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Conformational adaptability enabled higher-order self-sorting processes in coordination cages

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Understanding the key role of conformational adaptability in biological processes is crucial to mimic the remarkable applications inherent to biological systems. Motivated by the efficacy of conformational adaptability, we equipped a conformationally-adaptive ligand in low-symmetry *cis*-Pd₂L₂^aL₂^x-type coordination cages. A family of five *cis*-Pd₂L₂^aL₂^x-type cages was assembled by complementary ligand pairing of a conformationally adaptable converging ligand (L^a-type) in combination with diverging rigid ligands (L^x-type) of different lengths. Integrative self-sorting of the individual cages showed that the converging ligand adapts to three distinct conformations in the Pd₂L₂^aL₂^x-type architecture, to accommodate L^x-type ligands of varying sizes. Through a series of experiments, we found a higher order, *i.e.*, 2-fold heteromeric complete self-sorting outcomes of two co-existing Pd₂L₂^aL₂^x-type cages, where two chosen complementary rigid ligands could induce any two different conformations of the converging ligand in the co-existing cages. Then we further pushed the intricacy and demonstrated the unprecedented 3-fold heteromeric complete self-sorting in coordination cage systems, where the conformationally-adaptive ligand adapts three distinct conformations in three co-existing Pd₂L₂^aL₂^x-type cages. This study paves the way for the utility of conformational adaptability to achieve switchable size, shape, and functionality in supramolecular systems toward bio-relevant applications.

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Introduction

Coordination-driven self-assembly has been one of the most convenient strategies for constructing captivating nano-structured coordination architectures with applications such as molecular recognition, drug delivery, separation, catalysis, *etc.*^{1,2} Besides self-assembly, the controlled formation of well-defined coordination assemblies relies on the ability of the different components to associate together by mutual recognition, also known as self-sorting.³ Inspired by biological systems, mixed ligated coordination cages were achieved through self-sorting using various design strategies (*e.g.*, geometric complementarity, coordination sphere engineering, endohedral-functionalization, guest-templation) that employ more than one type of ligand component.⁴ A rational combination of up to four different ligands was used to selectively achieve discrete Pd(II)-based binuclear assemblies (*i.e.*, Pd₂-L₃^aL^b, *cis*-/*trans*-Pd₂L₂^aL₂^b, *cis*-/*trans*-Pd₂L₂^aL₂^bL^c, and Pd₂L^aL^bL^cL^d-type) *via* integrative self-sorting.⁵ However, in biological self-assembly, the encoded subcomponents assemble into more than one co-existing ensemble *via* orthogonal self-sorting.⁶

Recently, Clever group reported stoichiometrically controlled co-formation of two mixed ligated cages of Pd₂L₂^aL₂^b and Pd₂L₂^aL₂^c-type, also known as 2-fold heteromeric complete self-sorting by both direct ligand assembly with Pd(II) or cage fusion reaction of the three high-symmetry homoleptic assemblies.⁷ Later, we demonstrated a 2-fold heteromeric complete self-sorting outcome using a combination of two low-symmetry homoleptic cages and a high-symmetry homoleptic cage.⁸

Further, exploring increasingly-complex, higher-order self-sorting processes using coordination cages could be a formidable challenge, as it will require comprehensive pre-programming of the individual components along with interference-free interplay of multiple metal-ligand interactions.^{6,9} However, we intend to develop a design strategy to demonstrate the co-formation of three distinct Pd₂L₂^aL₂^x-type mixed ligated assemblies (*i.e.*, Pd₂L₂^aL₂^b, Pd₂L₂^aL₂^c, and Pd₂-L₂^aL₂^d-type, where x = b, c, and d) having a common L^a-type ligand. Such a higher-order self-sorting outcome, termed as “3-fold heteromeric complete self-sorting” is illustrated in Fig. 1. Designing the mutually shared ligand (L^a-type) is crucial for enabling such complexity in self-sorting processes. We presume that conformationally adaptable units embedded in a mutually shared ligand could enable the possibility of different co-existing conformations suitable for other complementary ligands (L^x-type, x = b, c, d, *etc.*) to form mixed ligated Pd₂L₂^aL₂^x-type cages using an adaptive shape-complementary approach.

