Active Template Rotaxane Synthesis Through the Ni-Catalyzed Cross-Coupling of Alkylzinc Reagents with Redox-Active Esters

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S1. General Methods and Abbreviations

S1.1 General methods

Unless stated otherwise, all reagents and solvents were purchased from commercial sources and used without further purification. Anhydrous DMF, CH$_2$Cl$_2$ and THF were obtained by passing the solvent (HPLC grade) through a Phoenix SDS System made by JC Meyers Solvent Systems. Flash column chromatography was carried out using Aldrich Si 60 Å (particle size 40–63 µm, Sigma Aldrich, UK) as the stationary phase. Analytical TLC was performed on pre-coated Merck silica gel plates (0.25 mm thickness, 60 F254) and observed under a 254 nm UV light or stained with a potassium permanganate solution. Preparative TLC separations were carried out using precoated Merck silica gel plates (1000 µm to 250 µm thickness, 60 F254). NMR spectra were recorded on a Bruker Avance III equipped with a cryoprobe (5 mm CPDCH 13C–1H/D) with an Oxford AS 600 magnet. $^1$H NMR spectra were recorded at 600 MHz and $^{13}$C spectra at 151 MHz. Chemical shifts are reported from high to low frequency in parts per million (ppm) relative to residual CHCl$_3$ ($\delta$H = 7.26, $\delta$C = 77.0) as the internal standard. All $^1$H NMR resonances are reported to the nearest 0.01 ppm, and all $^{13}$C resonances are reported to the nearest 0.01 ppm. Coupling constants are reported in hertz (Hz) and are reported to the nearest 0.1 Hz. Standard abbreviations indicating multiplicity were used as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet and br = broad. $^1$H NMR assignments were made using 2D NMR methods (COSY, HSQC and HMBC). Low resolution ESI mass spectrometry was performed with a Thermo Scientific LCQ Fleet Ion Trap Mass Spectrometer or an Advion Expression LCMS single quadrupole MS detector. High-resolution mass spectrometry was carried out by the EPSRC National Mass Spectrometry Service Centre (Swansea, UK) or by staff at the Mass Spectrometry Service, School of Chemistry, University of Manchester. Melting points were determined using a Büchi M–565 apparatus and are corrected. Macrocycle 1a was prepared according to a literature procedure.$^1$

S1.2 Abbreviations

DMAP, 4-dimethylaminopyridine. DMF, dimethyl formamide. EDCI, 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide. EDTA, ethylenediaminetetra-acetic acid. Na$_2$EDTA, ethylenediaminetetraacetic acid tetrasodium salt. NiCl$_2$·glyme, Nickel(II) chloride ethylene glycol dimethyl ether complex. PE, petroleum ether. Tf$_2$O, trifluoromethanesulfonic anhydride. THF, tetrahydrofuran. TIPS, triisopropylsilyl. TIPSCI, triisopropylsilyl chloride.
S2. General Procedures and Synthesis

S2.1 General procedure for synthesis of organozinc 3

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\text{Scheme S1. Synthesis of organozinc reagent 3. Reagents and conditions: (i) Mg, I}_2, \text{ r.t., 90 min. (ii) ZnCl}_2 (0.5 \text{ M in THF), 0 °C to r.t.}
\]

An oven-dried microwave vial equipped with a stirrer bar was charged with Mg turnings (0.54 g, 22.5 mmol, 1.5 equiv.) and I\(_2\) (38 mg, 0.15 mmol, 0.01 equiv.). The vial was purged with N\(_2\) before a solution of alkyl bromide S1 (4.43 g, 15.0 mmol, 1.0 equiv.) in THF (23 mL, 0.65 M) was added. After 5 min the solution turned colourless and was left stirring at room temperature for 90 min. An aliquot was titrated over a solution of I\(_2\) in THF to give a yield of around 60% (corresponding to a Grignard concentration of 0.39 M). In a separate vial equipped with a stirrer bar and flushed with N\(_2\), a 0.5 M solution of ZnCl\(_2\) in THF (2.5 mmol, 5.0 mL) was added, and the solution was cooled down to 0 °C, after which the 0.39 M solution Grignard reagent was added (12.9 mL, 5.0 mmol). The reaction was stirred and allowed to reach room temperature after which the organozinc solution 3 was ready to be used.
S2.2 General procedure for rotaxane formation

Scheme S2. Reagents and conditions: (i) NiCl$_2$·glyme, DMF, r.t., 5 min, then THF, r.t., 18 h.

