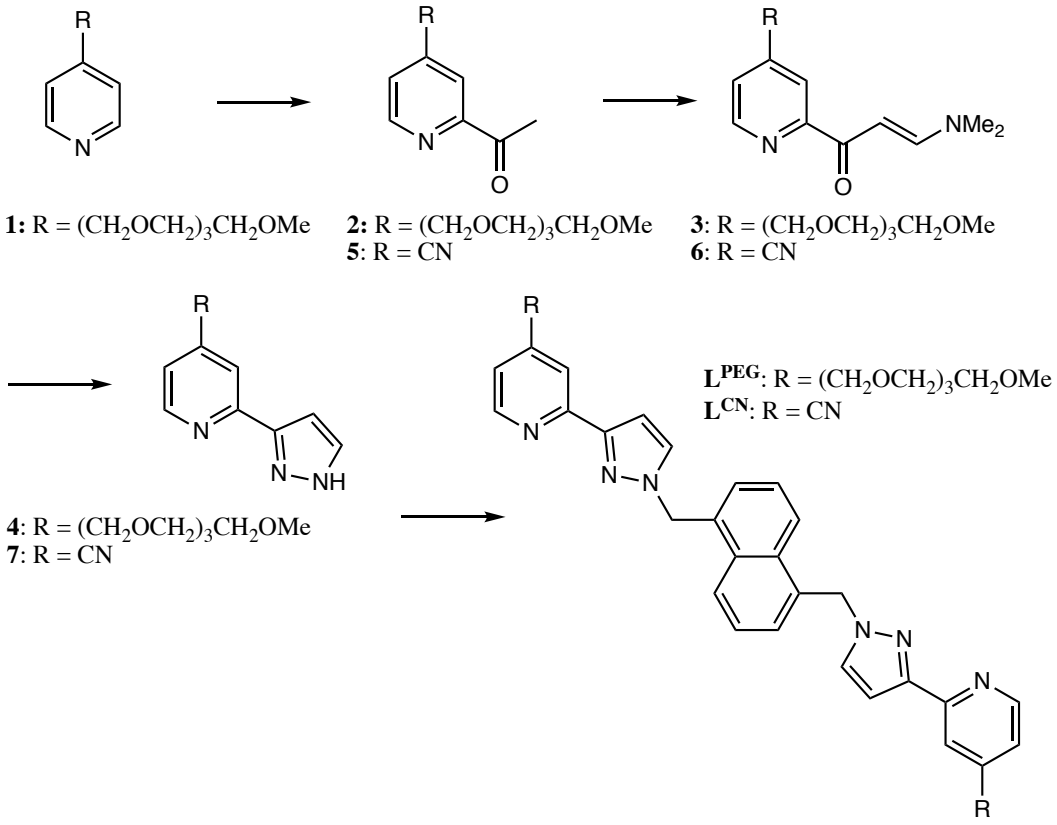
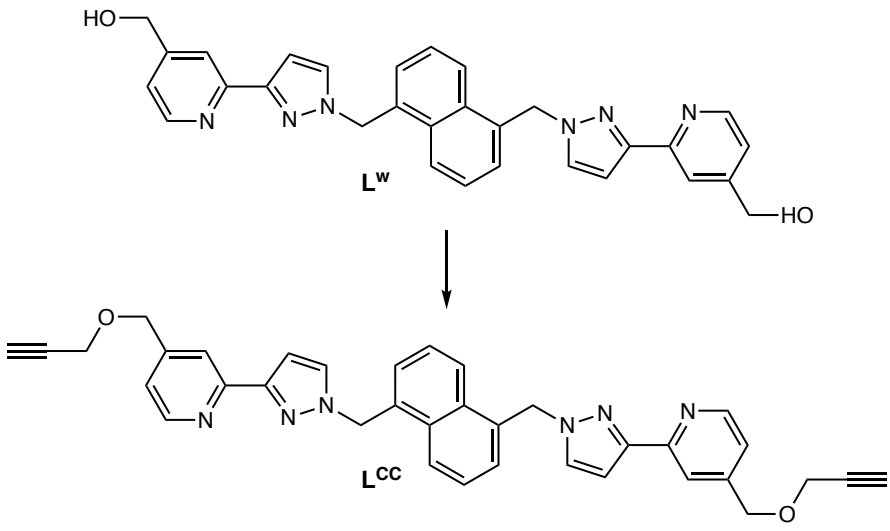
New synthetic routes to externally-functionalised coordination cages

Garrett D. Jackson, Max Tipping, Christopher G. P. Taylor, Jerico R. Piper, Callum Pritchard, Cristina Mozaceanu and Michael D. Ward

Supporting information: synthetic details for ligands and complexes



Scheme S1: Synthetic route to L^{CN} and L^{PEG}



Scheme S2: Synthetic route to L^{CC}

Synthesis of 4-(2,5,8,11-tetraoxadodecyl)pyridine (1)

To a stirred solution of 4-chloromethylpyridine hydrochloride (10.0 g, 61 mmol) in acetonitrile (400 cm^3) under an N_2 atmosphere was added triethylamine (17 cm^3, 122 mmol) and triethyleneglycol monomethylether (12.68 cm^3, 80 mmol). After an hour, NaH (4.9 g, 122 mmol) was added in several small portions and the mixture was stirred at room temperature overnight. Upon reaction completion (followed by TLC), the solution was quenched with methanol, filtered through Celite and concentrated under reduced pressure. Column chromatography on silica, eluting with EtOAc/CH_2Cl_2 (2:3, *v/v*) yielded **1** as an orange oil. Yield: 17.43 g, 56%.

^{1}H-NMR (400 MHz, $CDCl_3$, 298 K): δ 8.53 (2H, dd, J = 4.5 and 1.4 Hz, pyridyl $H^{2/6}$); 7.24 (2H, dd, J = 4.5 and 1.4 Hz, pyridyl $H^{3/5}$); 4.56 (2H, s, $ArCH_2O$); 3.75-3.48 (12H, m, OCH_2CH_2O); 3.35 (3H, s, OMe).

