram
Figure S10. a,b) TEM and cryo-SEM images of Cu-bis(oxazoline) loaded polymersomes. c) EDX image of three Cu-bis(oxazoline) loaded polymersomes. d) STEM image of the same sample.
Figure S11. \( ^1 \text{H} \) NMR spectra cyclopropanes
Figure S12. Chiral GC spectrum of product asymmetric cyclopropanation reaction between styrene and EDA in polymersomes functionalized with catalyst C2 (bottom) and in CH$_2$Cl$_2$ with catalyst C2 (top).
Figure S13. Chiral GC spectrum of product asymmetric cyclopropanation reaction between styrene and EDA in Milli-Q with catalyst C2
Figure S14. Chiral GC and HPLC spectra of cyclopropanes

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