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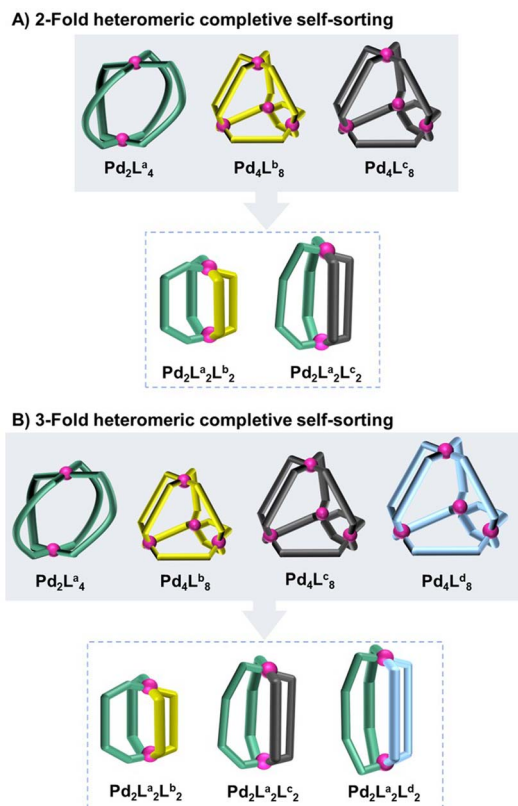


Fig. 1 (A) 2-Fold heteromeric complete self-sorting of three homoleptic assemblies into two coexisting mixed ligated assemblies. (B) 3-Fold heteromeric complete self-sorting of four homoleptic assemblies into three coexisting mixed ligated assemblies.

Though conformational adaptability plays a key role in various biological processes (such as enzymatic catalysis, allosteric signalling, ligand binding in proteins, *etc.*), achieving conformational control in synthetic supramolecular hosts requires substantial effort.^{10,11} We envisaged that the conformational flexibility of amides stemming from the possible free rotation around $C_{R1}-C_{\text{carbonyl}}$ and $C_{R2}-N_{\text{amide}}$ bonds could potentially serve this purpose.¹² A significant challenge in utilizing amide-incorporated ligands for constructing mixed ligated cages would be controlling the inherently flexible nature of the ligands. However, we believe, a delicate balance between flexibility and rigidity in the ligand designs may bring the required structural diversity in mixed ligated assemblies to achieve a 3-fold heteromeric complete self-sorting outcome.

In this report, we have designed a di-amide incorporated converging bidentate ligand (L^a -type) and explored the conformationally adaptive trait of the ligand with a series of pillar-type diverging bidentate ligands (L^x -type) of appropriate lengths (Fig. 2) to construct a family of $cis\text{-Pd}_2L_2^aL_2^x$ -type mixed ligated assemblies. The conformation of the L^a -type ligand (*syn-syn*, *syn-anti*, or *anti-anti*) in the formed coordination assembly is dictated by the length of the L^x -type diverging ligands employed for complexation. The conformational adaptability of the L^a -type ligand was further utilized to demonstrate the first example of a 3-fold heteromeric complete self-sorting in coordination cage systems. The three distinct coexisting binuclear assemblies

($\text{Pd}_2L_2^aL_2^b$, $\text{Pd}_2L_2^aL_2^c$, and $\text{Pd}_2L_2^aL_2^d$ -type) were achieved by cage fusion of four carefully chosen homoleptic assemblies ($\text{Pd}_2L_4^a$, $\text{Pd}_4L_8^b$, $\text{Pd}_4L_8^c$, and $\text{Pd}_4L_8^d$ -type), where the mutually shared L^a -type ligand is locked in three different conformations in the three mixed ligated cages. Further, we have also studied the conformational adaptability of three converging ligands having di-, mono-, and non-amide moieties in their backbone for constructing $cis\text{-Pd}_2L_2^aL_2^x$ -type mixed ligated assemblies.