^{13}C-NMR (100 MHz, $CDCl_3$, 298 K): δ 149.8 (pyridyl $C^{2/6}$), 147.8 (pyridyl C^4), 121.9 (pyridyl $C^{3/5}$), 72.0, 71.6, 70.8, 70.7, 70.7, 70.6, 70.3 (CH_2-[-CH_2CH_2O-]$_3$), 59.1 (OCH_3).

ESMS: *m/z* observed, 278.1. Calculated for $C_{15}H_{23}NO_5Na^+$ [$M + Na^+$], 278.1.

ν_{max}/cm^{-1}: 2919s, 2852m, 1715w, 1694w, 1576m, 1465s, 1350m, 1095s, 799w, 720w, 648w.

Synthesis of 1-(4-(2,5,8,11-tetraoxadodecyl)pyridin-2-yl)ethan-1-one (2)

To a biphasic mixture of water (200 cm^3) and CH_2Cl_2 (200 cm^3) was added **1** (17.4 g, 68 mmol), pyruvic acid (14.4 ml, 204 mmol), and ammonium persulphate (31.1 g, 136 mmol). Following the slow addition of silver nitrate (1.2 g, 6.8 mmol), the mixture was warmed to reflux, and monitored by TLC. After 3h the vessel was cooled to room temperature, neutralised with 25% NaOH solution and the product was extracted with DCM (3 x 200 cm^3). The organic layers were combined, dried over $MgSO_4$, and the solvent was removed under reduced pressure. Column chromatography on silica, eluting with EtOAc/CH_2Cl_2 (2:3, *v/v*) yielded **2** as a yellow oil. Yield: 6.90 g, 34%.

^{1}H-NMR (300 MHz, $CDCl_3$, 298 K): δ 8.61 (1H, d, J = 4.9 Hz, pyridyl H^6); 7.95 (1H, s, pyridyl H^3); 7.48 (1H, d, J = 4.9 Hz, pyridyl H^5); 4.62 (2H, s, pyridyl-C**H**$_2$O); 3.73-3.50 (12H, m, OC**H**$_2$C**H**$_2$O); 3.35 (3H, s, OMe); 2.70 (3H, s, $COCH_3$).

^{13}C-NMR (100 MHz, $CDCl_3$, 298 K): δ 200.2 (**C**=O), 153.7 (pyridyl C^2) 149.2 (pyridyl C^6), 149.0 (pyridyl C^4) 125.2 (pyridyl C^5), 119.8 (pyridyl C^3), 72.0, 71.4, 70.8, 70.6, 70.4, 70.3 (**C**H_2-[-**C**H_2**C**H_2O-]$_3$), 59.1 (OMe), 26.0 (CO**C**H_3).

ES-MS: *m/z* observed, 320.2. Calculated for $C_{15}H_{23}NO_5Na^+$ [M + Na^+], 320.2.

ν_{max}/cm^{-1}: 2867m, 1697s, 1601w, 1352m, 1283m, 1185m, 1099s, 840m, 590m.

Synthesis of (*E*)-1-(4-(2,5,8,11-tetraoxadodecyl)pyridin-2-yl)-3-(dimethylamino)prop-2-en-1-one (3)

A solution of **2** (6.90 g, 23 mmol) and *N,N*-dimethylformamide-dimethylacetal (9.3 cm^3, 69 mmol) in toluene (25 cm^3) was heated to reflux overnight. Excess solvents were removed under reduced pressure, leaving product 3 as a brown oil. Yield: 7.90 g, 97%.

^{1}H-NMR (400 MHz, $CDCl_3$, 298 K): δ 8.60 (1H, d, J = 4.9 Hz, pyridyl H^6); 8.06 (1H, s, pyridyl H^3); 7.92 (1H, d, J = 12.8 Hz, C**H**NMe_2); 7.42 (1H, d, J = 4.9 Hz, pyridyl H^5); 6.44 (1H, d, J = 12.8 Hz, C**H**CO); 4.64 (2H, s, pyridyl-C**H**$_2$O); 3.75–3.50 (12H, m, OC**H**$_2$C**H**$_2$O); 3.38 (3H, s, OMe); 3.18 (3H, s, NMe_2); 2.99 (3H, s, NMe_2).

^{13}C-NMR (100 MHz, $CDCl_3$, 298 K): δ 186.9 (**C**=O); 156.3 (pyridyl C^2); 154.9 (**C**HNMe_2); 148.6 (pyridyl C^4); 148.6 (pyridyl C^6), 123.6 (pyridyl C^5); 120.2 (pyridyl C^3); 91.4 (**C**HCO); 72.0, 71.7, 70.8, 70.7, 70.6, 70.6, 70.3 (**C**H_2-[-**C**H_2**C**H_2O-]$_3$-); 59.1 (OMe); 45.2, 37.5 (N(**C**H_3)$_2$).

ES-MS: *m/z* observed, 375.3. Calculated for $C_{18}H_{28}N_2O_5Na^+$ [M + Na^+], 375.2.

ν_{max}/cm^{-1}: 2870m(br), 1642s , 1603w , 1417s, 1468m, 1346s, 1267m, 1095s, 1066s, 988w, 867w, 800w, 730m , 689m.

Synthesis of 4-(2,5,8,11-tetraoxadodecyl)-2-(1H-pyrazol-3-yl)pyridine (4)

A solution of **3** (7.9 g, 22 mmol) and hydrazine monohydrate (22 cm^3, 440 mmol) in ethanol (100 cm^3) was heated to 60°C for 1h. Once at room temperature, the solvent was removed under vacuum and the mixture quenched with water. The product was extracted with CH_2Cl_2 (3 x 50 cm^3) and washed with brine. Subsequently, the organic layers were dried and solvent was removed by rotary evaporation. Purification by column chromatography on alumina (2% *v/v* MeOH in CH_2Cl_2 afforded **4** as a clear orange oil. Yield: 3.46 g, 49%.

