Diastereoselective Synthesis of *O* Symmetric Heterometallic Cubic Cages

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Contents

I. Physical measurements

The C, H, N microanalyses were carried out with a CE instruments EA 1110 elemental analyzer. The FT-IR spectra were recorded from KBr pellets in the range 4000-400 cm^{-1} with a Nicolet AVATAR FT-IR360 spectrometer. UV-Vis spectra were recorded on a Varian Cary5000 UV-VIS-NIR Spectrophotometer. Circular dichroism (CD) was measured using a Jasco J-810 spectrodichrometer. NMR data were recorded on a Bruker Avance II spectrometer (400 MHz) and Avance III (500 MHz). Mass spectra were recorded on a Bruker AccuTOF CS JMS-T100CS (ESI-TOF) and a Bruker En Apex ultra 7.0T Fourier-transform ion cyclotron resonance mass spectrometer (FT-ICR-MS).

II . X-ray Crystallography.

Diffraction data were collected on an Agilent SuperNova X-Ray diffractometer at 100K using micro-focus X-ray sources (Cu Kα, λ = 1.54184 Å for **1a**, **1a**, **2**). The crystals were fragile and easily lost solvent molecules. TGA spectra of crystalline samples of **1a** and **2** (Figure S28 & S29) confirmed that they have lots of cocrystallized solvents. Thus rapid handing of the samples was needed. Absorption corrections were applied by using the program CrysAlis (multi-scan). The structures were solved by direct methods. Non-hydrogen atoms except counteranions were refined anisotropically by least-squares on F^2 using the SHELXTL program. The hydrogen atoms of organic ligands were generated geometrically. Due to the large unit cell and small size of crystals, the diffractions were relatively weak. Not all the counter-anions were found because of the weak data and high symmetry. Especially for **1a** and **1b**, only eight capsulated tetrafluoroborate anions were located and refined. The correct chemical formula reported in CIF took the undefined counter-ions into consideration for charge balance. This resulted in three false A level alerts in checkCIF warning that the calculated and reported molecular weights have large difference. The crystals have large solvent accessible voids since a large number of disordered solvent molecules and counter-anions were not resolved. Thus SQUEEZE routines in PLATON were employed in the structural refinements.

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III. Synthesis

All reagents employed were commercially available and used without further purification. The solvents used were of analytical grade.

Synthesis of ligand $\mathbf{L^1}$:

Cs_2CO_3 (4.3 g, 13.2 mmol), $Pd(PPh_3)_4$ (1.0 g, 0.87 mmol), 4-pyridineboronic acid pinacol ester (2.7 g, 13.1 mmol), and 5-bromo-2-formylpyridine (2.05 g, 11.0 mmol) were added stepwise into a 500 mL schlenk flask. THF (200 mL) was poured into the flask to make a suspension, and then N_2 was pumped into the suspension for 5 minutes. The mixture was refluxed at 68 ℃ for 36 h in a nitrogen atmosphere in the absence of light. The reaction was stopped by adding water (100 mL) into it. Then the resulting solution was extracted with EtOAc (3 × 120 mL). The combined organic layers were dried with anhydrous Na_2SO_4. The final solution was concentrated under reduced pressure to give a brown solid, which was purified by flash column chromatography on silica gel (EtOAc : hexane = 1:1) to afford 1.75g (86.5% yield) target product as a white power.

^{1}H NMR (500.2 MHz, CD_3CN, ppm): δ10.09 (s, H = 1), 9.14 (s, H = 1), 8.74 (d, J = 5.5 Hz, H = 2), 8.28 (d, J = 8.0 Hz, H = 1), 8.06 (d, J = 8.0 Hz, H = 1), 7.72 (d, J = 5.0 Hz, H = 2). ^{13}C NMR (125.8 MHz, CD_3CN, ppm): δ193.10, 152.84, 150.61, 148.74, 143.81, 137.51, 135.82, 121.81, 121.61. FT-ICR-MS (positive mode, CH_3OH, m/z): calculated for $[\mathbf{L^1}+H]^+$: 185.07094, found: 185.07092. Anal. Calcd. for $C_{11}N_2H_8O$ (%): C 71.73, H 4.38, N 15.21. Found: C 71.78, H 4.59, N 14.81. IR (KBr, cm^{-1}): ν1699.1 (br, C=O).

Synthesis of cage **1a** and **1b**:

$\mathbf{L^1}$ (50 mg, 271.7 μmol) was dissolved with 10 mL acetonitrile, S-1-phenylethylamine (34.7 μL, 271.7 μmol) was injected into the solution. The mixture was refluxed at 70℃ for 3 h to give ligand $\mathbf{L^2}$. After cooling to room temperature, zinc tetrafluoroborate hexahydrate (31.4 mg, 90.6 μmol) was added. Then the solution was stirred for 6 h before tetrakis(acetonitrile)palladium(II) tetrafluoroborate (30.2 mg, 67.9 μmol) was added. The resultant yellow solution was further stirred overnight then filtrated. The filtrate was transferred to thin tubes, and diethyl ether was layered on them. After several days, pale yellow crystals of **1a** were collected.Yield:ca.80%. Cage **1b** (the enantiomer of **1a**) was prepared in the similar manner by used R-1-phenylethylamine instead.

Note: The synthesis of **1** can be simplified to a two-step preparation. After $\mathbf{L^2}$ or $\mathbf{L^3}$ is formed from the condensation of $\mathbf{L^1}$ with a chiral amine *in situ*, $Zn(BF_4)_2$ and $Pd(BF_4)_2$ are added simultaneously. The cubic cage product can also be isolated in high yield. However, one pot reaction of $\mathbf{L^1}$, amine and metal salts leads to the formation of a mixture even at a much longer reaction time, which is indicated by the complicated ^{1}H NMR spectrum. More than one species are formed in the one-pot preparation as the formylpyridine of $\mathbf{L^1}$ may compete in the coordination with metal ions.

^{1}H NMR (500.2 MHz, CD_3CN, ppm): δ8.51 (d, J = 6.5 Hz, H = 48), 8.48 (s, H = 24), 8.03 (d, J = 8.0 Hz, H = 24), 7.97(s, H = 24), 7.81 (d, J = 6.5 Hz, H = 48), 7.40 (d, J = 8.0 Hz, H = 24), 7.19 (t, J = 7.5 Hz, H = 24), 7.04 (t, J = 8.0 Hz, H = 48), 6.70 (d, J = 7.5 Hz, H = 48), 5.43 (q, J = 6.0 Hz, H = 24), 1.76 (d, J = 6.5 Hz, H = 72). ^{13}C NMR (125.8 MHz, CD$_3$CN, ppm): δ162.62, 151.71, 147.14, 146.96, 146.24, 140.85, 140.37, 136.32, 130.59, 129.10, 127.91, 125.80, 125.52, 64.13, 23.11. ESI-MS (positive mode, CH$_3$CN, m/z): calculated for [**1a**-10BF$_4$]$^{10+}$: 962.0334, found: 962.0334; calculated for [**1a**-9BF$_4$]$^{9+}$: 1078.5931, found: 1078.5930; calculated for [**1a**-8BF$_4$]$^{8+}$: 1224.2928, found: 1224.2973; calculated for [**1a**-7BF$_4$]$^{7+}$: 1411.4781, found: 1411.4807; calculated for [**1a**-6BF$_4$]$^{6+}$: 1661.2251, found: 1661.2247. Anal. Calcd. for $C_{456}H_{408}B_{28}F_{112}N_{72}Pd_6Zn_8\ (H_2O)_{40}$ (%): C 48.86, H 4.39, N 9.00. Found: C 49.03, H 4.75, N 9.05. IR (KBr, cm^{-1}): υ1617.7 (br, C=N).

Synthesis of cage **2**：

Crystals of cage **2** were prepared in similar process to cage **1a** or **1b**, by substituting S-1-phenylethylamine to equivalent 4-toluidine solid. Bright yellow crystals of **2** were obtained in two weeks. Yield: 50%.

^{1}H NMR (500.2 MHz, CD$_3$CN, ppm): δ8.57 (d, J = 6.5 Hz, H = 48), 8.53 (s, H = 24), 8.51 (s, H = 24), 8.48 (d, J = 8.5 Hz, H = 24), 8.25 (d, J = 8.5 Hz, H = 24), 8.03 (d, J = 6.5 Hz, H = 48), 7.12 (d, J = 8.0 Hz, H = 48), 6.17 (d, J = 8.0 Hz, H = 48), 2.35 (s, H = 72). ^{13}C NMR (125.8 MHz, CD$_3$CN, ppm): δ163.20, 151.72, 147.93, 147.45, 147.24, 144.30, 141.76, 139.07, 137.73, 130.65, 129.99, 126.26, 121.33, 20.03. ESI-MS (positive mode, CH$_3$CN, m/z): calculated for [**2**-10BF$_4$]$^{10+}$: 928.3957, found: 928.4038; calculated for [**2**-9BF$_4$]$^{9+}$: 1041.2179, found: 1041.2267; calculated for [**2**-8BF$_4$]$^{8+}$: 1182.1208, found: 1181.1317. Anal. Calcd. for $C_{432}H_{360}B_{28}F_{112}N_{72}Pd_6Zn_8\ (H_2O)_{45}$ (%): C 47.33, H 4.14, N 9.20. Found: C 47.46, H 4.24, N 9.13. IR (KBr, cm^{-1}): υ1619.7 (br, C=N).

Synthesis of ligand **L^5**：

4-Ethynylpyridine hydrochloride (1.50 g, 10.75 mmol), 5-bromo-2-formylpyridine (2.39 g, 12.9 mmol), triphenylphosphine(71mg, 0.27 mmol), PdCl$_2$(PPh$_3$)$_2$ (377 mg, 0.54 mmol) and cuprous iodide (52mg 0.27 mmol) were mixed together in a 500 mL schlenk flask, then the flask were sparged with N$_2$. 150 mL THF was injected into the mixture, followed by adding 4.48 mL triethylamine. The resultant solution was refluxed at 50 ℃. The reaction was monitored by TLC and cooled to room temperature on completion. The solution was diluted with 1:1 hexane and ethyl acetate 150 mL, and washed with 100 mL water for twice. The organic layer was dried over anhydrous sodium sulfate. Solvents were removed under reduce pressure. Pure yellow solid product (1.20 g) was obtained after chromatography. Yield: 53.7%.

^{1}H NMR (500.2 MHz, CD$_3$CN, ppm): δ10.05 (s, H = 1), 8.97 (s, H = 1), 8.67 (d, J = 6.0 Hz, H = 2), 8.14 (d, J = 8.0 Hz, H = 1), 7.98 (d, J = 9.0 Hz, H = 1), 7.52 (d, J = 6.0 Hz, H = 2). ^{13}C NMR (125.8 MHz, CD$_3$CN, ppm): δ192.72, 152.58, 151.79, 150.13, 140.08, 126.04, 125.44, 123.30, 121.05, 92.11, 89.13. FT-ICR-MS (positive mode, CH$_3$OH, m/z): calculated for [**L^5**+H]$^+$: 209.07094, found: 209.07098. Anal. Calcd. for $C_{13}N_2H_8O$ (%): C 74.99, H 3.87, N 13.45. Found: C 75.44, H 4.03, N 13.62. IR (KBr, cm^{-1}): υ1701.1 (br, C=O).

Synthesis of cage **3**:

The synthesis process is similar to that of cage **1a** using **L^5** instead of **L^1**. The filtration was added diethyl ether to precipitate the crude product. Yield: ca. 80%.