Results and discussion

To study the utility of conformational adaptability in shape complementary $cis\text{-Pd}_2L_2^aL_2^x$ -type mixed ligated cages,^{5b,13} first, we designed a pair of converging bidentate ligands (L^a -type) **L1** (rigid) and **L2** (conformationally adaptable) (Fig. 2A). The converging ligands were designed to understand the relevance of rigidity *vs.* adaptability in the assembly of the desired mixed ligated cages, in combination with well-suited rigid diverging ligands (L^x -type) and Pd(II). Ligand **L2** was designed by embedding di-amide functionality in the 1,2-diphenylacetylene spaced ligand **L1**. We presume that the bidentate ligand bearing di-amide moieties (**L2**) could possibly orient in three distinct conformational states (namely *syn-syn*, *syn-anti*, or *anti-anti*) in mixed ligated $\text{Pd}_2L_2^aL_2^x$ -type assembly, when paired alongside carefully designed diverging ligands (L^x -type, $x = A-G$) and Pd(II).

Due to the partial delocalization across the amide bond of **L2**, the rotation around the CO–NH bond will be constrained; however, rotation around $C_{\text{phenyl}}-C_{\text{carbonyl}}$ as well as $C_{\text{pyridyl}}-N_{\text{amide}}$ bonds could result in several possible conformations. Out of all the possible conformations of **L2**, the three chosen conformations are shown in Fig. 2B. The three conformations were selected for their potential ability to form a shape complementary $cis\text{-Pd}_2L_2^aL_2^x$ -type assembly when paired with a suitable diverging ligand and Pd(II). Initial DFT (B3LYP/6-31g(d)) calculations revealed the approximate $N_{\text{py}} \cdots N_{\text{py}}$ distance of **L2** in different conformations to be around 9.6 Å (*syn-syn*, **L2^{SS}**), 12.1 Å (*syn-anti*, **L2^{SA}**) and 15.2 Å (*anti-anti*, **L2^{AA}**) (Fig. 2B). In a $cis\text{-Pd}_2L_2^aL_2^x$ -type assembly, **L2** could adapt any of the three conformations dictated by the complementary diverging ligand. Hence, we have chosen a series of pillar-type rigid ligands (L^A-L^G) of varied lengths ($N_{\text{py}} \cdots N_{\text{py}}$ distance ranging from around 5.6 to 16.8 Å). These ligands possess an approximate bent angle of 120°, which could potentially dictate the conformation of **L2** in the $cis\text{-Pd}_2L_2^aL_2^x$ -type cage (Fig. 2C).^{14–19} The combination of **L2** and the rigid pillar-type ligands (L^A-L^G) was expected to result in a library of $cis\text{-Pd}_2L_2^aL_2^x$ -type mixed ligated cages. Also, **L1** could form $cis\text{-Pd}_2L_2^aL_2^x$ -type assemblies when paired with a diverging ligand of appropriate length (from the series of L^A-L^G) and Pd(II), owing to the shape complementary nature. However, the number of $cis\text{-Pd}_2L_2^aL_2^x$ -type assemblies and extent of adaptability will be limited due to the rigid backbone of **L1**. To achieve our objective, we synthesized the ligands, and the detailed synthetic procedure is given in the SI, see Section S2.

Initially, we explored the self-assembly of individual ligand components (**L1** and **L2**) with Pd(II). Complexation of $\text{Pd}(\text{NO}_3)_2$