An oven-dried microwave vial equipped with a stir bar was charged with redox-active ester 2 (1.0 equiv. or 5.0 equiv.) and the vial was purged with N$_2$. A solution of macrocycle 1a or 1b (0.05 mmol, 1.0 equiv.) and NiCl$_2$·glyme (5.4 mg, 0.025 mmol, 0.5 equiv.) stirred under N$_2$ in DMF (1.0 mL) for 5 min was added to the vial containing the redox-active ester 2. The mixture was stirred for 1 min before the corresponding amount of organozinc solution 3 in THF (twice the equivalents of redox-active ester 2) was added. The solution was left stirring at room temperature for 18 h. The reaction was quenched with a saturated aqueous solution of NH$_4$Cl and diluted with CH$_2$Cl$_2$ and the solution was washed with a saturated aqueous solution of Na$_2$EDTA. The aqueous phase was extracted with CH$_2$Cl$_2$ twice and the combined organic phases were further washed with water and then with brine. The organic phase was dried over Na$_2$SO$_4$, filtered and concentrated under reduced pressure and the crude was placed under high vacuum for 30 min before analysis by $^1$H NMR. The conversion was calculated by comparing the ratio of free macrocycle 1a or 1b to rotaxane by $^1$H NMR in CDCl$_3$. The crude mixture was purified by flash chromatography (SiO$_2$, n-hexane/EtOAc 6:1) to collect both rotaxanes (homodimer and heterodimer) as a mixture. Further separation by preparative thin-layer chromatography (1000 µm, 2 elutions, CH$_2$Cl$_2$) afforded the heterodimer as the upper band and the homodimer as the lower band.
S2.3 Procedure for preparative scale synthesis of rotaxanes

An oven-dried round bottom flask equipped with a stir bar was charged with redox-active ester 2 (1.25 mmol, 681 mg, 5.0 equiv.) and the flask was purged with N₂. A solution of macrocycle 1a or 1b (0.25 mmol, 128 mg, 1.0 equiv.) and NiCl₂·glyme (0.125 mmol, 27.5 mg, 0.5 equiv.) stirred under N₂ in DMF (5 mL) for 5 min was added to the flask containing the redox-active ester 2. The mixture was stirred for 1 min before the freshly prepared organozinc solution 3 in THF (2.5 mmol, 18 mL, 10.0 equiv.) was added. The solution was left stirring at room temperature for 18 h. The reaction was quenched with a saturated aqueous solution of NH₄Cl (10 mL), diluted with CH₂Cl₂ and the solution was washed with a saturated aqueous solution of Na₂EDTA. The aqueous phase was extracted with CH₂Cl₂ twice and the combined organic phases were further washed with water and brine. The organic phase was dried over Na₂SO₄, filtered and concentrated under reduced pressure and the crude was placed under high vacuum for 30 min before analysis by ¹H NMR. The yield was calculated by comparing the ratio of free macrocycle 1a or 1b to rotaxane by ¹H NMR in CDCl₃. The determined NMR yields were 30 % for the heterodimer and 13 % for the homodimer. The crude mixture was purified by flash chromatography (SiO₂, n-hexane/EtOAc 6:1) to collect both rotaxanes (homodimer and heterodimer) as a mixture with further impurities. Purification by GPC in CHCl₃/0.1% Et₃N and preparative thin-layer chromatography (1000 µm, 1 elution, CH₂Cl₂) afforded the heterodimer (77 mg, 33 %) as the upper band ($R_f = 0.5$) and the homodimer (30 mg, 13 %) as the lower band ($R_f = 0.3$).
S2.4 Synthesis of organozinc precursor S1

\[
\text{Br} \quad \begin{array}{c} \text{OH} \end{array} \quad \xrightarrow{(i)} \quad \begin{array}{c} \text{Br} \end{array} \quad \begin{array}{c} \text{O} \quad \text{Si} \end{array}
\]

Scheme S3. Reagents and conditions: (i) TIPSCI, imidazole, CH₂Cl₂, r.t., 1 h, quant.

S1

A solution of 3-bromo-1-propanol (1.8 mL, 20 mmol) in dry CH₂Cl₂ (40 mL) was treated with TIPSCI (4.3 mL, 20 mmol) and imidazole (3.4 g, 50 mmol). The solution was stirred at room temperature for 1 h. The reaction mixture was washed with H₂O (50 mL) and brine (50 mL), dried over MgSO₄, filtered and concentrated under reduced pressure to afford the desired compound as a colourless oil (5.9 g, quantitative). Characterisation data is in agreement with the literature.²

\(^1\text{H NMR}\) (600 MHz, CDCl₃) δ 3.82 (t, \(J = 5.7\) Hz, 2H, c), 3.56 (t, \(J = 6.5\) Hz, 2H, e), 2.06 (p, \(J = 6.1\) Hz, 2H, d), 1.13 – 1.04 (m, 21H, a + b).
S2.5 Synthesis of macrocycle 1b

Scheme S4. Reagents and conditions: (i) 1,6-dibromohexane, K$_2$CO$_3$, MeCN, 90 °C, 24 h, 82%. (ii) conc. HBr, CH$_2$Cl$_2$, r.t., 3 h, 96%. (iii) NaH (60% in mineral oil), (6-bromo-pyridin-2-yl)methanol, DMF, 0 °C, then r.t., 1 h, 60%. (iv) NiBr$_2$(PPh$_3$)$_2$, Mn, Et$_4$Ni, PPh$_3$, DMF, 50 °C, 1 h, then S4, 5 h, 50 °C, 55%.