^{1}H NMR (500.2 MHz, CD_3CN, ppm): δ8.62 (d, J = 6.0 Hz, H = 48), 8.36 (s, H = 24), 8.16 (d, J = 8.5 Hz, H = 24), 7.94 (s, H = 24), 7.63 (d, J = 6.5 Hz, H = 48), 7.43 (d, J = 8.0 Hz, H = 24), 7.18 (t, J = 7.5 Hz, H = 24), 7.03 (t, J = 7.5 Hz, H = 48), 6.69 (d, J = 8.0 Hz, H = 48). ^{13}C NMR (100 MHz, CD_3CN, ppm): δ162.08, 151.74, 145.61, 143.68, 140.44, 134.59, 129.55, 129.12, 128.85, 127.96, 126.92, 125.56, 123.40, 92.67, 90.68, 64.44, 22.82. ESI-MS (positive mode, CH_3CN, m/z): only fragment. Anal. Calcd. for $C_{504}H_{408}B_{28}F_{112}N_{72}Pd_6Zn_8$ $(H_2O)_{65}$ (%): C 49.47, H 4.43, N 8.24. Found: C 49.25, H 4.22, N 8.12. IR (KBr, cm^{-1}): υ1612.3 (br, C=N).

IV. Supporting figures

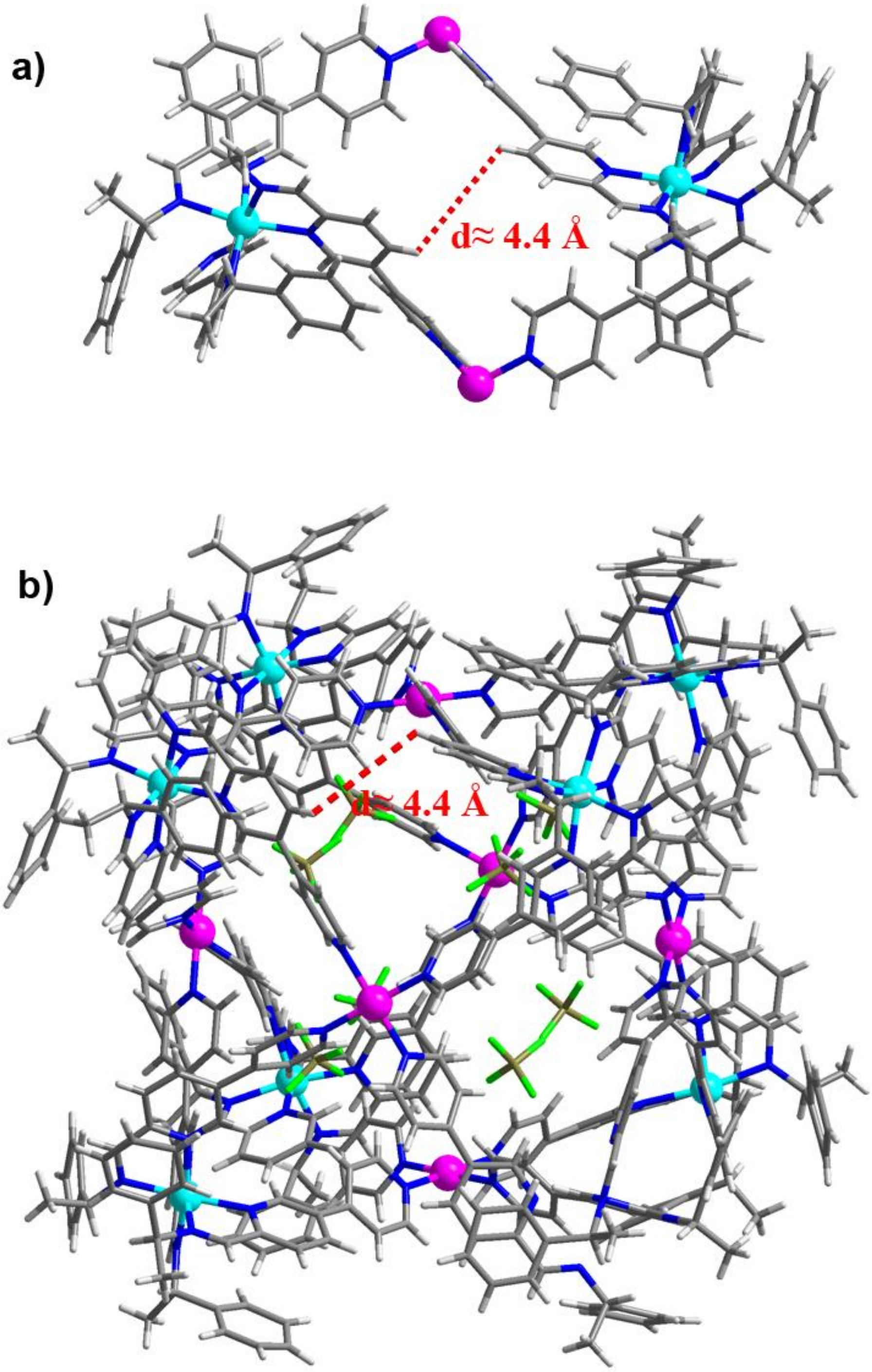

Figure S1. A) Rhombus window (d ≈ 4.4 Å) on the edges of the cube **1a**. B) Molecular structure **1a** with the eight tetrafluoroborate anions enclosed.

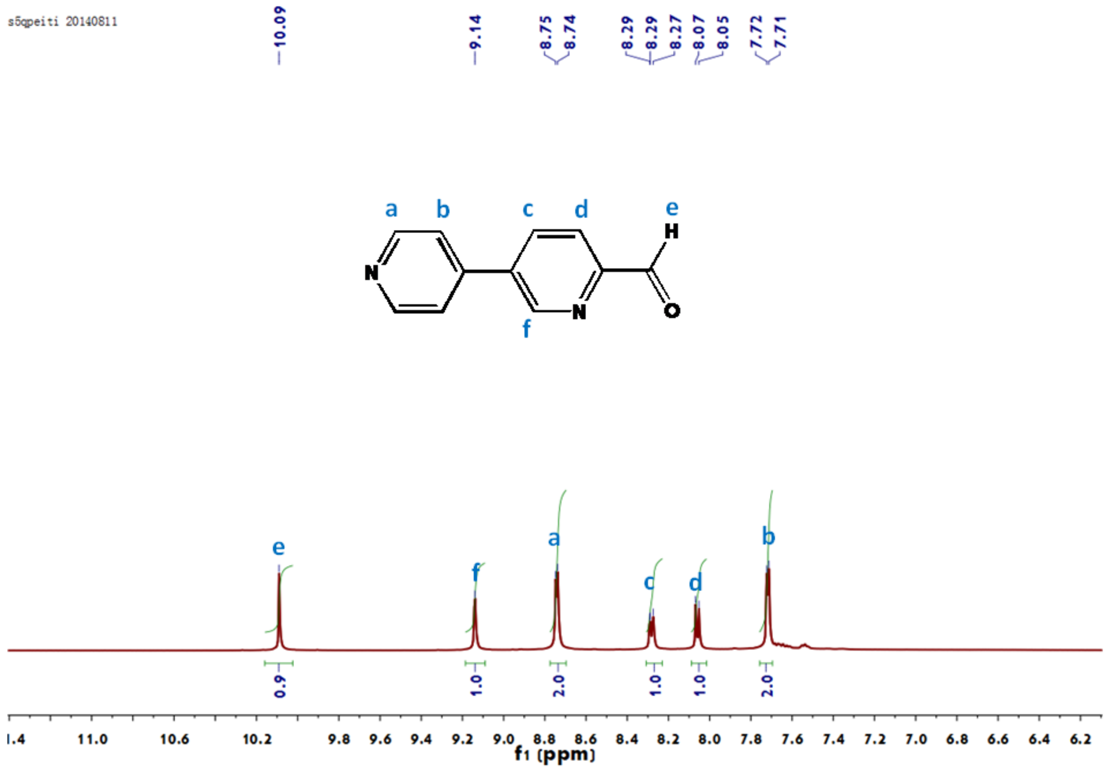

Figure S2. ^{1}H NMR **(**500.2 MHz**)** spectrum of $\mathbf{L^1}$ in CD_3CN

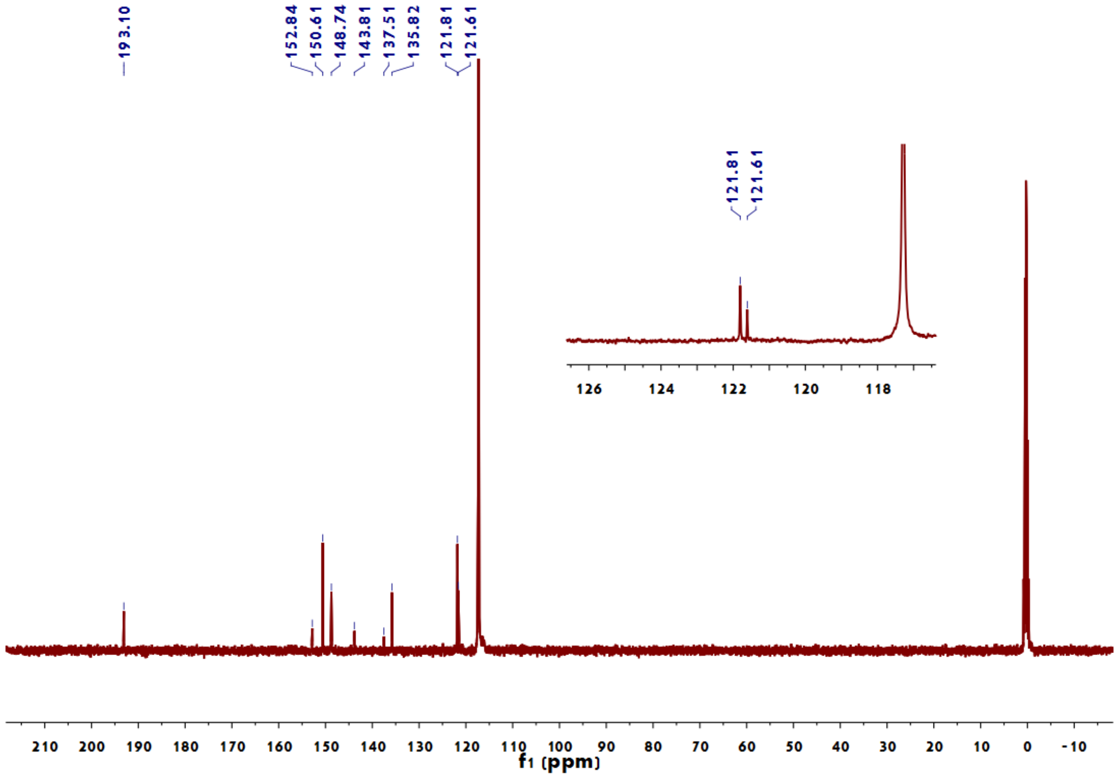

Figure S3. ^{13}C NMR (125.8 MHz) spectrum of $\mathbf{L^1}$ in CD_3CN.