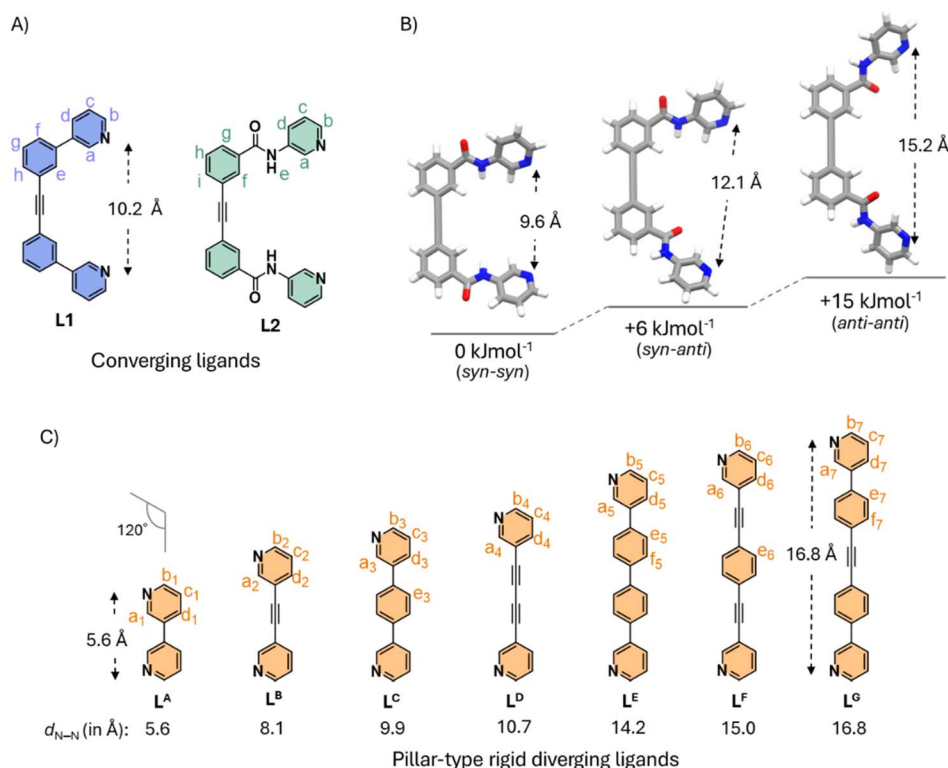


Fig. 2 Ligand designs: (A) Chemical structures of L1 and L2; (B) DFT optimized structure of chosen conformations of L2 (named as *syn-syn*, *syn-anti* and *anti-anti*) conformation, the term *syn* and *anti* are used to define the relative orientation of amide (NH) and pyridine (N) vectors; (C) Structures of ligands L^A–L^G in increasing order of N_{py}⋯N_{py} distances (in Å). The N_{py}⋯N_{py} distances are calculated from the optimized structures (Fig. S184).

with L1 (1 : 2 ratio) in DMSO-*d*₆ at room temperature was monitored by ¹H NMR spectroscopy (Fig. S12). After 12 hours, a single species showing a characteristic complexation-induced downfield shift of the pyridine- α CH protons ($\Delta\delta_{\text{Complex-Ligand}}$ (H_a) = 0.93 ppm & $\Delta\delta_{\text{Complex-Ligand}}$ (H_b) = 0.76 ppm) was observed in the ¹H NMR spectrum. Formation of the cage [Pd₂(L1)₄](NO₃)₄, 1·4NO₃ was supported based on ESI-MS data. To attain a parallel coordination vector for a Pd₂L₄-type assembly, the converging ligand L1 needs to undergo twisting around the two Pd(II) centres. Hence, the formed cage was expected to be a helical Pd₂L₄-type assembly (Fig. S186). Likewise, the self-assembly of L2 with Pd(II) was anticipated to result in a helical Pd₂L₄-type architecture (Fig. S186).^{5a,13} Complexation of Pd(NO₃)₂ with L2 (1 : 2 ratio) in DMSO-*d*₆ at room temperature for 12 hours led to the formation of a discrete product, as confirmed by ¹H NMR spectroscopy (Fig. S17). ESI-MS analysis confirms the composition [Pd₂(L2)₄](NO₃)₄, 2·4NO₃ for the resultant cage assembly. Further, ¹H-¹H NOE spectrum analysis of the cage showed cross-peak correlations of amide protons (NH_e) with outward-pointing protons H_d and H_g (Fig. S21), suggesting an all-(*anti-anti*) conformer of L2 in the cage structure.

Pd(II)-based coordination complexes featuring L^B, L^C, L^E, L^F, and L^G have been previously reported.^{16,19–21} In this work, we carried out the individual complexation of all the ligands with Pd(NO₃)₂ (reported cages were reproduced; see SI Section S2.4). Among the reported cases, L^B and L^C gave their respective Pd₄L₈

(tetrahedron)-type (*i.e.*, B·8NO₃ and C·8NO₃, respectively) architecture upon complexation with Pd(NO₃)₂.^{16,20} When L^A was treated with Pd(NO₃)₂ at a 2 : 1 ratio in DMSO-*d*₆ at room temperature for 24 hours, the ¹H NMR spectrum showed unassignable complicated signals due to the formation of a mixture of products. Complexation of Pd(NO₃)₂ with L^D at a 1 : 2 ratio in DMSO-*d*₆ at room temperature for 3 hours resulted in a well-resolved ¹H NMR spectrum consisting of two products. The resultant assemblies are proposed to be a mixture of Pd₄L₈ (tetrahedron) (major) and Pd₃L₆ (minor)-type cages (*i.e.*, D·8NO₃ and D'·6NO₃). Similarly, L^E and L^F also produced a mixture of Pd₄L₈ (tetrahedron) (major) and Pd₃L₆ (minor)-type cages (*i.e.*, E·8NO₃ and E'·6NO₃/F·8NO₃ and F'·6NO₃).^{16,21} However, when a longer ligand L^G was treated with Pd(NO₃)₂ (2 : 1 ratio), a single set of peaks were observed in the ¹H NMR spectrum, suggesting the formation of a single species, a Pd₃L₆-type (G·6NO₃) architecture was further confirmed by ESI-MS data analysis (Fig. S96).¹⁹