S3

A suspension of 4-hydroxybenzyl alcohol (6.2 g, 50 mmol), 1,6-dibromohexane (3.9 mL, 25 mmol) and K$_2$CO$_3$ (17.3 g, 125 mmol) in MeCN (200 mL) was heated to 90 °C. After 12 h, more MeCN (25 mL) was added and stirring was continued for 12 h until the reaction was allowed to cool to room temperature. Solids were removed by filtration and the filtrate was concentrated to give a crude solid that was triturated in acetone (100 mL) and collected by filtration to give S2 as a colourless solid (6.8 g, 82%) that was used in the next step without further purification. A solution of S2 (6.8 g, 21 mmol) in CH$_2$Cl$_2$ (100 mL) was treated with conc. HBr (48%, 50 mL) and the biphasic mixture was vigorously stirred at room temperature for 3 h. The reaction mixture was diluted with water (100 mL), the layers were separated, and the aqueous layer was extracted with CH$_2$Cl$_2$ (3 x 60 mL). Combined organic layers were dried over Na$_2$SO$_4$, filtered and concentrated to give S3 as a colourless solid (9.0 g,
96%) that was used in the next step without further purification. Characterisation data is in agreement with the literature.\(^3\)

\(^1\)H NMR (600 MHz, CDCl\(_3\)) \(\delta\) 7.31 (d, \(J = 8.6\) Hz, 4H, F), 6.85 (d, \(J = 8.6\) Hz, 4H, G), 4.51 (s, 4H, E), 3.96 (t, \(J = 6.4\) Hz, 4H, H), 1.81 (dd, \(J = 8.4, 4.9\) Hz, 4H, I), 1.54 (dd, \(J = 7.6, 3.9\) Hz, 4H, J).

**S4**

\[
\begin{array}{c}
\text{A} \quad \text{B} \quad \text{C} \\
\text{D} \quad \text{E} \quad \text{F} \\
\text{G} \quad \text{H} \quad \text{I} \\
\text{J} \quad \text{K} \quad \text{L} \\
\text{M} \quad \text{N}
\end{array}
\]

To a solution of S3 (2.3 g, 5.0 mmol) in DMF (25 mL) at 0 °C was added NaH (660 mg, 60% dispersion in mineral oil, 16.5 mmol) portion-wise over 10 min under vigorous stirring, followed by the addition of (6-bromo-pyridin-2-yl)methanol (2.1 g, 11 mmol). The reaction mixture was stirred at room temperature for 1 h before H\(_2\)O (60 mL) was added. The suspension was filtered and the retained solid dissolved in CHCl\(_3\) (40 mL). The organic layer was washed with brine (40 mL), dried over Na\(_2\)SO\(_4\), filtered and concentrated under reduced pressure. Purification by flash chromatography (SiO\(_2\), CH\(_2\)Cl\(_2\):PE:EtOAc 11:11:2) afforded S4 as a colourless solid (2.0 g, 60%).