^{1}H-NMR (400 MHz, $CDCl_3$, 298 K: δ 12.17 (1H, br s, N**H**); 8.62 (1H, d, J = 5.1 Hz, pyridyl **H^6**); 7.77 (1H, s, pyridyl H^3); 7.66 (1H, d, J = 2.2 Hz, pyrazole H^5); 7.21 (1H, d, J = 5.1 Hz, pyridyl H^5); 6.83 (1H, d, J = 2.2 Hz, pyrazole H^4); 4.62 (2H, s, pyridyl-C**H$_2$**O); 3.73-3.50 (12H, m, OC**H$_2$**C**H$_2$**O); 3.34 (3H, s, OMe).

^{13}C-NMR (100 MHz, $CDCl_3$): δ 149.8 (pyridyl C^2); 149.4 (pyridyl C^6); 148.8 (pyridyl C^4), 145.5 (pyrazole C^3); 136.8 (pyrazole C^5); 120.9 (pyridyl C^5); 118.2 (pyridyl C^3); 103.6 (pyrazole C^4); 72.0, 71.5, 70.7, 70.6, 70.3 (**C**H$_2$-[-**C**H$_2$**C**H$_2$O-]$_3$-); 59.0 (OMe).

ES-MS: *m/z* observed, 344.2. Calculated for $C_{16}H_{23}N_3O_4Na^+$ [M + Na^+], 344.2.

ν_{max}/cm^{-1}: 3182w br, 2870m br , 1607m, 1558w, 1450w, 1352m, 1246w, 1199w, 1093s, 924w, 848m, 779m..

Synthesis of 1,5-bis((3-(4-(2,5,8,11-tetraoxadodecyl)pyridin-2-yl)-1H-pyrazol-1-yl)-methyl)naphthalene (L^{PEG})

To a solution of 1,5-bis(bromomethyl)naphthalene (0.42 g, 1.3 mmol) and **4** (0.90 g, 2.8 mmol) in THF (60 cm^3) was added aqueous NaOH (5.5 M, 5 cm^3, 27.5 mmol) and a catalytic amount of tetrabutylammonium iodide. The mixture was heated to reflux for two days, after which time it was diluted with H_2O (40 cm^3), and the volume was then reduced by 50% *in vacuo*. The product was extracted with CH_2Cl_2 (3 x 50 m^3), dried over $MgSO_4$, and volatiles removed under reduced pressure. Column chromatography of the residue on alumina eluting with 1.5% (*v/v*) EtOH in CH_2Cl_2 afforded L^{PEG} as a brown oil. Yield. 1.36 g, 91%.

^{1}H-NMR (500 MHz, $CDCl_3$, 298 K): δ 8.60 (2H, d, J = 5.0 Hz, pyridyl H^6); 8.03 (2H, d, J = 8.5 Hz, naphthyl $H^{4/8}$); 7.92 (2H, s, pyridyl H^4); 7.48 (2H, t, J = 7.8 Hz, naphthyl $H^{3/7}$); 7.31 (2H, d, J = 6.7 Hz, naphthyl $H^{2/6}$); 7.28-7.23 (4H, m, pyrazole H^4 + pyridyl H^5); 6.89 (2H, d, J = 2.3 Hz, pyrazole H^4); 5.86 (4H, s, pyridyl-C**H$_2$**N); 4.63 (4H, s, pyridyl-C**H$_2$**O); 3.75-3.50 (24H, m, OC**H$_2$C H$_2$**O); 3.35 (6H, s, OMe).

^{13}C-NMR (125 MHz, $CDCl_3$): δ 152.0 (pyridyl C^2); 151.4 (pyrazole C^3); 149.3 (pyridyl C^6); 148.6 (pyridyl C^4); 132.3 (naphthyl **$C^{1/5}$** or **$C^{9/10}$**); 131.7 (naphthyl **$C^{9/10}$** or **$C^{1/5}$**), 130.9 (pyrazole C^5); 127.4 (naphthyl $C^{2/6}$); 126.5 (naphthyl $C^{3/7}$); 124.3, (naphthyl $C^{4/8}$); 120.7 (pyridyl C^5); 118.3 (pyridyl C^3); 105.2 (pyrazole C^4); 71.9, 71.7, 70.6, 70.2 (**C**H_2-[-**C**H_2**C**H_2O-]$_3$-), 59.0 (O**Me**), 54.7 (pyridyl-**C**H_2N).

High-resolution ES-MS: *m/z* observed, 795.4052. Calculated for $C_{44}H_{55}N_6O_8^+$ [M + H^+], 795.4076. Observed, 817.3878. Calculated for $C_{44}H_{54}N_6O_8Na^+$ [M + Na^+], 817.3895.

ν_{max}/cm^{-1}: 2867m (br), 1606m, 1558w, 1492w, 1468w, 1413w, 1351w, 1327w, 1281w, 1247w, 1197w. 1099s, 1046m, 995w, 854w. 789m, 774m, 753w

Synthesis of $[Co_8(L^{PEG})_{12}(BF_4)_{16}$ $[Co•H^{PEG}]$

Cobalt(II) tetrafluoroborate hexahydrate (128 mg, 309 μmol) and L^{PEG} (400 mg, 506 μmol) were stirred in methanol (15 cm^3) and warmed to 60°C overnight. Following cooling to room temperature, the solvent was removed under reduced pressure and the cage purified on G-50 Sephadex eluting with water yielding a brown solid. Yield: 290 mg, 61%.