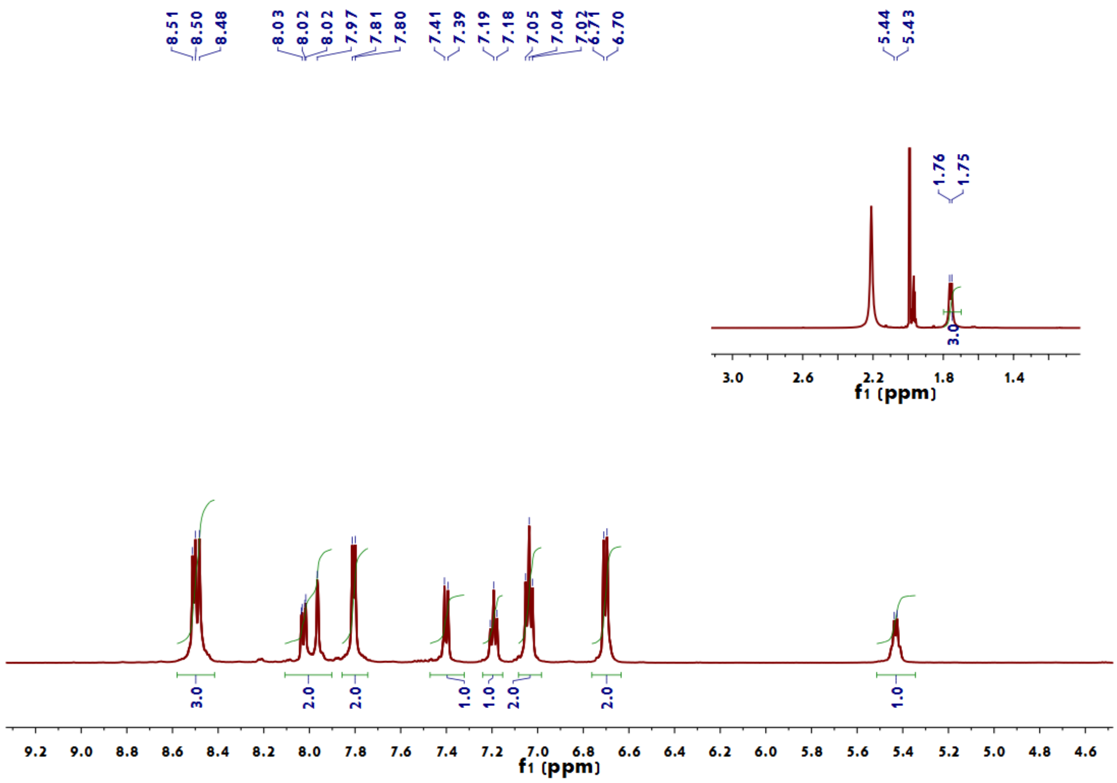

Figure S4. ^{1}H NMR **(**500.2 MHz**)** spectrum of **1a** in CD_3CN.

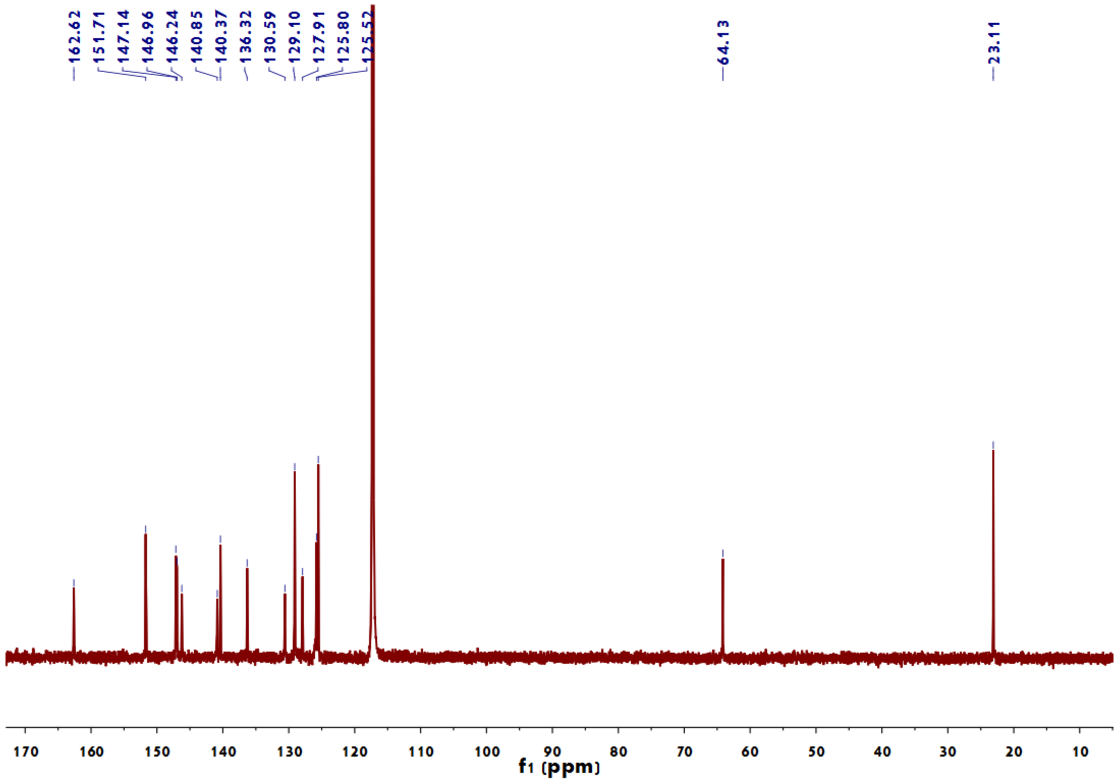

Figure S5. ^{13}C NMR (125.8 MHz) spectrum of **1a** in CD_3CN.

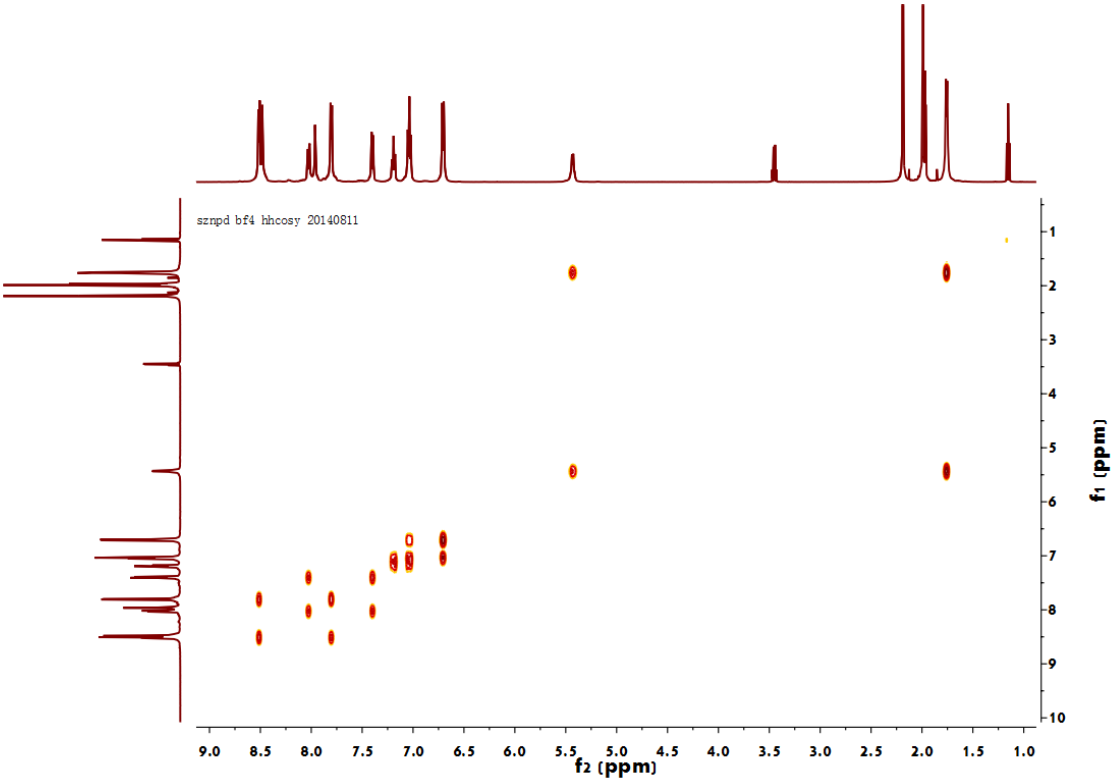

Figure S6. 2D H-H COSY NMR (500.2 MHz) spectrum of **1a** in CD_3CN.

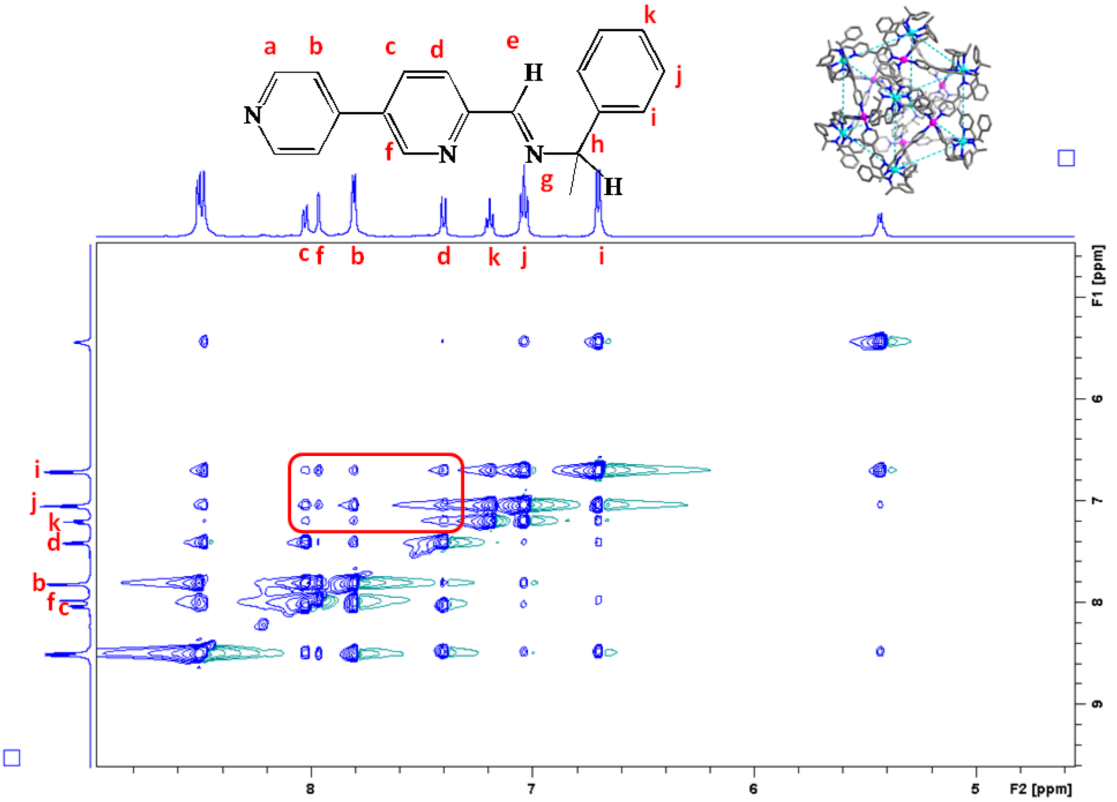

Figure S7. NOEXY NMR (500.2 MHz) spectrum of **1a** in CD_3CN, the red box shows the NOE effects between the phenyl ring and the hydrogen of adjacent pyridine unit.