\(^1\)H NMR (600 MHz, CDCl\(_3\)) \(\delta\) 7.55 (t, \(J = 7.7\) Hz, 2H, C), 7.46 (d, \(J = 7.6\) Hz, 2H, D), 7.37 (d, \(J = 7.8\) Hz, 2H, B), 7.28 (d, \(J = 8.6\) Hz, 4H, I), 6.88 (d, \(J = 8.6\) Hz, 4H, J), 4.62 (s, 4H, F), 4.57 (s, 4H, G), 3.97 (t, \(J = 6.5\) Hz, 4H, L), 1.81 (p, \(J = 6.8\) Hz, 4H, M), 1.55 – 1.51 (m, 4H, N). \(^{13}\)C NMR (151 MHz, CDCl\(_3\)) \(\delta\) 160.66 (E), 159.04 (K), 141.37 (A), 139.11 (C), 129.69 (H), 129.68 (I), 126.67 (B), 120.09 (D), 114.60 (J), 72.94 (G), 72.09 (F), 68.00 (L), 29.34 (M), 26.02 (N); M.p. 77 – 81 °C; HRMS (ESI+) Calc. C\(_{32}\)H\(_{34}\)N\(_2\)O\(_4\)Br\(_2\)K [M+K]\(^+\) 707.0517, Obs. 707.0509.
A flask was charged with NiBr$_2$(PPh$_3$)$_2$ (745 mg, 1.00 mmol), Mn (540 mg, 10.0 mmol), Et$_4$Ni (207 mg, 1.00 mmol), PPh$_3$ (525 mg, 2.00 mmol) and DMF (10 mL). The suspension was sonicated for 10 min and subsequently heated to 50 °C for 1 h. S4 (670 mg, 1.00 mmol) was added dropwise to the mixture as a solution in DMF (10 mL) over 4 h and after the addition had finished, stirring continued at 50 °C for 1 h. The suspension was allowed to cool to room temperature and CH$_2$Cl$_2$ (50 mL) and EDTA-NH$_3$ (50 mL) were added. The mixture was stirred for 5 min and then filtered through a pad of Celite®. The organic layer was washed with H$_2$O (2 x 50 mL), brine (50 mL), dried over Na$_2$SO$_4$, filtered and concentrated. PPh$_3$ was removed by filtration over a plug of silica (PE: CH$_2$Cl$_2$ 1:1) and the fractions containing product were repurified by flash chromatography (SiO$_2$, PE: Et$_2$O 1:1) to yield 1b as a colourless solid (282 mg, 55%).

$^1$H NMR (600 MHz, Chloroform-d) δ 7.77 (dd, $J = 7.8$, 1.2 Hz, 2H, B), 7.73 (t, $J = 7.7$ Hz, 2H, C), 7.44 (dd, $J = 7.6$, 1.1 Hz, 2H, D), 7.19 (d, $J = 8.6$ Hz, 4H, I), 6.76 (d, $J = 8.6$ Hz, 4H, J), 4.66 (s, 4H, G), 4.57 (s, 4H, F), 3.96 (t, $J = 6.3$ Hz, 4H, L), 1.76 (p, $J = 6.7$ Hz, 4H, M), 1.47 (p, $J = 3.5$ Hz, 4H, N); $^{13}$C NMR (151 MHz, CDCl$_3$) δ 159.31 (E), 158.99 (K), 156.17 (A), 137.28 (C), 130.31 (I), 129.79 (H), 121.02 (D), 120.53 (B), 114.89 (J), 72.79 (G), 71.68 (F), 67.99 (L), 28.79 (M), 25.41 (N); M.p. 122 – 124 °C; HRMS (ESI+) Calc. C$_{32}$H$_{34}$N$_2$O$_4$Na [M+Na]$^+$ 533.2411, Obs. 533.2394.
S2.6 Synthesis of redox-active ester 2

Scheme S5. Reagents and conditions: (i) 3,5-di-tert-butylbenzaldehyde, malonic acid, piperidine, pyridine, 120 °C, 3.5 h, quant. (ii) H₂, Pd/C, THF, r.t., 2 h, 98%. (iii) N-hydroxy-tetrachlorophthalimide, EDCI·HCl, DMAP, CH₂Cl₂, r.t., 2 h, 70%.

A solution of 3,5-di-tert-butylbenzaldehyde (1.4 g, 6.4 mmol) in pyridine (30 mL) was treated with malonic acid (1.0 g, 9.6 mmol) and heated to 120 °C. Piperidine (0.19 mL, 1.9 mmol) was added dropwise to the reaction. After 3 h, more malonic acid (0.5 g, 4.8 mmol) was added and stirring continued for 30 min. The reaction was allowed to cool to room temperature and diluted with 1 M HCl (100 mL). The pH was adjusted to pH = 1 with conc. HCl (ca. 15 mL) upon which a white solid precipitated. The aqueous layer was extracted with EtOAc (3 x 50 mL) and the combined organic layers were washed with brine (100 mL), dried over MgSO₄, filtered and concentrated to afford S5 as a colourless solid (1.69 g, quantitative) that was used without further purification. A solution of S5 (1.69 g, 6.4 mmol) in dry THF (25 mL) was treated with 10% palladium on activated carbon (0.17 g) and the solution was sparged with H₂ for 2 h at room temperature. The reaction mixture was filtered through a pad of Celite® and concentrated under reduced pressure to give S6 as a colourless solid (1.65 g, 98%) that was used in the next step without further purification. Characterisation data is in agreement with the literature.⁴

¹H NMR (600 MHz, CDCl₃): δ 10.77 (br. s, 1H, i), 7.29 (t, J = 1.8 Hz, 1H, d), 7.06 (d, J = 1.8 Hz, 2H, e), 2.97 (dd, J = 9.0, 7.1 Hz, 2H, g), 2.74 – 2.67 (m, 2H, h), 1.32 (s, 18H, a).
A solution of S6 (1.28 g, 4.89 mmol) in dry CH₂Cl₂ (40 mL) was treated with N-hydroxytetrachloro-phthalimide (1.47 g, 4.89 mmol), EDCl·HCl (1.03 g, 5.37 mmol), and DMAP (60 mg, 0.45 mmol). The reaction was stirred at room temperature for 2 h before it was concentrated and purified by flash chromatography (SiO₂, n-hexane:EtOAc 19:1 to 9:1) to afford the desired compound as a colourless solid (1.87 g, 70%).