High resolution ES-MS: *m/z* 2763.0835 ($[Co_8(L^{PEG})_{12}(BF_4)_{12}]^{4+}$), 2193.0709 ($[Co_8(L^{PEG})_{12}(BF_4)_{11}]^{5+}$), 1813.0548 ($[Co_8(L^{PEG})_{12}(BF_4)_{10}]^{6+}$), 1541.6179 ($[Co_8(L^{PEG})_{12}(BF_4)_9]^{7+}$), 1338.0409 ($[Co_8(L^{PEG})_{12}(BF_4)_8]^{8+}$).

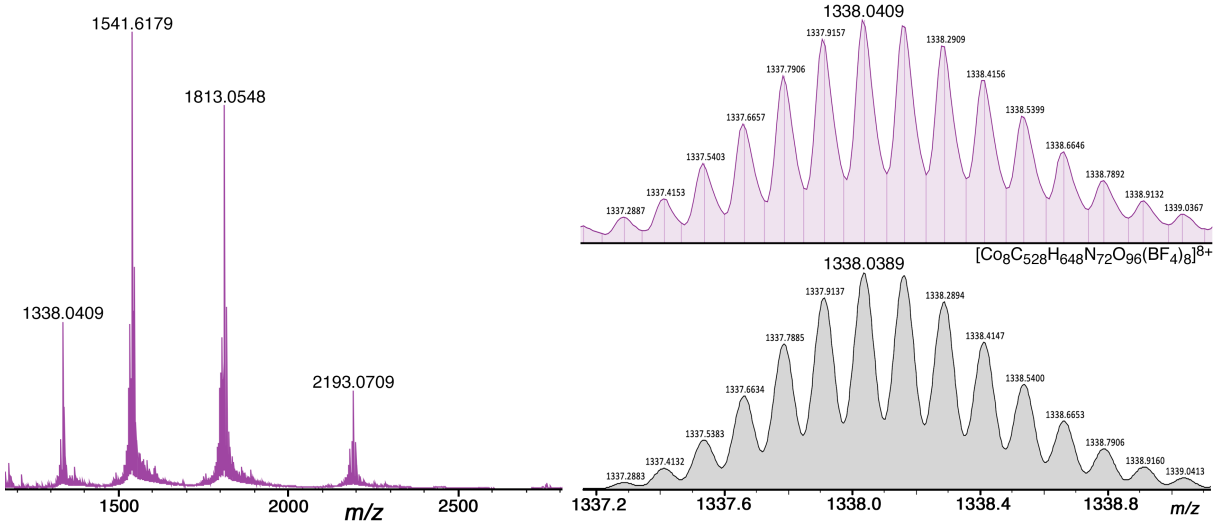


Fig. S1. *High-resolution ES MS of $[Co_8(L^{PEG})_{12}](BF_4)_{16}$: left, the sequence of main peaks for intact cage with successive loss of counter-ions; right, expansion of the peak at m/z 1338.0409 for $[Co_8(L^{PEG})_{12}(BF_4)_8]^{8+}$, showing observed (top) and calculated (bottom) isotope pattern.*

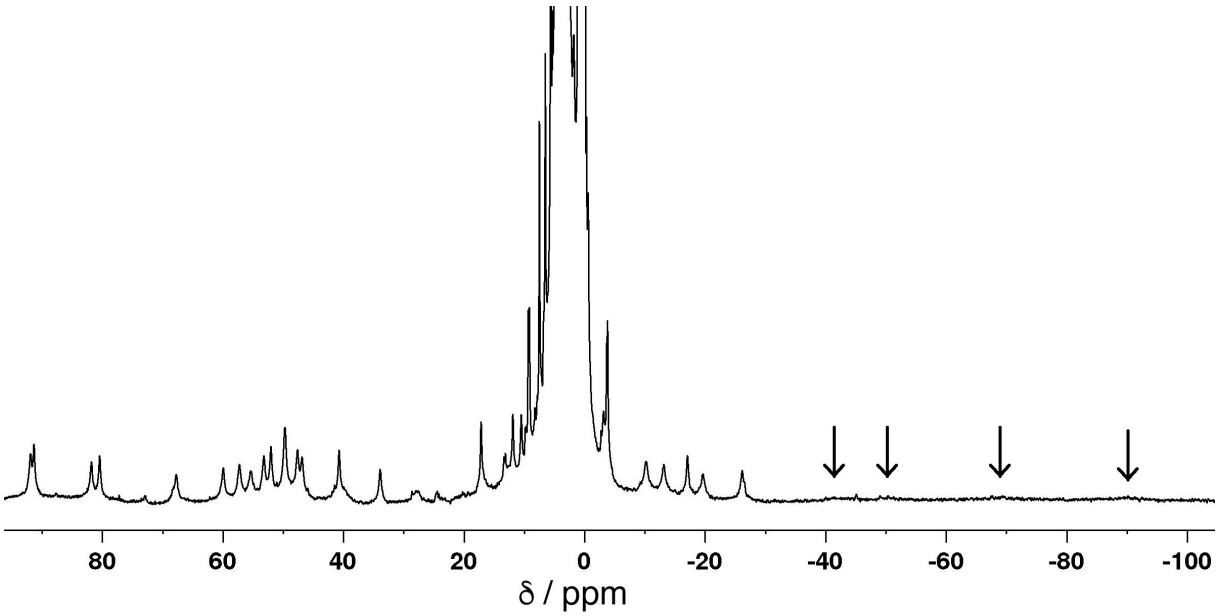


Fig. S2*. ^1H NMR spectrum of $[Co_8(L^{PEG})_{12}](BF_4)_{16}$ (D_2O, RT, 300 MHz). The signals are broadened beyond the effects of the paramagnetism by the PEG-ylation of the cage which results in slow tumbling in solution. The expected four very broad signals characteristic of these Co(II) cubic cages (refs. 29 and 35 in main text), between –40 and –90 ppm, are shown with arrows.*

Synthesis of $[Cd_8(L^{PEG})_{12}](NO_3)_{16}$ $[Cd{\bullet}H^{PEG}]$

This was prepared exactly as above for the Co(II) complex, but using cadmium(II) nitrate tetrahydrate (120 mg, 309 µmol), forming a yellow solid. Yield**:** 285 mg, 59%.