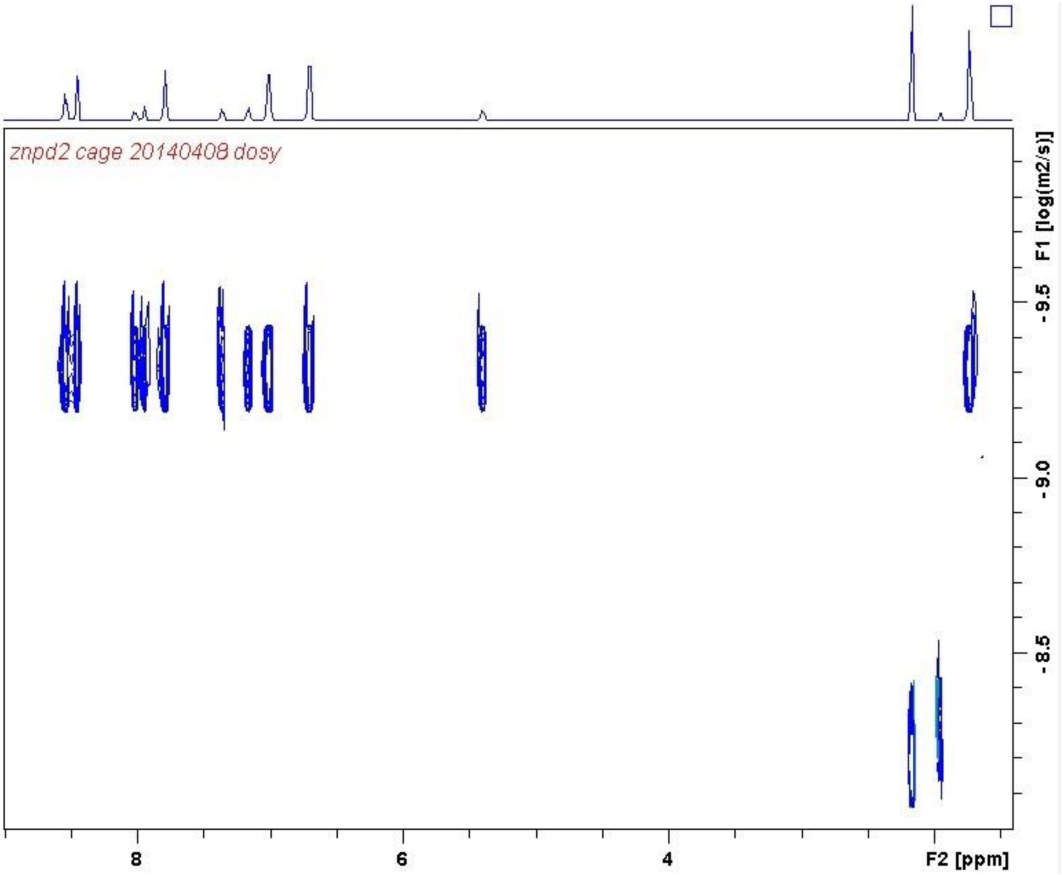

Figure S8. 2D Diffusion Ordered Spectroscopy (DOSY) NMR (500.2 MHz, 298K) spectrum of **1a** in CD_3CN. Average diffusion coefficient $D = 4.0\times10^{-10}$ m^2/s. According to the Stockes-Einstein equation $r = (K_B*T) / (6\pi*\eta*D)$, the dynamic radius is calculated to be about 16 Å.

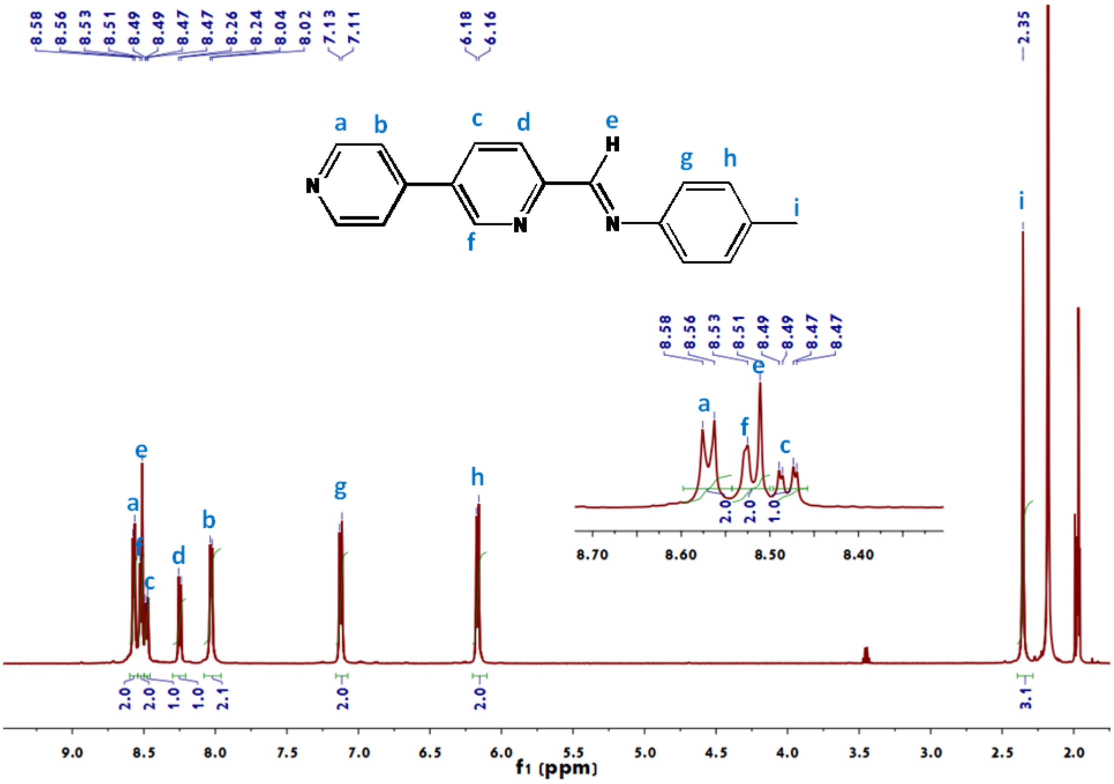

Figure S9. ^{1}H NMR **(**500.2 MHz**)** spectrum of **2** in CD_3CN.

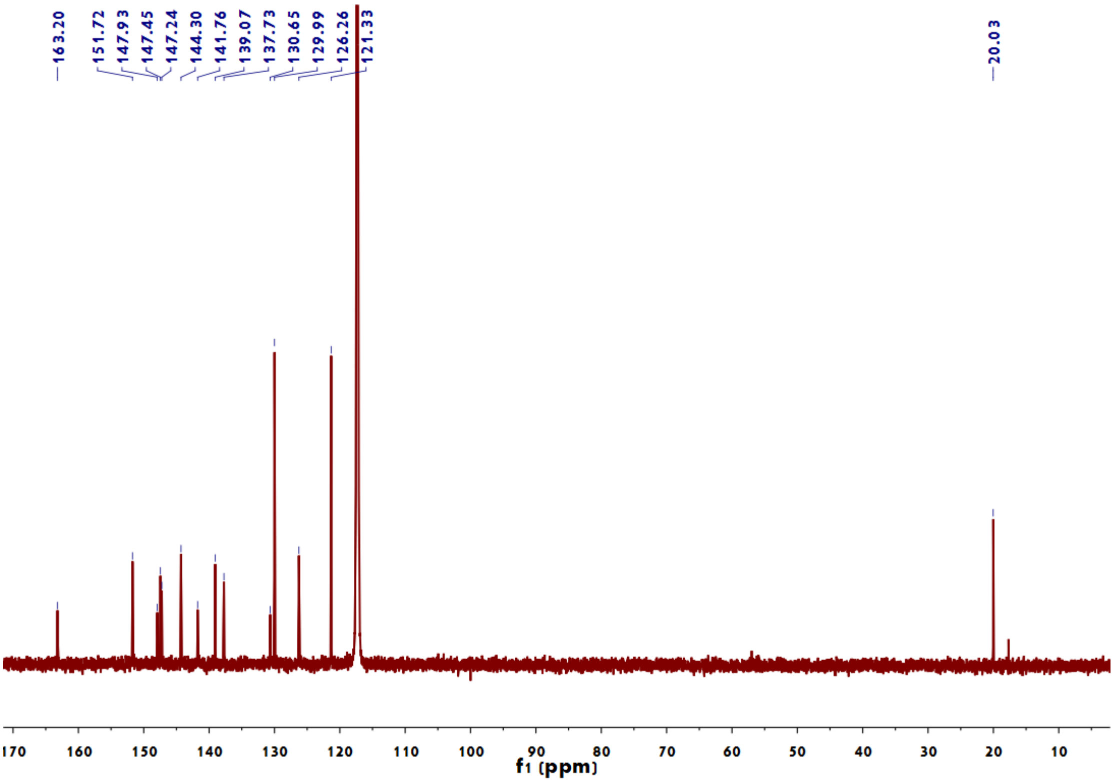

Figure S10. ^{13}C NMR (125.8 MHz) spectrum of **2** in CD_3CN.

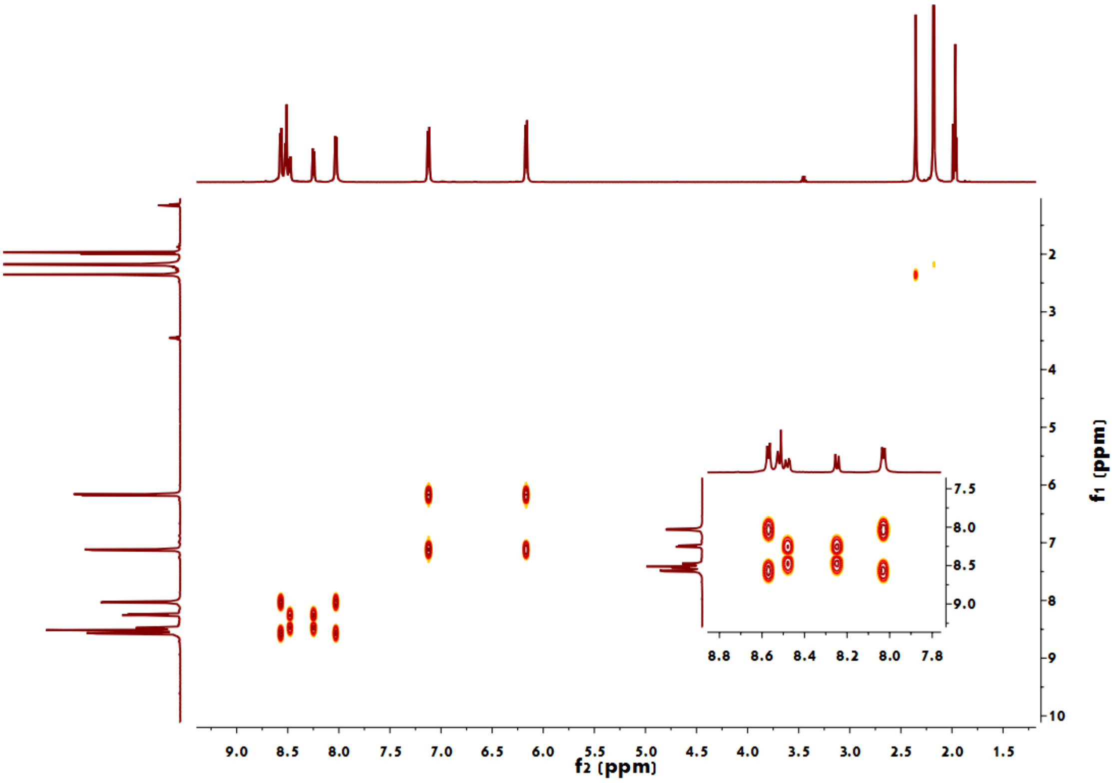

Figure S11. 2D H-H COSY NMR (500.2 MHz) spectrum of **2** in CD_3CN.