¹H NMR (600 MHz, CDCl₃) δ 7.32 (t, J = 1.8 Hz, 1H, d), 7.08 (d, J = 1.8 Hz, 2H, e), 3.09 (dd, J = 9.4, 6.7 Hz, 2H, g), 3.01 – 2.96 (m, 2H, h), 1.33 (s, 18H, a); ¹³C NMR (151 MHz, CDCl₃): δ 168.77 (i), 157.68 (j), 151.35 (c), 141.18 (k/l/m), 138.25 (f), 130.64(k/l/m), 124.86(k/l/m), 122.58 (e), 121.00 (d), 35.00 (b), 33.09 (h), 31.62 (a), 31.25 (g); M.p. 170 – 175 °C. HRMS (ESI-) Calc. C₂₆H₂₈NO₅ [M+MeO] 576.0698, Obs. 576.0706.

S2.7 Synthesis of cross-coupling free thread 6

Scheme S6. Reagents and conditions: (i) Tf₂O, Et₃N, CH₂Cl₂, r.t., 4 h, quant. (ii) pent-4-yn-1-ol, Pd(PPh₃)₂Cl₂, Cul, Et₃N, THF, 80 °C, 14 h, 56%. (iii) H₂, Pd/C 20 h, then Pt/C 45 min, THF, r.t., quant. (iv) TIPSCI, imidazole, CH₂Cl₂, r.t., 20 h, 70%.

A solution of 3,5-di-tert-butylpheanol (1.00 g, 4.85 mmol) in dry CH₂Cl₂ (20 mL) was cooled to 0 °C and NEt₃ (1.35 mL, 9.70 mmol) was added. Trifluoromethanesulfonic anhydride (1 M in
CH₂Cl₂, 5.8 mL, 5.8 mmol) was added dropwise and the reaction was allowed to warm to room temperature. After 3 h, more trifluoromethanesulfonic anhydride (1 M in CH₂Cl₂, 3.0 mL, 3.0 mmol) was added and the reaction was stirred for another 30 min. The mixture was washed with H₂O (25 mL), sat. aq. NaHCO₃ (25 mL) and brine (25 mL). The organic layer was dried over MgSO₄, filtered and concentrated to give a brown oil. Purification by flash chromatography (SiO₂, n-hexane) afforded compound S7 as a colourless, low-melting solid (1.65 g, quantitative). Characterisation data was in agreement with the literature.⁵

¹H NMR (600 MHz, Chloroform-d) δ 7.41 (t, J = 1.6 Hz, 1H, e), 7.06 (d, J = 1.6 Hz, 2H, c), 1.32 (s, 18H, g).

S8

A flask was charged with S7 (740 mg, 2.20 mmol), Pd(PPh₃)₂Cl₂ (154 mg, 0.220 mmol) and CuI (82 mg, 0.44 mmol). Solids were dissolved in dry degassed THF (10 mL), NEt₃ (4 mL) and pent-4-yn-1-ol (0.41 mL, 4.4 mmol) were added to the reaction and the mixture was heated at 80 °C for 14 h. The mixture was filtered through a pad of Celite® and concentrated under reduced pressure. The residue was taken up in EtOAc (25 mL) and washed with 1 M HCl (2 x 25 mL), sat. aq. NaHCO₃ (25 mL) and brine (25 mL). The organic layer was dried over MgSO₄, filtered and concentrated under reduced pressure. Purification by flash chromatography (SiO₂, PE:EtOAc 90:10 to 85:15) afforded compound S8 as a low melting solid (338 mg, 56%).

¹H NMR (600 MHz, Chloroform-d) δ 7.34 (t, J = 1.9 Hz, 1H, j), 7.25 (d, J = 1.8 Hz, 2H, h), 3.84 (q, J = 5.9 Hz, 2H, b), 2.55 (t, J = 6.9 Hz, 2H, d), 1.88 (p, J = 6.7 Hz, 2H, c), 1.50 (t, J = 5.5 Hz, 1H, a), 1.30 (s, 18H, l). ¹³C NMR (151 MHz, CDCl₃) δ 150.84 (i), 125.91 (h), 122.69 (g), 122.32 (j), 87.98 (e), 82.29 (f), 62.13 (b), 34.91 (k), 31.59 (c), 31.47 (l), 16.19 (d).