High resolution ES-MS: *m/z* 2224.1881 ($[Cd_8(L^{PEG})_{12}(NO_3)_{11}]^{5+}$), 1843.1583 ($[Cd_8(L^{PEG})_{12}(NO_3)_{10}]^{6+}$), 1570.9953 ($[Cd_8(L^{PEG})_{12}(NO_3)_9]^{7+}$), 1366.8731 ($[Cd_8(L^{PEG})_{12}(NO_3)_8]^{8+}$).

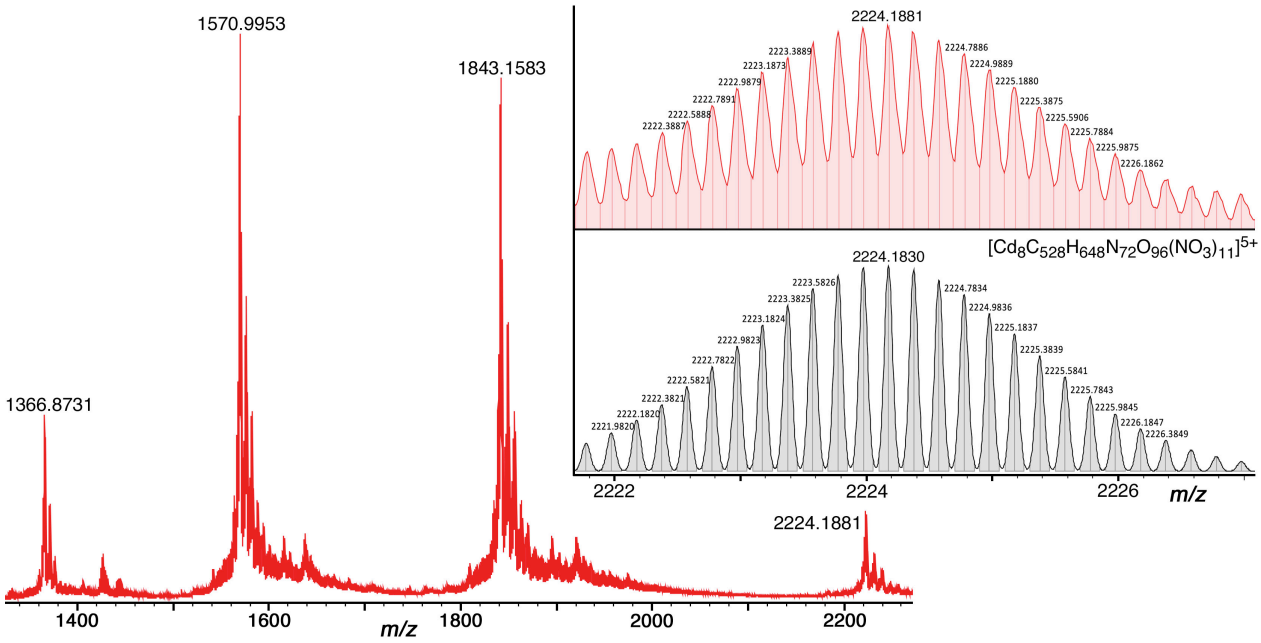


Fig. S3. *High-resolution ES MS of $[Cd_8(L^{PEG})_{12}](NO_3)_{16}$: left, the sequence of main peaks for intact cage with successive loss of counter-ions; right, expansion of the peak at m/z 2224.1881 for $[Cd_8(L^{PEG})_{12}(NO_3)_{11}]^{5+}$, showing observed (top) and calculated (bottom) isotope patterns.*

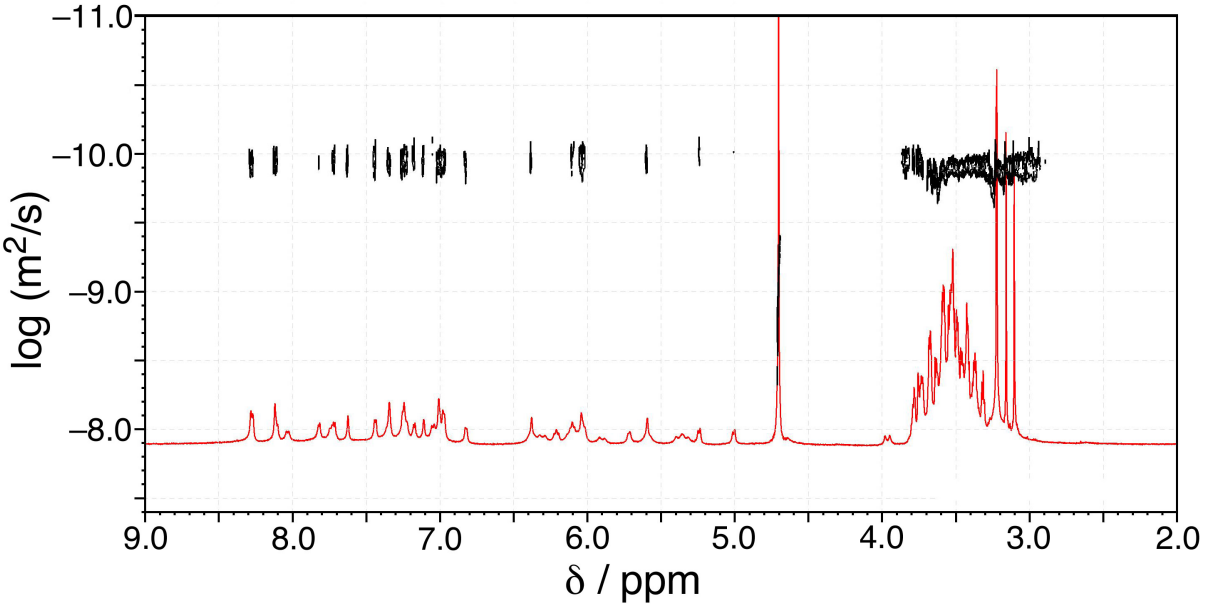


Fig S4. *^{1}H NMR (red) and DOSY (block) spectra of $[Cd_8(L^{PEG})_{12}](NO_3)_{16}$ (D_2O, RT). The broadness of the NMR signals arises from the PEG-ylation of the cage which results in slow tumbling in solution, precluding assignment of individual signals, but the DOSY spectrum confirms that a single species is present.*