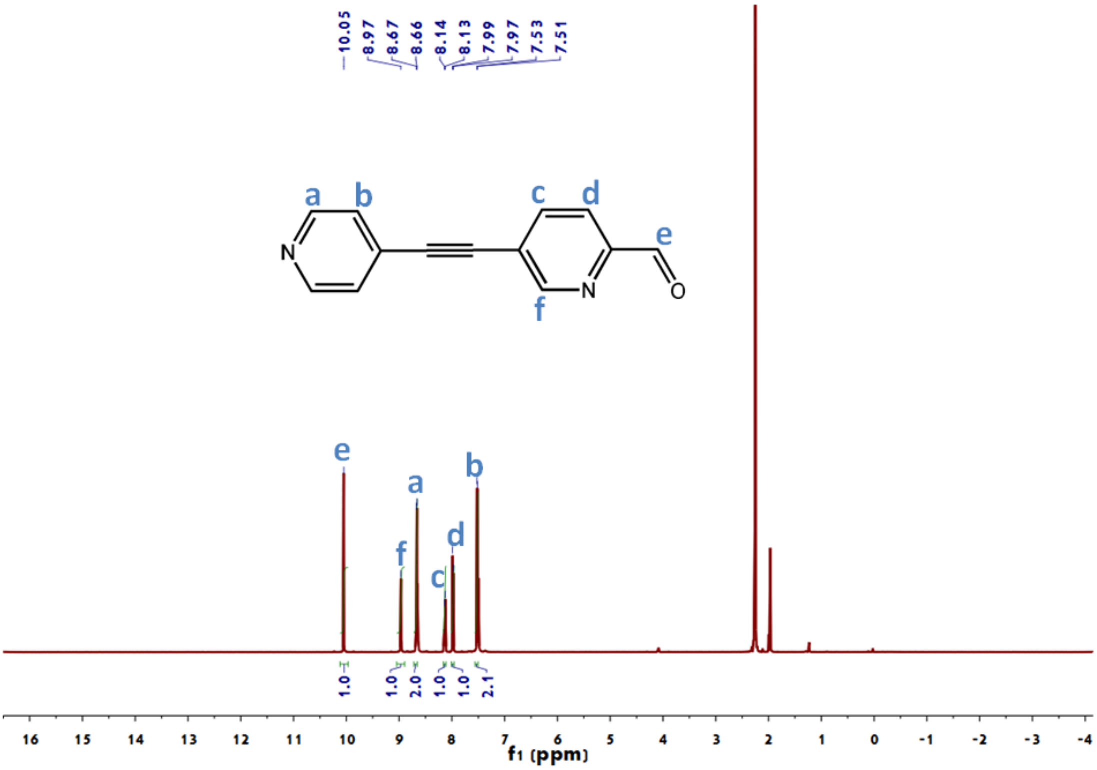

Figure S12. ^{1}H NMR (500.2 MHz) spectrum of $\mathbf{L^5}$ in CD_3CN.

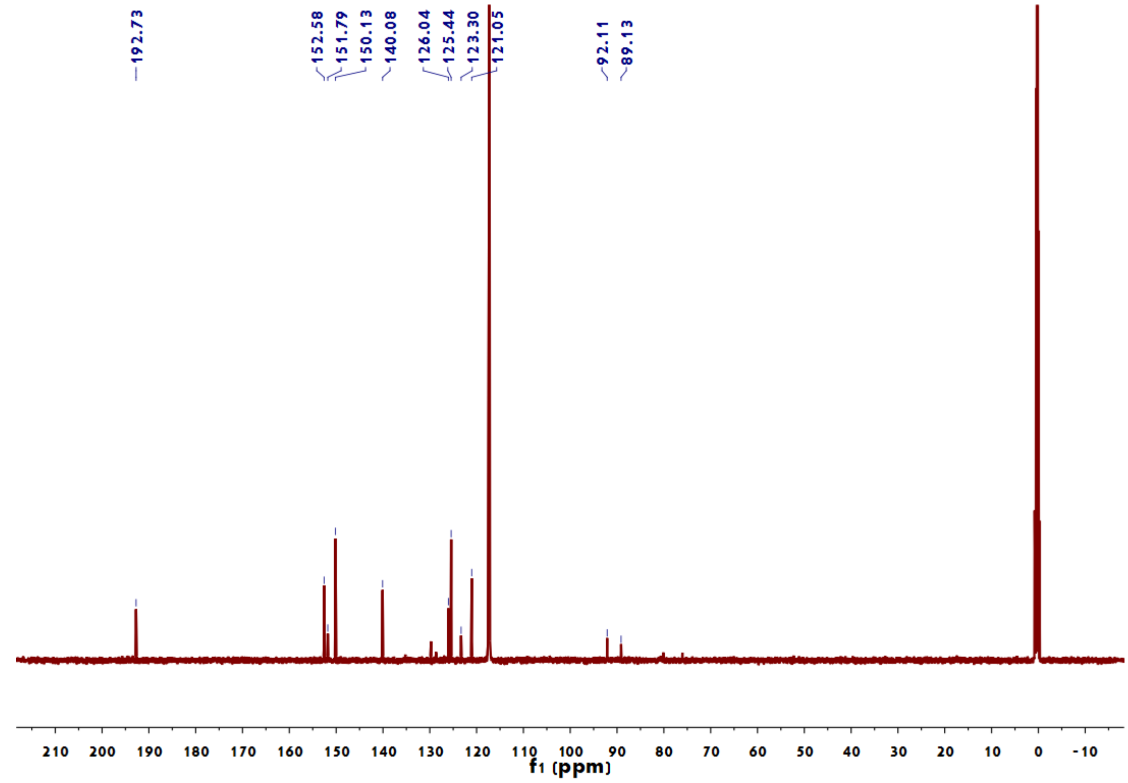

Figure S13. ^{13}C NMR (125.8 MHz) spectrum of $\mathbf{L^5}$ in CD_3CN.

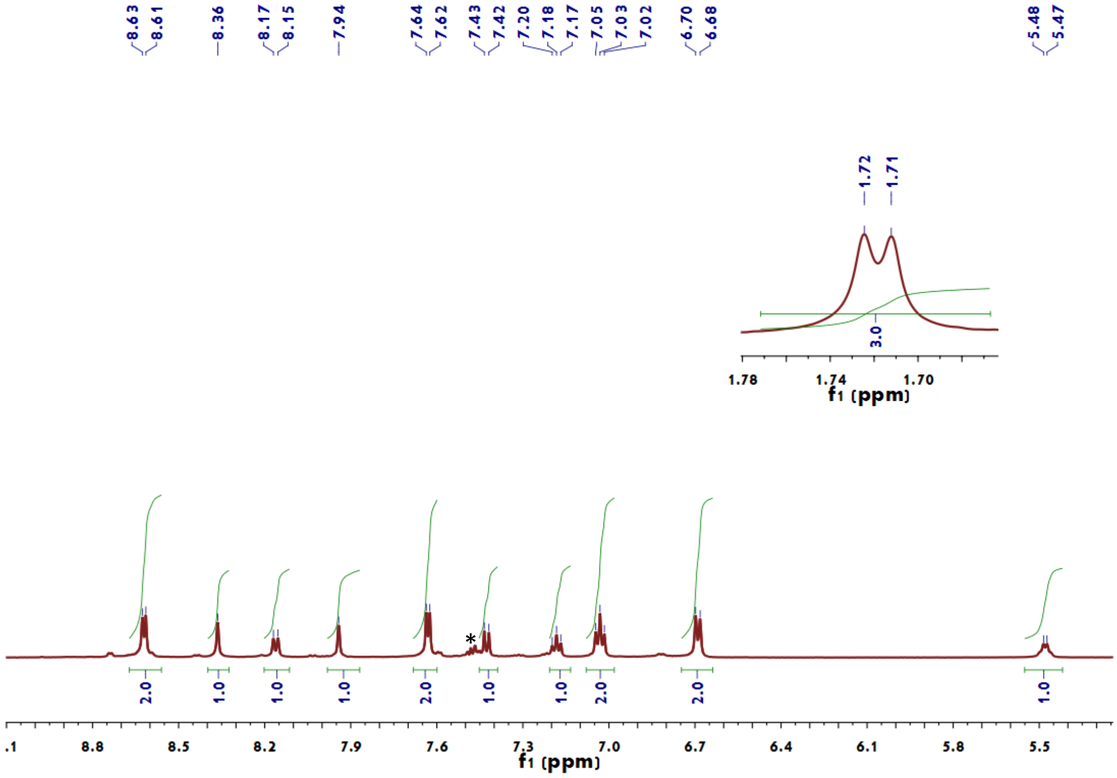

Figure S14. ^{1}H NMR (500.2 MHz) spectrum of **3** in CD_3CN. The excess S-1-phenylethylamine is marked with *.

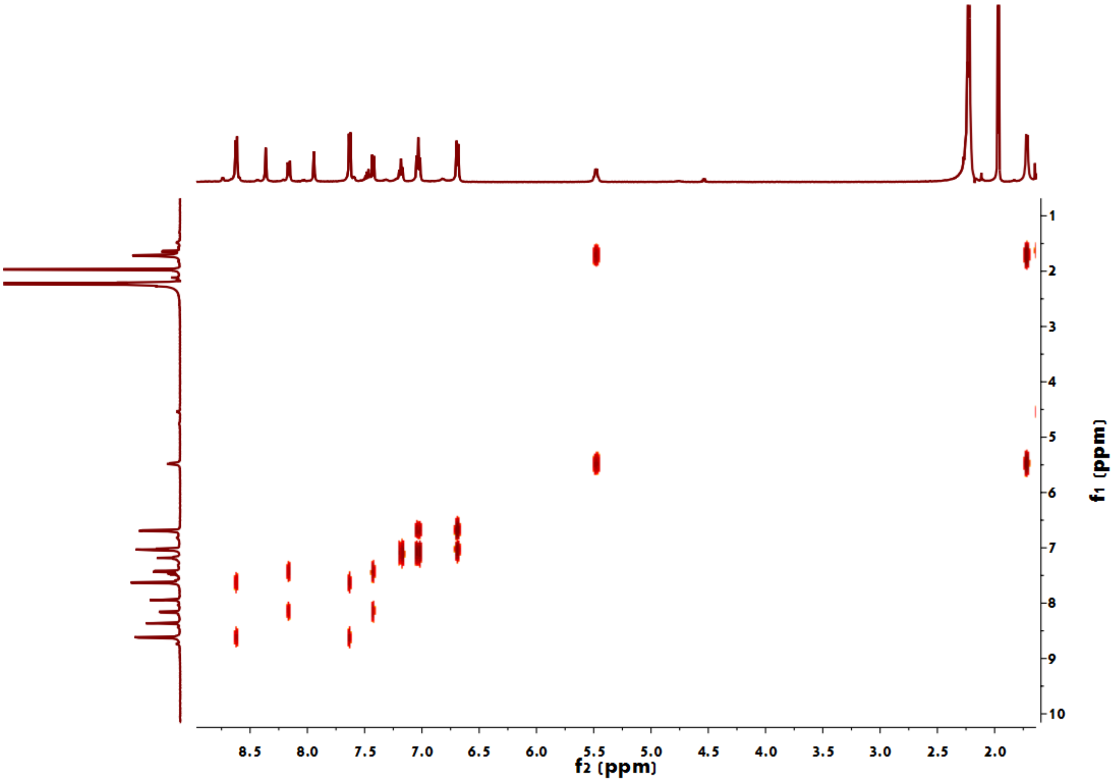

Figure S15. 2D H-H COSY NMR (500.2 MHz) spectrum of **3** in CD_3CN.

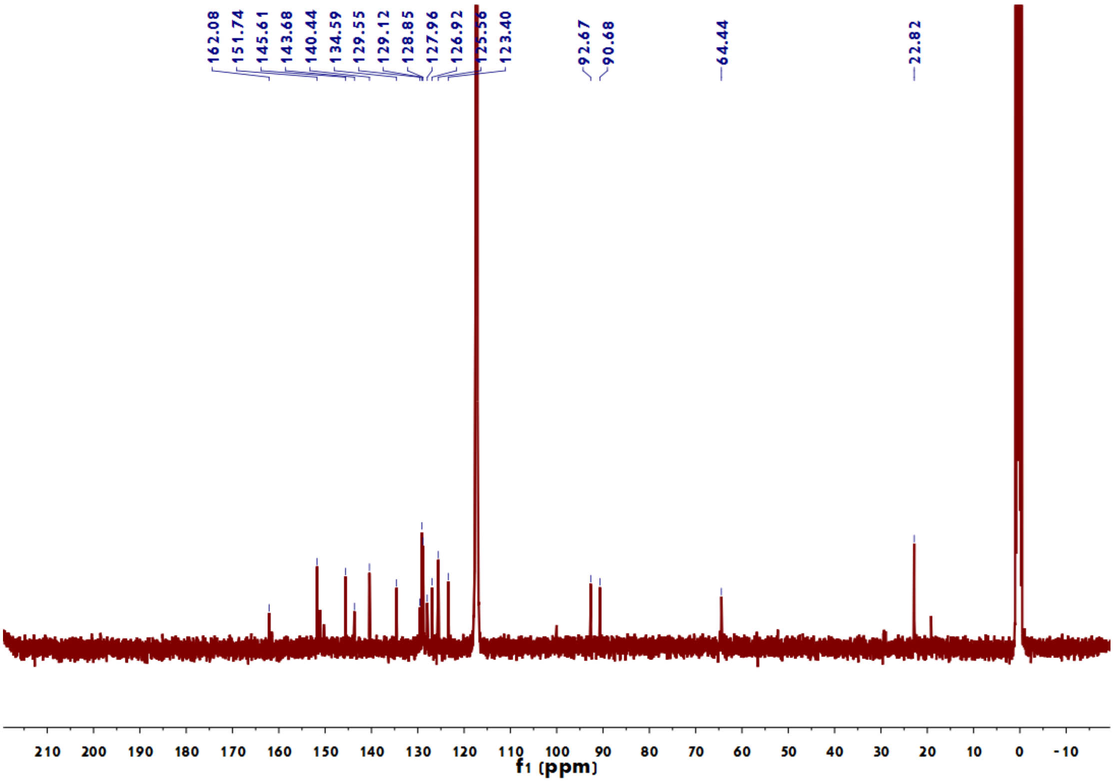

Figure S16. ^{13}C NMR (100 MHz) spectrum of **3** in CD_3CN.