6

A solution of S8 (328 mg, 1.20 mmol) in dry THF (10 mL) was charged with palladium on carbon (10% wt. loading, 35 mg). The mixture was sparged with hydrogen and stirred under
an atmosphere of hydrogen at room temperature for 20 h. Platinum on carbon (10% wt. loading, 30 mg) and dry THF (10 mL) were added to the mixture and the reaction was sparged with hydrogen for another 45 min. The mixture was filtered through a pad of Celite® and the organic layer was concentrated under reduced pressure to yield S9 as a yellow oil (324 mg, quantitative) that was used in the next step without further purification. A solution of S9 (300 mg, 1.08 mmol) in dry CH$_2$Cl$_2$ (5 mL) was charged with imidazole (188 mg, 2.71 mmol). TIPSCI (0.23 mL, 1.08 mmol) was added dropwise at room temperature and the reaction was stirred for 20 h. The mixture was diluted with CH$_2$Cl$_2$ (25 mL) and washed with H$_2$O (3 x 25 mL) and brine (25 mL). The organic layer was dried over MgSO$_4$, filtered and concentrated to give a yellow oil. Purification by flash chromatography (SiO$_2$, PE to PE:EtOAc 95:5) afforded 6 as a colourless oil (331 mg, 70%).

$^1$H NMR (600 MHz, CDCl$_3$) δ 7.25 (t, J = 1.8 Hz, 1H, k), 7.03 (d, J = 1.8 Hz, 2H, i), 3.69 (t, J = 6.6 Hz, 2H, c), 2.63 – 2.56 (m, 2H, g), 1.67 – 1.62 (m, 2H, f), 1.62 – 1.57 (m, 2H, d), 1.48 – 1.40 (m, 2H, e), 1.32 (s, 18H, m), 1.11 – 1.04 (m, 21H, a + b). $^{13}$C NMR (151 MHz, CDCl$_3$) δ 150.59 (j), 142.02 (h), 122.71 (i), 119.76 (k), 63.55 (c), 36.82 (g), 34.90 (l), 33.06 (d), 31.88 (f), 31.67 (m), 26.03 (e), 18.21 (a), 12.16 (b). HRMS (ESI+) Calc. C$_{28}$H$_{52}$OSiK [M+K]$^+$ 471.3419, Obs. 471.3425.

S2.8 Synthesis of homo-coupling free thread 7

![Scheme S7](image)

Scheme S7. Reagents and conditions: (i) TIPSCI, imidazole, CH$_2$Cl$_2$, r.t., 1 h, 96%.

7

A solution of hexane-1,6-diol (0.59 g, 5.0 mmol) and imidazole (1.7 g, 25 mmol) in dry CH$_2$Cl$_2$ (10 mL) was treated with TIPSCI (2.1 mL, 10 mmol) and stirred at room temperature for 1 h. The mixture was diluted with CH$_2$Cl$_2$ (15 mL) and washed with H$_2$O (3 x 25 mL) and brine (25 mL). The organic layer was dried over MgSO$_4$, filtered and concentrated to give 7 as a colourless oil (2.1 g, 96%).

$^1$H NMR (600 MHz, CDCl$_3$) δ 3.67 (t, J = 6.7 Hz, 4H, c), 1.55 (m, 4H, d), 1.36 (m, 4H, e), 1.05 (m, 42H, a + b). $^{13}$C NMR (151 MHz, CDCl$_3$) δ 63.58 (c), 33.19 (d), 25.82 (e), 18.19 (a), 12.16 (b). HRMS (ESI+) Calc. C$_{28}$H$_{54}$O$_2$Si$_2$Na [M+Na]$^+$ 453.3560, Obs. 453.1657.
S2.9 Synthesis of rotaxanes 4a, 4b, 5a, and 5b

Rotaxane 4a was synthesised according to general procedure S2.2 (using 5.0 equivalents of 2 and 10.0 equivalents of 3) in 19\% yield (determined by $^1$H NMR).