Next, we explored the mixed ligand complexation behavior of L1 and L2 when paired with a rigid diverging ligand of suitable length and Pd(II). Based on the DFT calculated structure, we presume that L1 (N_{py}⋯N_{py} = 10.2 Å) and L^B (N_{py}⋯N_{py} = 8.1 Å) could be the best fit for a *cis*-Pd₂L₂³L₂-type arrangement (Fig. S186).²² Self-assembly of Pd(NO₃)₂ with L1 and L^B in a 1 : 1 : 1 ratio in DMSO-*d*₆ at room temperature for 30 minutes resulted in the clean formation of a discrete cage, as demonstrated by ¹H NMR spectroscopy. Further evidence for the formation of the



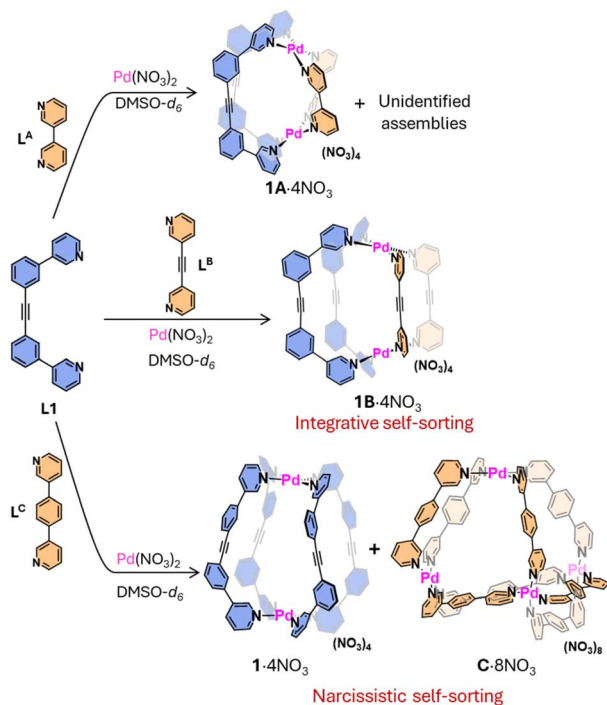


Fig. 3 Schematic representation for mixed ligand complexation of $\text{Pd}(\text{NO}_3)_2$ with L1 and $\text{L}^{\text{A}}-\text{L}^{\text{C}}$.

mixed ligated cage $[\text{Pd}_2(\text{L1})_2(\text{L}^{\text{B}})_2](\text{NO}_3)_4$, $\mathbf{1B} \cdot 4\text{NO}_3$ was provided by ESI-MS data, which shows isotopic peak patterns at $m/z = 681.09$ and 433.30 corresponding to the loss of two and three NO_3^- ions, respectively. Subsequently, we performed complexation of $\text{Pd}(\text{NO}_3)_2$ with L1 and $\text{L}^{\text{A}}/\text{L}^{\text{C}}$ (shorter/longer than L^{B}) (Fig. 3). Mixing $\text{Pd}(\text{NO}_3)_2$, L1 and L^{A} in a 1 : 1 : 1 ratio in $\text{DMSO}-d_6$ showed formation of a mixture of assemblies with one dominant species in the ^1H NMR spectrum (Fig. S31). ESI-MS data showing characteristic peak patterns for the sequential loss of NO_3^- ions supported the composition of $[\text{Pd}_2(\text{L1})_2(\text{L}^{\text{A}})_2](\text{NO}_3)_4$, $\mathbf{1A} \cdot 4\text{NO}_3$. However, pairing the rigid ligand L1 with a relatively longer ligand L^{C} and $\text{Pd}(\text{NO}_3)_2$ resulted in a mixture of homoleptic assemblies (narcissistic self-sorting), as evident from the ^1H NMR spectrum (Fig. S44). Further employing longer ligands $\text{L}^{\text{D}}-\text{L}^{\text{G}}$ for complexation with $\text{Pd}(\text{NO}_3)_2$ and L1 also resulted in narcissistic self-sorting (Fig. S45–S48). Integratively self-sorted *cis*- $\text{Pd}_2\text{L}_2^{\text{A}}\text{L}_2^{\text{X}}$ -type assembly was only successful for the self-assembly L1 with L^{B} and $\text{Pd}(\text{II})$, whereas due to the rigid backbone of L1 and incompatible lengths of the ligand pairs, the mixed ligand assembly of L1 , and other ligands from the series, *i.e.*, L^{A} , $\text{L}^{\text{C}}-\text{L}^{\text{G}}$ was unsuccessful.