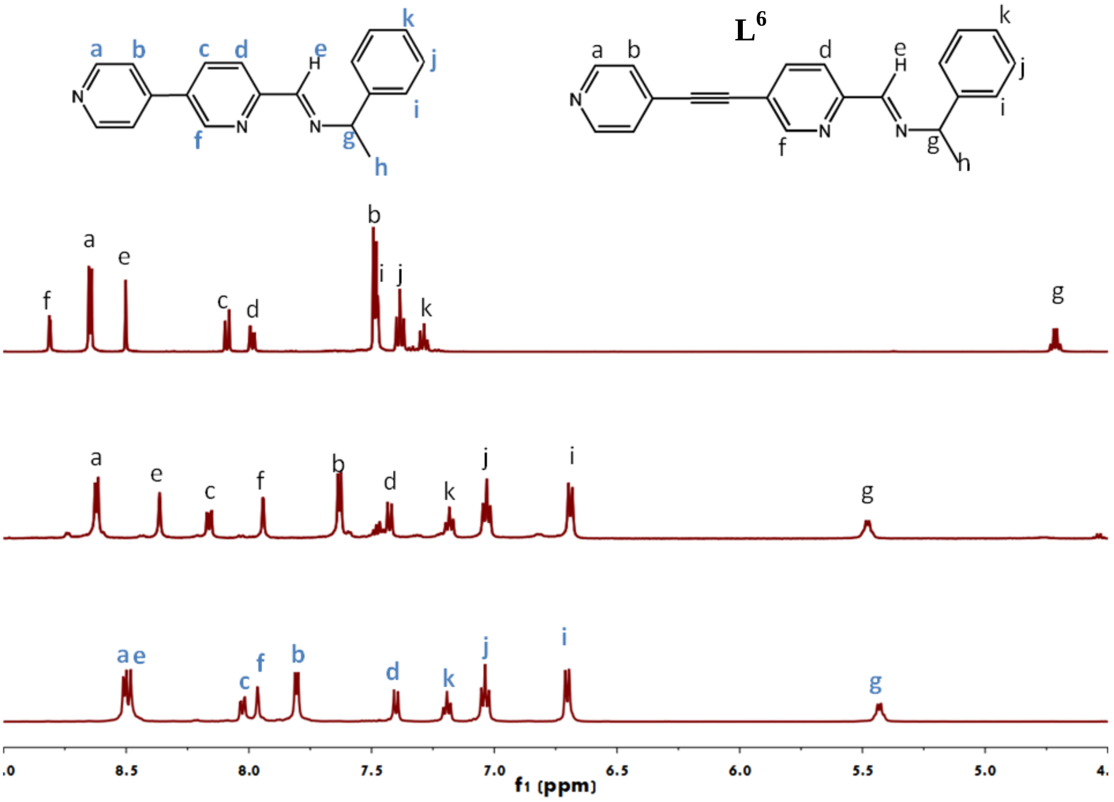

Figure S17. ^{1}H NMR (500.2 MHz) spectra of **L^6** (top), **3** (middle) and **1a** (bottom). Compared with **L^6**, most signals of **3** are shifted to a pattern similar to **1a**, indicating self-assembling into a cubic cage.

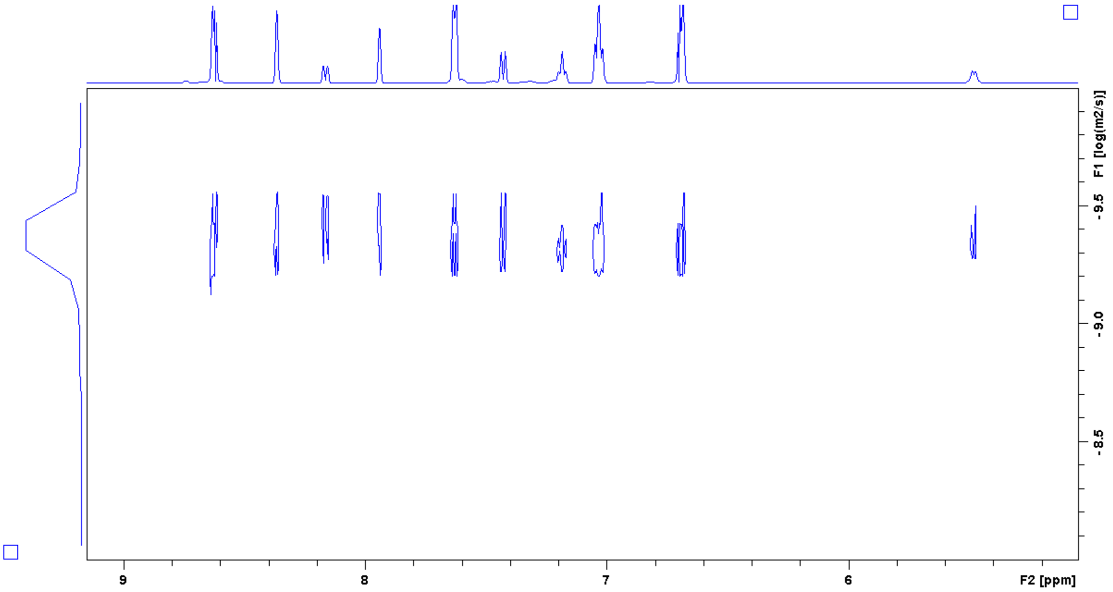

Figure S18. 2D Diffusion Ordered Spectroscopy (DOSY) NMR (500.2 MHz, 298K) spectrum of **3** in CD$_3$CN. Average diffusion coefficient D = 3.60×10^{-10} m^2/s, corresponding to a species with dynamic radius approximate to 18 Å.

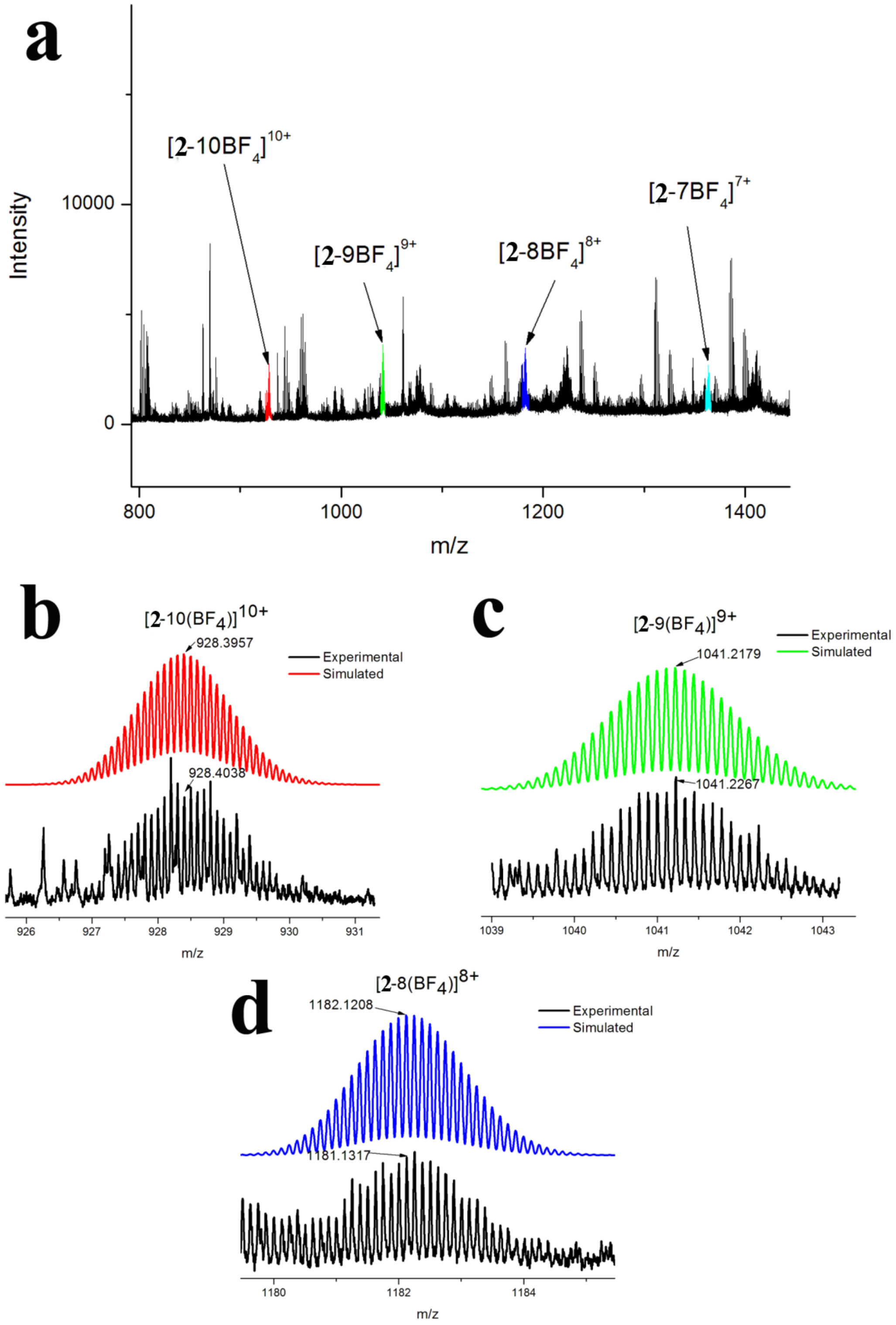

Figure S19 a: ESI-MS spectrum of the **2** in MeCN, molecular ion peaks are shown in different colors. The experimental (bottom trace) and simulated (top trace) isotopic patterns of the molecular ion peaks of b: [**2**-10(BF_4)]$^{10+}$, c: [**2**-9(BF_4)]$^{9+}$, d: [**2**-8(BF_4)]$^{8+}$.