$^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 7.69 (t, $J$ = 7.8 Hz, 2H, C), 7.59 (d, $J$ = 7.7 Hz, 2H, B), 7.47 (d, $J$ = 7.7 Hz, 2H, D), 7.21 (t, $J$ = 1.9 Hz, 1H, k), 7.10 – 7.06 (m, 4H, I), 6.74 (d, $J$ = 1.8 Hz, 2H, i), 6.63 (m, 4H, J), 4.64 – 4.53 (m, 4H, G), 4.42 (s, 4H, F), 4.05 – 3.92 (m, 4H, L), 2.06 – 1.86 (m, 4H, M), 1.65 – 1.57 (m, 2H, g), 1.34 (s, 18H, m), 1.06 – 0.96 (m, 21H, a-b), 0.57 (p, $J$ = 8.0 Hz, 2H, d), 0.24 – 0.09 (m, 4H, e-f). $^{13}$C NMR (151 MHz, CDCl$_3$): $\delta$ 159.06 (E and K), 156.37 (A), 149.93 (j), 143.15 (h), 136.93 (C), 130.30 (I), 130.02 (H), 122.76 (i), 120.49 (B/D), 120.43 (B/D), 119.22 (k), 115.30 (J), 72.50 (G), 70.95 (F), 67.03 (L), 64.04 (c), 36.23 (g), 34.90 (l), 33.62 (d), 31.83 (m), 31.57 (e), 25.05 (M/f), 25.00 (M/f), 18.27 (a), 12.17 (b). HRMS (ESI+) Calc. C$_{58}$H$_{83}$N$_2$O$_5$Si [M+H]$^+$ 915.6071, Obs. 915.6061.

Rotaxane 5a was synthesised according to general procedure S2.2 (using 5.0 equivalents of 2 and 10.0 equivalents of 3) in 20\% yield (determined by $^1$H NMR).

$^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 7.70 (t, $J$ = 7.8 Hz, 2H, C), 7.55 (d, $J$ = 7.7 Hz, 2H, B), 7.45 (d, $J$ = 7.7 Hz, 2H, D), 7.21 – 7.16 (m, 4H, I), 6.81 – 6.76 (m, 4H, J), 4.63 (s, 4H, G), 4.37 (s, 4H, F), 4.02 – 3.96 (m, 4H, L), 3.03 – 2.96 (m, 4H, c), 1.96 – 1.88 (m, 4H, M), 1.06 – 0.90 (m, 42H, a-b), 0.60 (p, $J$ = 7.7 Hz, 4H, d), 0.07 (p, $J$ = 3.5 Hz, 4H, e). $^{13}$C NMR (151 MHz, CDCl$_3$): $\delta$ 159.19 (K), 159.00 (E), 156.38 (A), 136.85 (C), 130.34 (I), 130.04 (H), 120.47 (B), 120.32 (D), 115.47 (J), 72.59 (G), 70.91 (F), 67.10 (L), 63.97 (c), 33.34 (d), 24.94 (e), 24.90 (M), 18.27 (a), 12.14 (b). HRMS (ESI+) Calc. C$_{54}$H$_{85}$N$_2$O$_6$Si$_2$ [M+H]$^+$ 913.5946, Obs. 913.5936.
Rotaxane 4b was synthesised according to general procedure S2.2 (using 5.0 equivalents of 2 and 10.0 equivalents of 3) in 38\% yield (determined by $^1$H NMR). The reaction was performed on a larger scale according to general procedure S2.3, affording 77 mg of a colourless oil (33\% yield) after isolation.

$^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 7.78 – 7.74 (m, 2H, B), 7.65 (t, $J$ = 7.8 Hz, 2H, C), 7.49 – 7.45 (m, 2H, D), 7.20 (t, $J$ = 1.9 Hz, 1H, k), 7.09 (d, $J$ = 8.5 Hz, 4H, I), 6.72 (d, $J$ = 1.8 Hz, 2H, i) 6.65 (d, $J$ = 8.5 Hz, 4H, J), 4.63 (d, $J$ = 2.3 Hz, 4H, G), 4.52 (s, 4H, F), 3.88 (td, $J$ = 6.3, 4.4 Hz, 4H, L), 2.92 (t, $J$ = 7.4 Hz, 2H, c), 1.75 – 1.77 (m, 4H, M), 1.60 – 1.55 (m, 2H, g), 1.43 (h, $J$ = 4.1, 3.2, 4H, N), 1.35 (s, 18H, m), 1.05 – 0.95 (m, 21H, a-b), 0.51 (p, $J$ = 7.5 Hz, 2H, d), 0.37 (p, $J$ = 8.1 Hz, 2H,), 0.16 – 0.06 (m, 2H, e). $^{13}$C NMR (151 MHz, CDCl$_3$): $\delta$ 159.00 (E), 158.85 (K), 156.05 (A), 150.03 (j), 142.82 (h), 136.99 (C), 129.88 (H), 129.59 (I), 122.58 (i), 120.19 (D), 120.15 (B), 119.32 (k), 114.90 (J), 72.12 (G), 70.92 (F), 67.77 (L), 63.92 (c), 36.21 (g), 34.90 (l), 32.90 (d), 31.81 (m), 31.41 (i), 29.26 (M), 25.58 (N), 25.45 (e), 18.30 (a), 12.16 (b). HRMS (ESI+) Calc. C$_{60}$H$_{87}$N$_2$O$_5$Si [M+H]$^+$ 943.6379, Obs. 943.6378.