Then, we studied the adaptive self-assembly behavior of the ligand L2 in the presence of a range of diverging ligands towards the assembly of *cis*- $\text{Pd}_2\text{L}_2^{\text{A}}\text{L}_2^{\text{X}}$ -type cages. We thought L^{B} ($N_{\text{py}} \cdots N_{\text{py}} = 8.1 \text{ \AA}$) would be suitable for the *syn-syn* conformation (L2^{SS} , $N_{\text{py}} \cdots N_{\text{py}} = 9.6 \text{ \AA}$). Upon treating L2 and L^{B} with $\text{Pd}(\text{NO}_3)_2$ in a 1 : 1 : 1 ratio in $\text{DMSO}-d_6$ at room temperature for 30 minutes, the ^1H NMR spectrum showed a single set of signals for the formation of a discrete species. The spectrum showed the characteristic complexation-induced downfield shift in the position of the inwards pointed pyridine- $\alpha\text{CH}_{\text{IN}}$ of both the

ligands ($\Delta\delta_{\text{Complex-Ligand}}(\text{H}_{\text{a}}) = 0.51 \text{ ppm}$ & $\Delta\delta_{\text{Complex-Ligand}}(\text{H}_{\text{a2}}) = 1.41 \text{ ppm}$ for L2 and L^{B} respectively) (Fig. 4B(iii)). The formation of complex $[\text{Pd}_2(\text{L2})_2(\text{L}^{\text{B}})_2](\text{NO}_3)_4$, $\mathbf{2B} \cdot 4\text{NO}_3$ was further investigated by ESI-MS data analysis, where isotopic peak patterns at $m/z = 490.73$ and 352.55 was observed for the loss of three and four NO_3^- ions, respectively. Further, a single band in the ^1H DOSY spectrum confirmed that all the protons correspond to a single species in the solution with a diffusion coefficient of $1.21 \times 10^{-10} \text{ m}^2 \text{ s}^{-1}$ (Fig. S118).

To investigate the conformationally adaptive nature of ligand L2 , we performed its complexation with the next ligand in the series L^{C} ($N_{\text{py}} \cdots N_{\text{py}} = 9.9 \text{ \AA}$) and $\text{Pd}(\text{NO}_3)_2$ at a 1 : 1 : 1 ratio in $\text{DMSO}-d_6$. After 30 minutes, the ^1H NMR spectrum indicated the formation of a discrete product corresponding to cage $[\text{Pd}_2(\text{L2})_2(\text{L}^{\text{C}})_2](\text{NO}_3)_4$, $\mathbf{2C} \cdot 4\text{NO}_3$ where the pyridine- $\alpha\text{CH}_{\text{IN}}$ showed complexation-induced downfield shift ($\Delta\delta_{\text{Complex-Ligand}}(\text{H}_{\text{a}}) = 0.98 \text{ ppm}$ & $\Delta\delta_{\text{Complex-Ligand}}(\text{H}_{\text{a3}}) = 1.46 \text{ ppm}$ for L2 and L^{C} , respectively) for both the ligands (Fig. 4B(iv)). We presume L^{C} might be slightly longer to fit the *syn-syn* conformation of L2 in the *cis*- $\text{Pd}_2\text{L}_2^{\text{A}}\text{L}_2^{\text{X}}$ -type cage structure. Thus, L2 might have adapted *syn-anti* conformation (L2^{SA}) during the self-assembly process to form cage $\mathbf{2C} \cdot 4\text{NO}_3$ selectively. To further test our hypothesis for the conformational adaptability of L2 , we performed complexation of $\text{Pd}(\text{NO}_3)_2$ with L2 and L^{D} ($N_{\text{py}} \cdots N_{\text{py}} = 10.7 \text{ \AA}$) (1 : 1 : 1 ratio) in $\text{DMSO}-d_6$. After stirring the reaction at room temperature for 30 minutes, a discrete assembly was observed in the ^1H NMR spectrum (Fig. 4B(v)). The composition of the formed product was found to be $[\text{Pd}_2(\text{L2})_2(\text{L}^{\text{D}})_2](\text{NO}_3)_4$, $\mathbf{2D} \cdot 4\text{NO}_3$ from ESI-MS data analysis. The facile formation of complex $\mathbf{2D} \cdot 4\text{NO}_3$ confirms the ability of L2 to adapt to a different conformation to form an entropically more favourable mixed ligated cage.