Synthesis of 1-(2-(4-cyanopyridyl)-3-dimethylamino-2-propen-1-one (6)

A solution of 2-acetylpyridine-4-carbonitrile, compound **5** (4.00 g, 27.4 mmol) and *N,N*-dimethylformamide dimethylacetal (7.34 g, 61.6 mmol, 2.2 equiv) in toluene (60 cm^3) was heated to reflux for 24 h, during which time a dark brown colour developed. After cooling to room temperature, the solvents were removed under vacuum to yield a brown solid. The solid was washed with a mixture of light petroleum/Et_2O (100 cm^3: 3:1, *v/v*) and then dried under high vacuum. Yield: 4.74 g, 23.6 mmol, 86%.

^{1}H NMR (500 MHz, $CDCl_3$, 298K): δ 8.77 (1H, dd, *J* = 4.9, 0.8 Hz, pyridine H^6); 8.37 (1H, s, pyridine H^3); 7.95 (1H, d, *J* =12.6 Hz, alkene C**H**–NMe_2); 7.56 (1H, dd, *J* = 4.9, 1.6 Hz, pyridine H^5); 6.41 (1H, d, *J* = 12.6 Hz, alkene C(O)–C**H**); 3.21 (3H, s, methyl); 3.01 (3H, s, methyl).

^{13}C NMR (125 MHz, $CDCl_3$, 298K): δ 162.3 (**C**=O); 157.4 (pyridine C^2); 155.5 (alkene **C**H-NMe_2); 149.1 (pyridine C^6); 126.3 (pyridine C^5); 123.9 (pyridine C^3); 121.2 (pyridine C^4), 116.5 (nitrile **C**N), 90.5 (alkene C(O)–**C**H), 45.4 (*N*-methyl), 37.6 (*N*-methyl).

High resolution ES-MS: *m/z* observed 224.0794. Calculated for $C_{11}H_{11}N_3NaO$ $[M + Na]^+$, 224.0794.

Elemental analysis. Calcd. for $C_{11}H_{11}N_3O$: C, 65.7; H 5.5; N 20.9%. Found: C, 65.5; H, 5.4; N, 20.9%.

ν_{max}/cm^{-1}: 3079w, 3053w, 2914w, 2865w, 2806w, 2242w, 1641s, 1593m, 1542s, 1420s, 1349s, 1255s, 1072s.

Synthesis of 2-(1H-pyrazol-3-yl)isonicotinonitrile (7)

To a solution of (*E*)-2-(3-(dimethylamino)acryloyl)isonicotinonitrile, **6** (7.85 g, 39.0 mmol) in EtOH (60 cm^3) was added hydrazine monohydrate (1.95 g, 39.0 mmol, 1.0 equiv) was added in one portion and the entire solution was heated to 60 °C for 1 h, during which time it developed a red colour. After cooling to room temperature, the solvent was evaporated to give a sticky orange solid. Addition of CH_2Cl_2 (100 cm^3) and water (50 cm^3) precipitated out a beige solid, which was filtered off and dried under vacuum. The organic phase was then washed with H_2O (80 cm^3) and dried over $MgSO_4$ and the solvent evaporated. The product was then purified on an alumina column (Brockmann activity III), eluting using CH_2Cl_2/MeOH (98:2), and was isolated as a light-yellow powder which was dried under vacuum. Yield: 5.48 g, 32.2 mmol, 83%.

^{1}H NMR (500 MHz, $CDCl_3$, 298K): δ 8.78 (1H, d, J = 5.0 Hz, pyridine H^6); 8.08 (1H, s, pyridine H^3); 7.69 (1H, d, J = 2.2 Hz, pyrazole H^4); 7.43 (1H, dd, J = 5, 1.3 Hz, pyridine H^5); 6.93 (1H, d, J = 2.2 Hz, pyrazole H^5).

^{13}C NMR (125 MHz, $CDCl_3$, 298K): δ 156.7 (pyridine C^2); 150.4 (pyridine C^6); 145.4 (pyrazole C^3); 134.4 (pyrazole C^5); 123.7 (pyrdine C^5); 121.7 (pyridine C^3); 121.2 (pyridine C^4), 116.5 (nitrile **C**N), 104.4 (pyrazole C^4).

High resolution ES-MS: *m/z* observed 171.0666. Calculated for $C_9H_7N_4$ $[M + H]^+$, found 171.0665.

Elemental analysis. Calcd. for $C_9H_6N_4$•$0.8H_2O$: C, 58.6; H, 4.2; N, 30.4%. Found: C, 58.8; H, 4.50; N 30.3%.

ν_{max}/cm^{-1}: 3124w, 3041w, 2953w, 2901w, 2839w, 2239w, 1602m, 1554m, 1387m, 774s.