Rotaxane 5b was synthesised according to general procedure S2.2 (using 5.0 equivalents of 2 and 10.0 equivalents of 3) in 18\% yield (determined by $^1$H NMR). The reaction was performed on a larger scale according to general procedure S2.3, affording 30 mg of a colourless oil (13\% yield) after isolation.

$^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 7.75 (dd, $J$ = 7.8, 1.1 Hz, 2H, B), 7.70 (t, $J$ = 7.7 Hz, 2H, C), 7.48 (dd, $J$ = 7.6, 1.1 Hz, 2H, D), 7.16 – 7.12 (m, 4H, I), 6.75 – 6.71 (m, 4H, J), 4.64 (s, 4H, G), 4.49 (s, 4H, F), 3.91 (t, $J$ = 6.4 Hz, 2H, L), 2.96 (t, $J$ = 7.4 Hz, 2H, c), 1.74 – 1.69 (m, 4H, M), 1.41 (t, $J$ = 3.5 Hz, 2H, N), 1.11 – 0.96 (m, 42H, a-b), 0.63 – 0.55 (m, 4H, d), 0.05 (td,
$J = 7.8, 7.0, 3.1$ Hz, 4H, e). $^{13}$C NMR (151 MHz, CDCl$_3$): $\delta$ $158.99$ (E), $158.93$ (K), $156.07$ (A), $136.96$ (C), $129.88$ (H), $129.59$ (I), $120.11$ (B and D), $114.99$ (J), $72.17$ (G), $70.87$ (F), $67.87$ (L), $63.85$ (c), $33.06$ (d), $29.26$ (M), $25.49$ (N), $25.04$ (e), $18.30$ (a), $12.16$ (b). HRMS (ESI+) Calc. C$_{56}$H$_{88}$N$_2$O$_6$Si$_2$ [M+H]$^+$ $941.6254$, Obs. $941.6253$. 
S3. $^1$H NMR Stackplots of Rotaxanes

Figure S1: $^1$H NMR spectra (600 MHz, CDCl$_3$, 298 K) of (a) unsymmetrical thread 6, (b) rotaxane 4a, (c) macrocycle 1a, (d) rotaxane 5a, and (e) symmetrical thread 7. Assignments correspond to the labelling shown in Scheme 1 in main text of paper.

Figure S2: $^1$H NMR spectra (600 MHz, CDCl$_3$, 298 K) of (a) unsymmetrical thread 6, (b) rotaxane 4b, (c) macrocycle 1a, (d) rotaxane 5b, and (e) symmetrical thread 7. Assignments correspond to the labelling shown in Scheme 1 in main text of paper.
S4. $^1$H and $^{13}$C NMR Spectra

**Figure S3**: $^1$H NMR (600 MHz, CDCl$_3$) spectrum of S4.

**Figure S4**: $^{13}$C NMR (151 MHz, CDCl$_3$) spectrum of S4.
Figure S5: $^1$H NMR (600 MHz, CDCl$_3$) spectrum of 1b.

Figure S6: $^{13}$C NMR (151 MHz, CDCl$_3$) spectrum of 1b.
Figure S7: $^1$H NMR (600 MHz, CDCl$_3$) spectrum of 2.

Figure S8: $^{13}$C NMR (151 MHz, CDCl$_3$) spectrum of 2.
Figure S9: $^1$H NMR (600 MHz, CDCl₃) spectrum of S8.

Figure S10: $^{13}$C NMR (151 MHz, CDCl₃) spectrum of S8.
Figure S11: $^1$H NMR (600 MHz, CDCl$_3$) spectrum of 6.

Figure S12: $^{13}$C NMR (151 MHz, CDCl$_3$) spectrum of 6.
**Figure S13**: $^1$H NMR (600 MHz, CDCl$_3$) spectrum of 7.

**Figure S14**: $^{13}$C NMR (151 MHz, CDCl$_3$) spectrum of 7.
Figure S15: $^1$H NMR (600 MHz, CDCl$_3$) spectrum of 4a.

Figure S16: $^{13}$C NMR (151 MHz, CDCl$_3$) spectrum of 4a.
Figure S17: $^1$H NMR (600 MHz, CDCl$_3$) spectrum of 5a.

Figure S18: $^{13}$C NMR (151 MHz, CDCl$_3$) spectrum of 5a.
Figure S19: $^1$H NMR (600 MHz, CDCl$_3$) spectrum of 4b.

Figure S20: $^{13}$C NMR (151 MHz, CDCl$_3$) spectrum of 4b.
Figure S21: $^1$H NMR (600 MHz, CDCl$_3$) spectrum of 5b.

Figure S22: $^{13}$C NMR (151 MHz, CDCl$_3$) spectrum of 5b.
S5. References