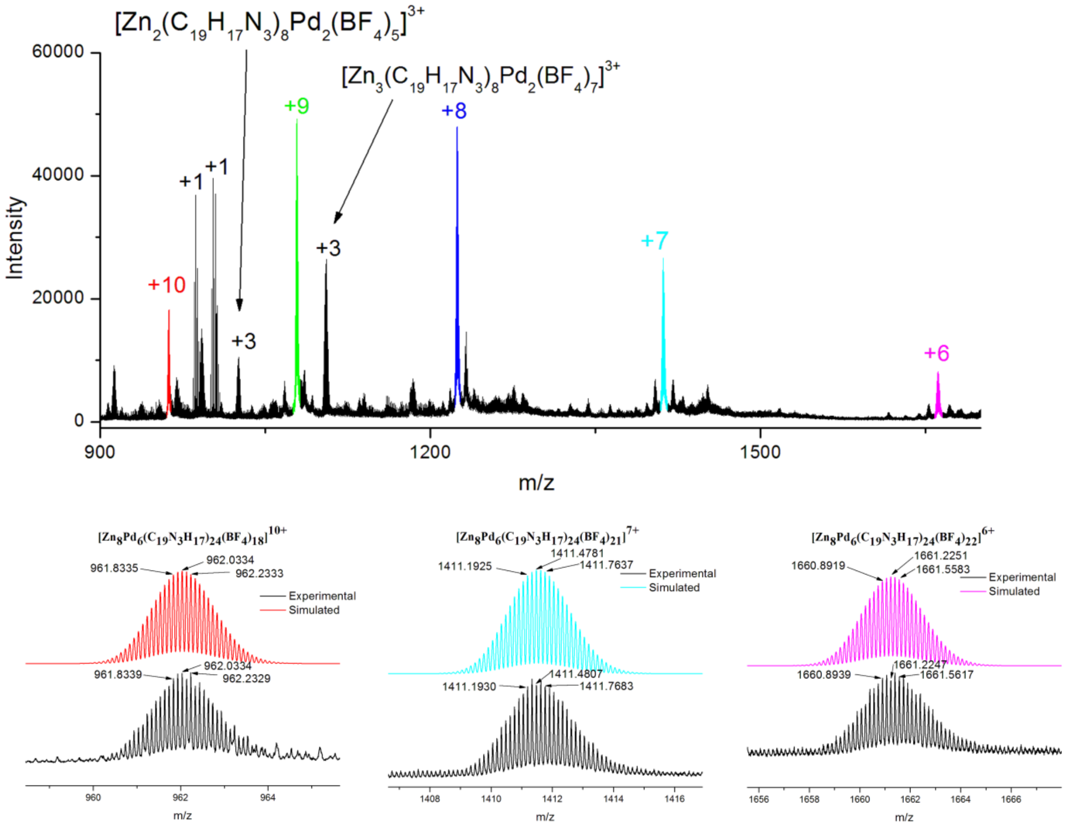

Figure S20 Top: ESI-MS spectrum of the **1a** in MeCN, multi-charge peaks of molecular ions are mark with different colours and charge state lables; bottom: the experimental (bottom trace) and simulated (top trace) isotopic patterns of the molecular ion peaks of [**1a**-10(BF$_4$)]$^{10+}$ (left), [**1a**-7(BF$_4$)]$^{7+}$ (middle) and [**1a**-6(BF$_4$)]$^{6+}$ (right).

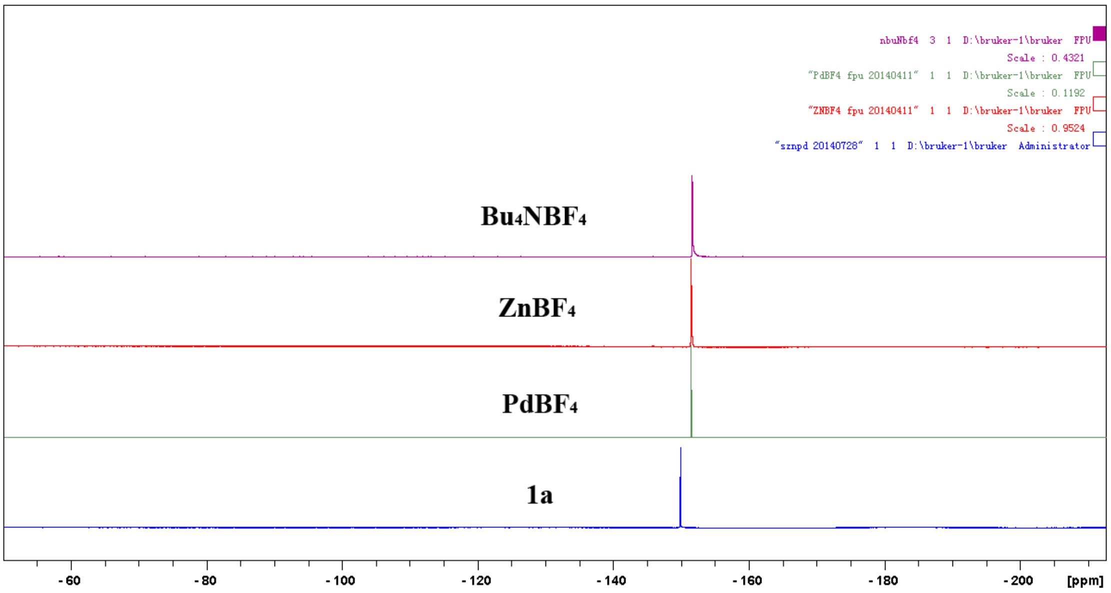

Figure S21. ^{19}F NMR (376.4 MHz) spectra of **1a** and PdBF$_4$, ZnBF$_4$, Bu$_4$NBF$_4$ in CD$_3$CN respectively.

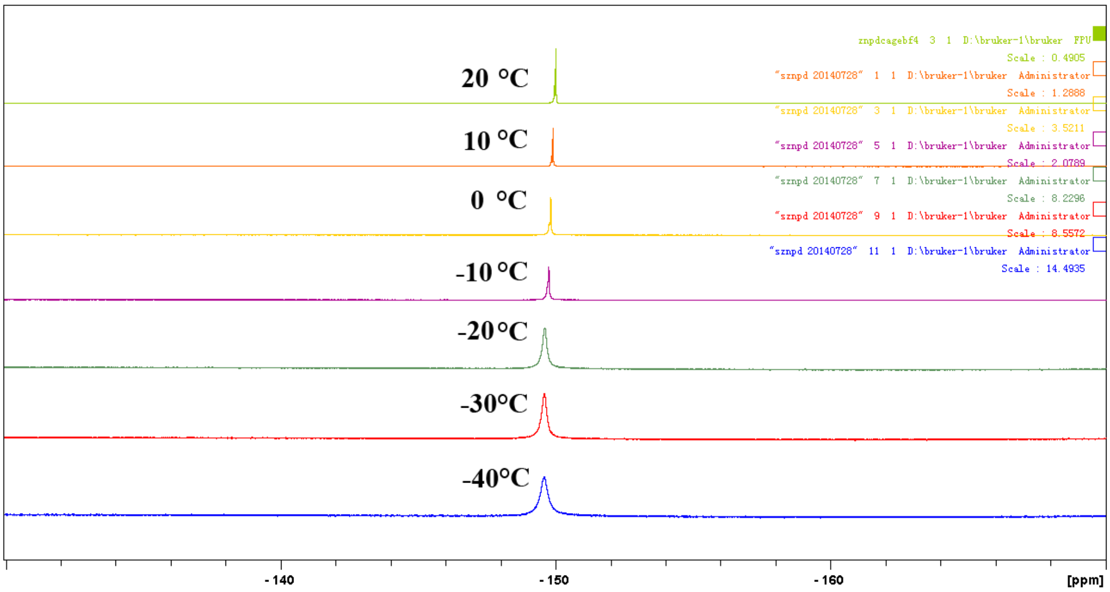

Figure S22. VT ^{19}F NMR (376.4 MHz) spectra of **1a** in CD_3CN. Lowering the temperature to -40 ℃, the peak slightly downfield shifts but remains a singlet.

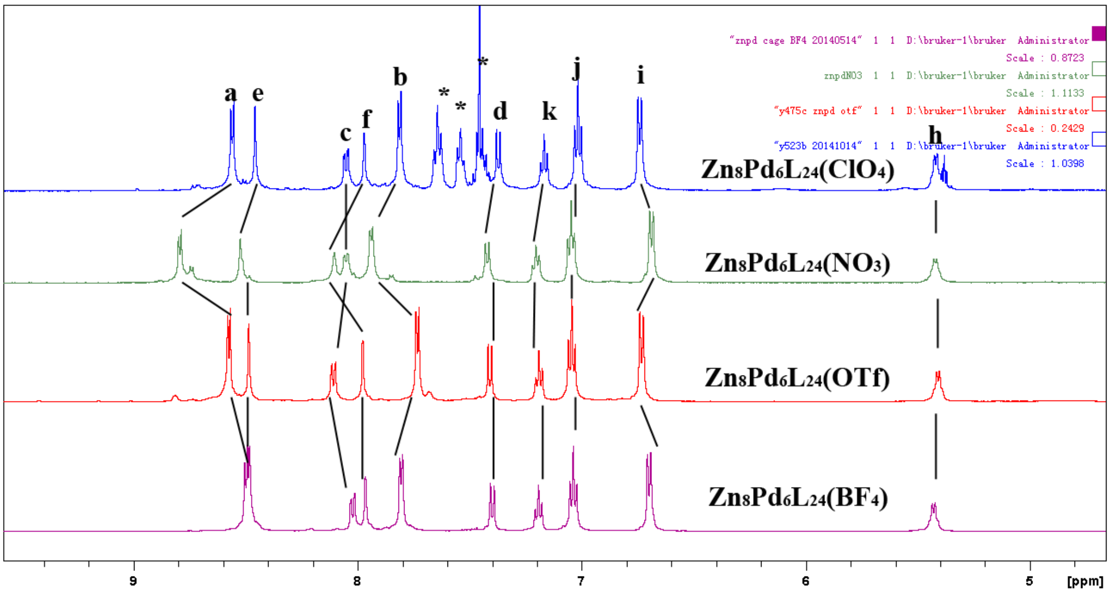

Figure S23 ^{1}H NMR (500.2 MHz) spectra of the chiral cubic cage **1** with different counterions in CD_3CN. (* represent for the excess 1-phenylethylamine)

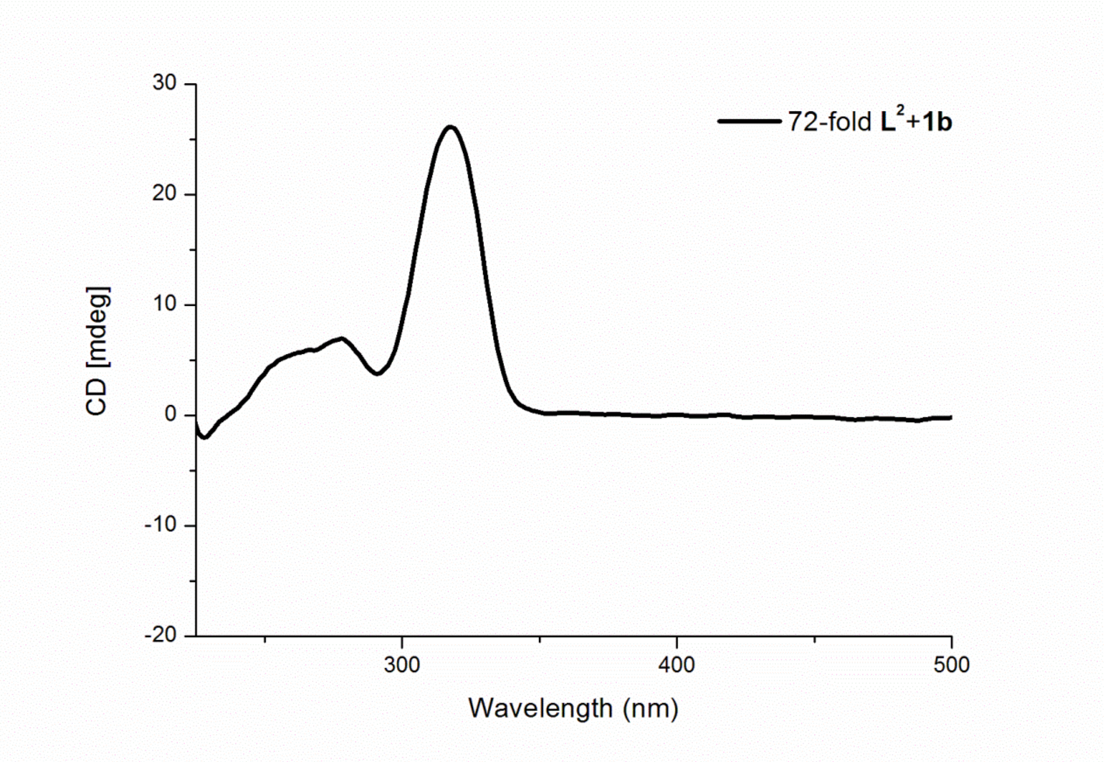

Figure S24 Adding large excess enantiomeric $\mathbf{L}^2$ into **1b** could not invert the characteristic CD signals around 300-350 nm of the cage. Signals around 250-280 nm belonging to the excess $\mathbf{L}^2$ overlay those of **1b**.