Synthesis of L^{CN}

2-(1H-pyrazol-3-yl)isonicotinonitrile (2.01 g, 11.8 mmol, 2.5 equiv) was carefully added to a stirred suspension of 90 wt% NaH (0.567 g, 14.2 mmol, 3.0 equiv) in dry THF (200 cm^3) under N_2 over a 20 min period, with vigorous effervescence being observed. The resulting yellow suspension was then heated to reflux for 1 h before slowly adding to it a solution of 1,5-bis(bromomethyl)naphthalene (1.48 g, 4.72 mmol, 1.0 equiv) in dry THF (150 cm^3), affording a bright orange suspension. The mixture was then refluxed under nitrogen for 18 h, after which the vessel was cooled to RT and then placed in an ice bath before slow addition of MeOH over a 20 min period. The resulting brown suspension was filtered off over celite®, from which it was separated by dissolution in CH_2Cl_2 (300 cm^3) which was then removed by evaporation. The crude product was purified using on a silica column using gradient elution with CH_2Cl_2/MeOH (gradually changing from from 99:1 to 98:3 *v/v*) to yield $\mathbf{L^{CN}}$ as a beige powder. Yield: 1.16 g, 2.36 mmol, 50%.

^{1}H NMR ($CDCl_3$, 500 MHz, 298K): δ 8.75 (2H, d, J = 5.0 Hz, pyridine H^6); 8.23 (2H, s, pyridine H^3), 8.07 (2H, d, J = 8.6 Hz, pyridine H^5), 7.53 – 7.50 (2H, m, napthyl H^3), 7.39 – 7.36 (4H, m, naphthyl H^2 and H^4), 7.31 (2H, d, J = 2.3 Hz, pyrazole H^5), 6.89 (2H, d, J = 2.3 Hz, pyrazole H^4), 5.86 (4H, s, CH_2).

^{13}C NMR ($CDCl_3$, 125 MHz, 298K): δ 153.6 (pyridyl C^2); 150.3 (pyridyl C^6), 150.0 (pyrazolyl C^3); 132.1 (naphthyl $C^{1/5}$); 131.8 (naphthyl $C^{9/10}$); 131.3 (pyrazolyl C^5); 127.6 (naphthyl $C^{3/7}$); 126.6 (pyridyl C^3); 124.5 (pyridyl C^5); 123.2 (naphthyl $C^{4/8}$), 121.9 (naphthyl $C^{2/6}$); 120.9 (pyridyl C^4); 116.7 (nitrile **C**N); 105.5 (pyrazolyl C^4), 54.9 (CH_2).

High resolution ES-MS: *m/z* observed 493.1886; calculated for $C_{30}H_{21}N_8$ $[M + H]^+$, 493.1885.

Elemental analysis. Calcd. for $C_{30}H_{20}N_8 \bullet H_2O$: C, 70.6; H, 4.3; N, 22.0. Found: C, 70.4, H, 4.4; N, 21.6%.

ν_{max}/cm^{-1}: 3126m, 3050m, 2906m, 2842m, 2775m, 2240w, 1664w, 1602m, 1555m, 1389s, 832m, 774s.

Synthesis of $[Cd_8(L^{CN})_{12}](BF_4)_{16}$ [Cd•H^{CN}]

A glass vial was charged with the nitrile ligand **L^{CN}** (34 mg, 0.068 mmol, 1.6 equiv), $Cd(BF_4)_2$•$6H_2O$ (12.2 mg, 0.043 mmol, 1.0 equiv) and MeOH (8 ml). This mixture was then placed within a Teflon liner and sealed within a solvothermal bomb apparatus, which was then heated to 120 °C at a rate of 0.1 °C min^{-1}: this temperature was sustained over a 12h period. The vessel was then cooled to RT at a rate of 0.1 °C min^{-1}. The resulting solid was separated by centrifugation and then washed sequentially with cold MeOH, cold CH_2Cl_2 and cold Et_2O. The final off-white fine powder was dried under high vacuum for 6 h and was analysed by ESI-MS. Yield: 37.1 mg, 0.0045 mmol, 85%. Single crystals for X-ray crystallographic analysis were grown by diffusion of di(isopropyl) ether vapour into a solution of the complex in MeCN.

High resolution ES-MS: *m/z* 1552.8919 $\{[Cd_8(L^{CN})_{12}](BF_4)_{11}\}^{5+}$; 1279.5803 $\{[Cd_8(L^{CN})_{12}](BF_4)_{10}\}^{6+}$; 1084.2118 $\{[Cd_8(L^{CN})_{12}](BF_4)_9\}^{7+}$; 938.1855 $\{[Cd_8(L^{CN})_{12}](BF_4)_8\}^{8+}$.

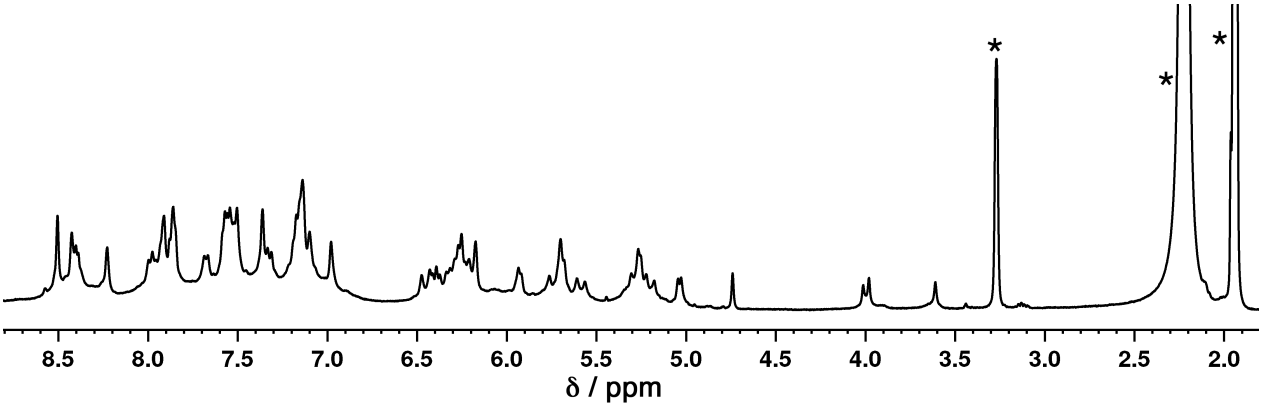


***Fig S5**. ^{1}H NMR spectrum of $[Cd_8(L^{CN})_{12}](BF_4)_{16}$ (CD_3CN, RT). The broadness of the NMR signals arises from the PEG-ylation of the cage which results in slow tumbling in solution, precluding assignment of individual signals. Signals labelled * are residual solvents (from left: MeOH, water, MeCN).*

This complex was also characterised by single-crystal X-ray crystallography: see main text.