Having found an adaptive ligand capable of switching its conformation to adopt a length suitable for fitting a complementary ligand in a $\text{Pd}_2\text{L}_2^{\text{A}}\text{L}_2^{\text{X}}$ -type cage, we next decided to attempt the complexation of $\text{Pd}(\text{NO}_3)_2$ with L2 and L^{E} ($N_{\text{py}} \cdots N_{\text{py}} = 14.2 \text{ \AA}$) or L^{F} ($N_{\text{py}} \cdots N_{\text{py}} = 15.0 \text{ \AA}$). A clean formation of the cage $[\text{Pd}_2(\text{L2})_2(\text{L}^{\text{E}})_2](\text{NO}_3)_4$, $\mathbf{2E} \cdot 4\text{NO}_3$ and $[\text{Pd}_2(\text{L2})_2(\text{L}^{\text{F}})_2](\text{NO}_3)_4$, $\mathbf{2F} \cdot 4\text{NO}_3$ was obtained *via* self-assembly of L2 with $\text{L}^{\text{E}}/\text{L}^{\text{F}}$ and $\text{Pd}(\text{NO}_3)_2$ respectively (Fig. 4B(vi and vii)). The formed mixed ligated assemblies were characterized by 1D and 2D NMR spectroscopy techniques and ESI-MS data. Based on the $N_{\text{py}} \cdots N_{\text{py}}$ distances of L^{E} and L^{F} , we could infer that the L2 is likely to be present in the *anti-anti* conformation (L2^{AA}). To examine the extent of conformational adaptability of L2 for the formation of $\text{Pd}_2\text{L}_2^{\text{A}}\text{L}_2^{\text{X}}$ -type assembly, we tried the complexation with the shortest/longest ligand in the chosen series, *i.e.*, L^{A} ($N_{\text{py}} \cdots N_{\text{py}} = 5.6 \text{ \AA}$) and L^{G} ($N_{\text{py}} \cdots N_{\text{py}} = 16.8 \text{ \AA}$). Expectedly, both ligands were found to yield either a narcissistic self-sorting outcome or a mixture of unidentified assemblies.

The comparative ^1H NMR spectral analysis of all five *cis*- $\text{Pd}_2\text{L}_2^{\text{A}}\text{L}_2^{\text{X}}$ -type cages, $\mathbf{2B} \cdot 4\text{NO}_3-\mathbf{2F} \cdot 4\text{NO}_3$, showed distinctive complexation-induced chemical shift changes ($\Delta\delta_{\text{Complex-Ligand}}$) for H_{a} and H_{d} (Fig. 4B). While the ^1H NMR spectrum of $\mathbf{2B} \cdot 4\text{NO}_3$ exhibited $\Delta\delta_{\text{Complex-Ligand}}$ for H_{a} about 0.51 ppm (downfield shift), the cages $\mathbf{2C} \cdot 4\text{NO}_3$ and $\mathbf{2D} \cdot 4\text{NO}_3$ displayed even higher $\Delta\delta_{\text{Complex-Ligand}}$ for H_{a} (0.98 ppm and 1.00 ppm). However, for