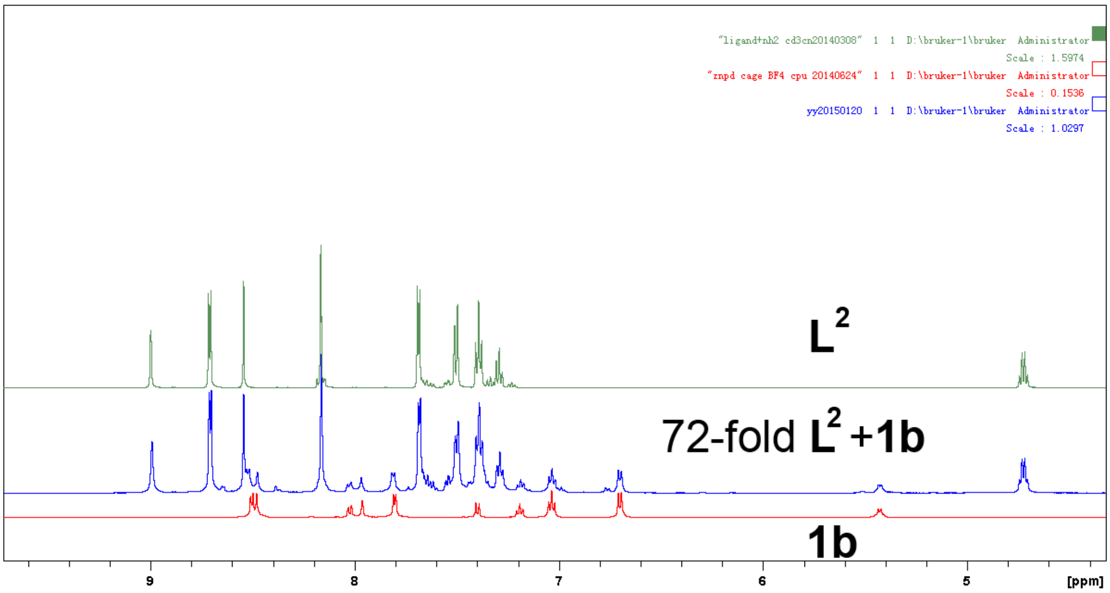

Figure S25 ^{1}H NMR (500.2 MHz) spectra of the $\mathbf{L}^2$ (green, top), mixture of 72-fold $\mathbf{L}^2$ and **1b** (blue, middle) and **1b** (red, bottom) in CD_3CN. **1b** could be clearly identified from the mixture remaining unchanged.

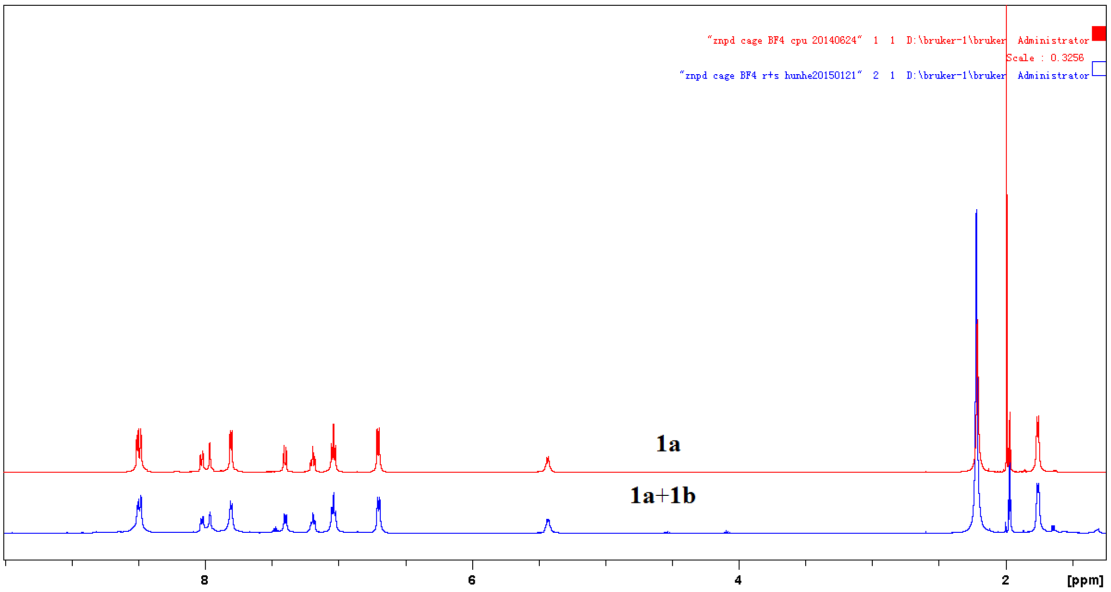

Figure S26 ^{1}H NMR (500.2 MHz) spectra of the **1a** (red, top) and mixture of **1a** and **1b** after stirring overnight (green, bottom) in CD_3CN.

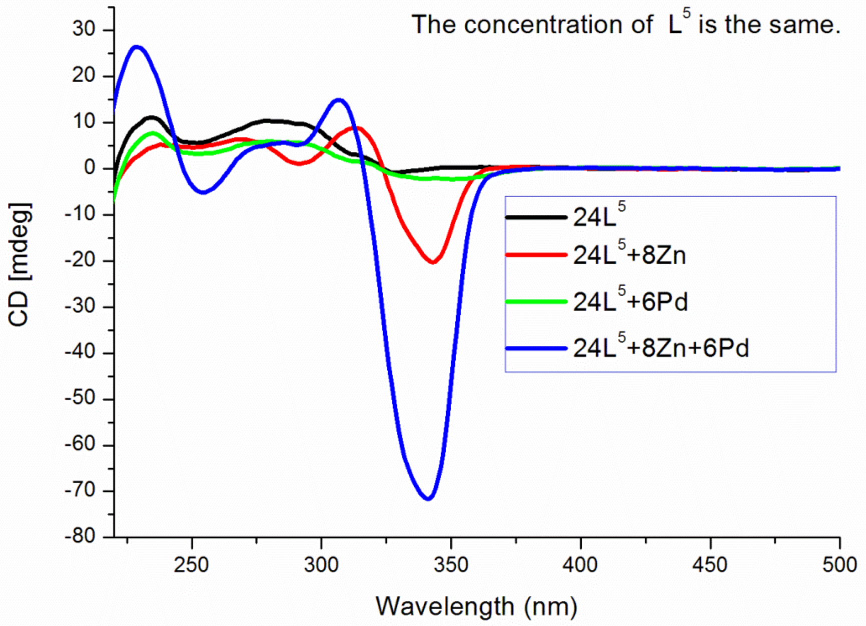

Figure S27. CD spectra of solutions: 24 equivalents of $\mathbf{L^6}$ (black); 24 equivalents of $\mathbf{L^6}$ and 8 equivalents of $Zn(BF_4)_2$ (red); 24 equivalents of $\mathbf{L^6}$ and 6 equivalents of $Pd(BF_4)_2$ (green); 24 equivalents of $\mathbf{L^6}$, 8 equivalents of $Zn(BF_4)_2$ and 6 equivalents of $Pd(BF_4)_2$ (blue). The concentration of $\mathbf{L^6}$ is the same (5.5×10^{-5} mol/L) in all these solutions. These mixtures had been stirred for 24 hours before CD measurement. Reaction mixture of 24 equivalents of $\mathbf{L^6}$ with 8 equivalents of $Zn(BF_4)_2$ and 6 equivalents of $Pd(BF_4)_2$ (blue) showed the same CD curve and similar ^{1}H NMR signals as those prepared from solid product of **3**.

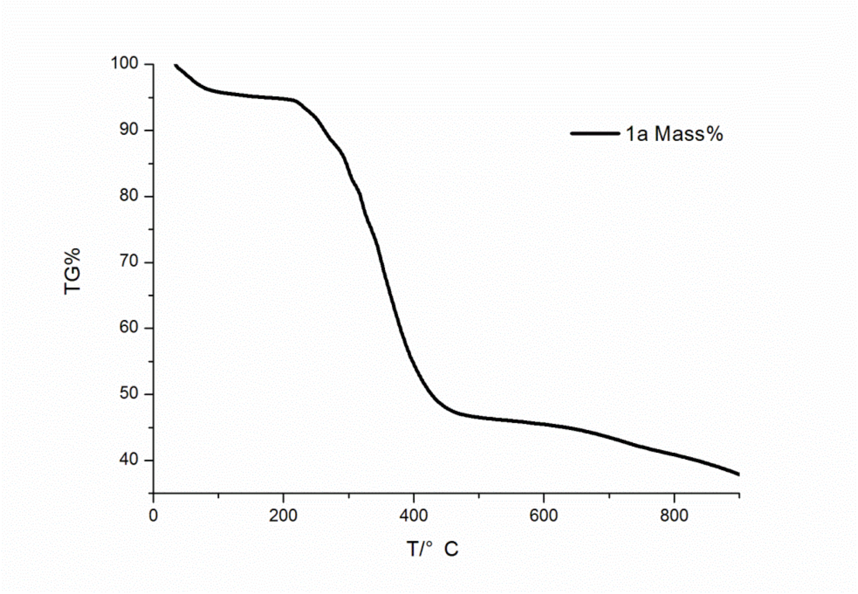

Figure S28. TGA spectrum of crystalline product of **1a** showed that it contained lots of solvent molecules in the crystals.

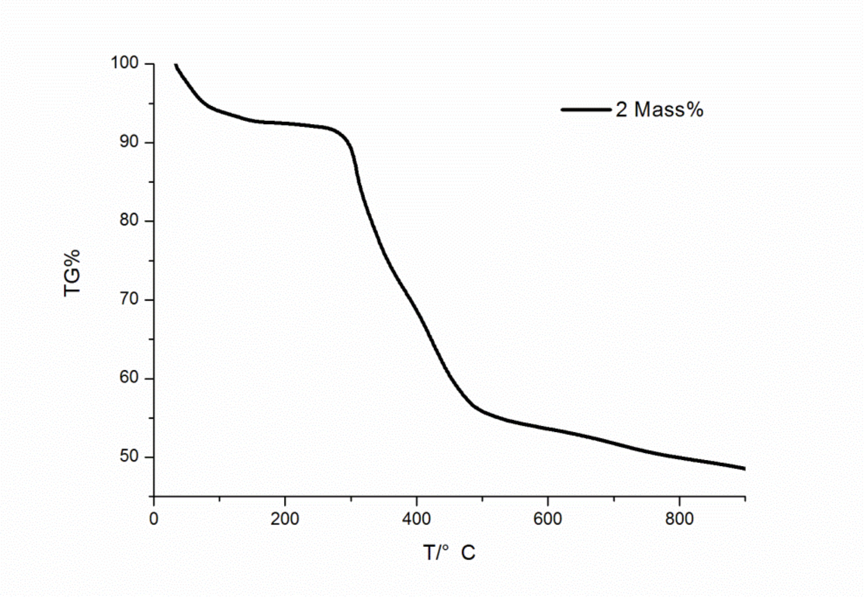

Figure S29. TGA spectrum of crystalline product of **2** showed that it contained lots of solvent molecules in the crystals.