Synthesis of 1,5-bis((3-(4-((prop-2-yn-1-yloxy)methyl)pyridin-2-yl)-1H-pyrazol-1-yl)methyl)naphthalene (L^{CC})

NaH (0.22 g, 5.472 mmol, 60 wt. % dispersion in mineral oil) and 15-crown-5 (0.43 cm^3, 2.189 mmol) were added to a flame dried two neck RBF charged with dry THF (50 cm^3): the mixture was stirred for 30 mins under N_2. To this suspension, a solution of $\mathbf{L^w}$ (0.55 g, 1.094 mmol) in dry THF (100 cm^3) was transferred *via* cannula and the resulting suspension was refluxed for 2 h before the addition of propargyl bromide (0.37 cm^3, 3.282 mmol, 80 wt. % in toluene) with an instant colour change to brown observed. The mixture was refluxed for 72 h, with a darker brown colour developing over time. Once cooled to room temperature, the reaction was quenched with the addition of MeOH (50 cm^3) and the solvents evaporated to give a brown oil. The mineral oil was removed by filtration through a celite®/CH_2Cl_2 plug. The crude product was then purified through an alumina column (Brockmann activity III) using CH_2Cl_2/MeOH (98:2) as eluent to remove unreacted starting material and a silica column using CH_2Cl_2/MeOH (96:4) as eluent to remove crown ether impurities. Yield: 0.580 g, 1.002 mmol, 92% (orange solid).

^{1}H-NMR (300 MHz, $CDCl_3$, 298K): δ 8.55 (2H, d, J = 5.1 Hz, pyridyl H^6); 7.97 (2H, d, J = 8.6 Hz, naphthyl $H^{4/8}$); 7.91 (2H, s, pyridyl H^3); 7.45-7.40 (2H, dt, J = 8.4, 7.1 Hz, naphthyl $H^{3/7}$); 7.26 (2H, d, J = 7.0 Hz, naphthyl $H^{2/6}$); 7.20-7.16 (4H, m, pyrazole H^5 + pyridyl H^5); 6.87 (2H, s, pyrazole H^4); 5.80 (4H, s, pyridyl-C**H_2**N); 4.61 (4H, s, pyridyl-C**H_2**O); 4.20 (4H, d, J = 2.4 Hz, CH_2-O-C**H_2**-C≡C); 2.43 (2H, t, J = 2.38 Hz, CH_2-C≡**H**).

^{13}C-NMR (100 MHz, $CDCl_3$, 298K): δ 152.3 (pyridyl C^2); 151.5 (pyrazole C^3); 149.6 (pyridyl C^6); 147.3 (pyridyl C^4); 132.4 (naphthyl $C^{1/5}$ or $C^{9/10}$); 131.7 (naphthyl $C^{9/10}$ or $C^{1/5}$), 130.9 (pyrazole C^5); 127.3 (naphthyl $C^{2/6}$); 126.5 (naphthyl $C^{3/7}$); 124.3 (naphthyl $C^{4/8}$); 120.8 (pyridyl C^5); 118.4 (pyridyl C^3); 105.1 (pyrazole C^4); 75.2 (**C**≡H), 70.0 (pyridyl-**C**H_2O), 57.9 (CH_2-O-**C**H_2-C≡C), 54.7 (pyridyl-**C**H_2N).

High-resolution ES-MS: *m/z* observed, 579.2502. Calculated for $C_{36}H_{31}N_6O_2^+$ [M + H^+], 579.2503. Observed, 601.2323. Calculated for $C_{36}H_{30}N_6O_2Na^+$ [M + Na^+], 601.2322.

ν_{max}/cm^{-1}: 3216w, 2925w, 2899w, 2860w, 2109w, 1607m, 1325m, 1095m, 1087m, 792m, 777s.

Synthesis of $[Ni_8(L^{CC})_{12}](BF_4)_{16}$ [Ni•H^{CC}]

A glass vial was carefully charged with the alkyne-substituted ligand $\mathbf{L}^{CC}$ (80 mg, 0.138 mmol, 1.5 equiv), $Ni(BF_4)_2.6H_2O$ (31.4 mg, 0.00922 mmol, 1.0 equiv) and MeOH (6 cm^3). This mixture was then placed within a Teflon liner and sealed within a solvothermal bomb apparatus, which was then heated to 120 °C at a rate of 0.1 °C min^{-1} and then sustained at this temperature over a 12 h period. The vessel was then cooled at a rate of 0.1 °C min^{-1} to r.t. to facilitate crystallisation. The resulting solid was then washed sequentially with cold MeOH, cold CH_2Cl_2, cold Et_2O and was finally separated by centrifugation. The final beige powder was dried under high vacuum for 2 h and then analysed by ESI-MS (below). Yield: 78.4 mg, 77%. Single crystals for X-ray crystallographic analysis were grown by vapour diffusion of diisopropyl ether into a solution of the complex in DMF.

High resolution ES-MS: *m/z* 1380.7444$\{[Ni_8(L^{CC})_{12}](BF_4)_{10}\}^{6+}$; 1171.2040 $\{[Ni_8(L^{CC})_{12}](BF_4)_9\}^{7+}$; 1013.3048$\{[Ni_8(L^{CC})_{12}](BF_4)_8\}^{8+}$.

This complex was also characterised by single-crystal X-ray crystallography: see main text.