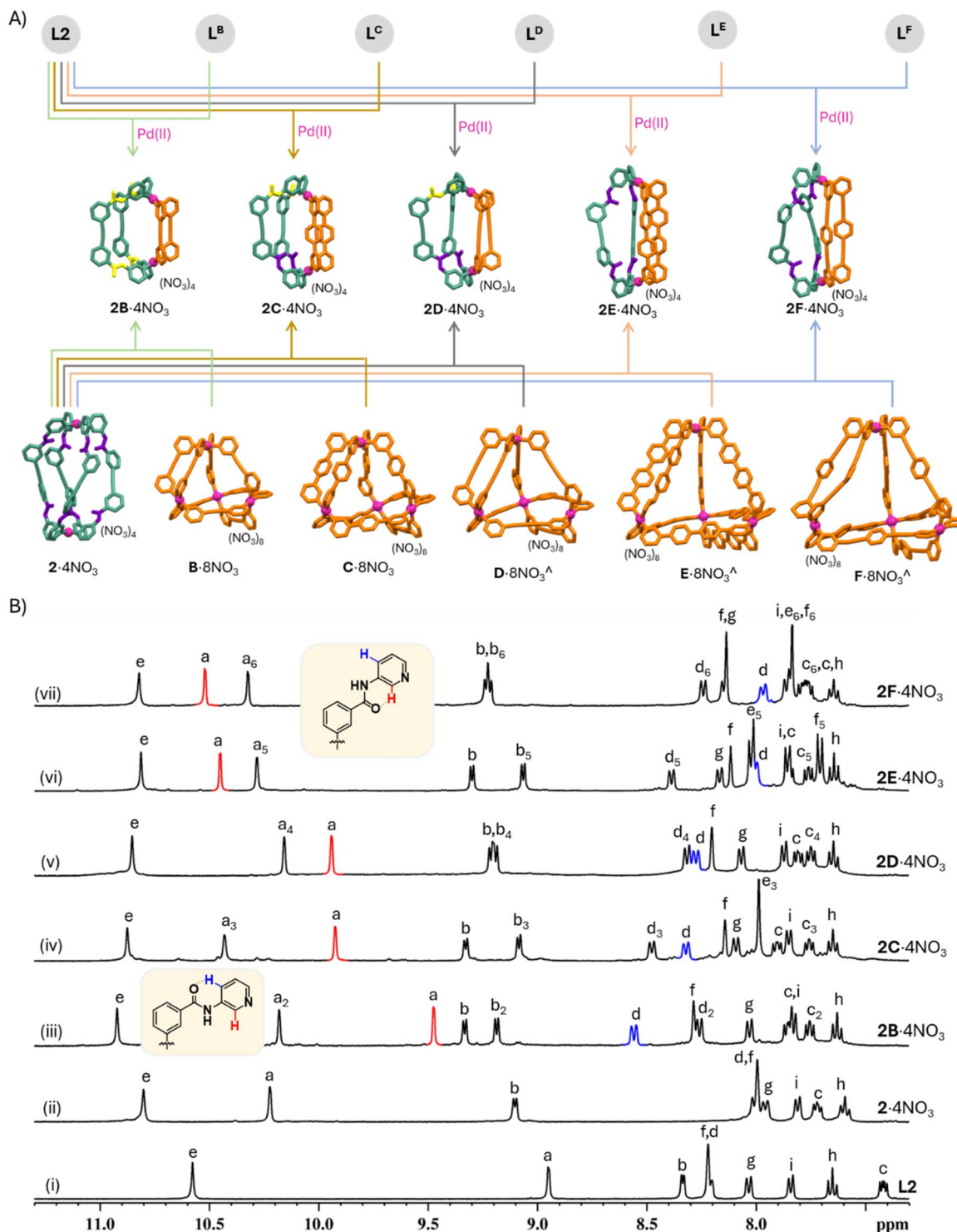


Fig. 4 (A) Self-assembly of a conformationally adaptive ligand to form a series of Pd₂L₂L₂-type mixed ligated cages. Energy-minimized structures of the cationic complexes were used to represent the cages. ^only the major product is shown; (B) Partial ¹H NMR spectra (400 MHz, 298 K, DMSO-*d*₆) of (i) L^A; (ii) [Pd₂(L^A)₂](NO₃)₄, 2·4NO₃; (iii) [Pd₂(L^A)₂(L^B)₂](NO₃)₄, 2B·4NO₃; (iv) [Pd₂(L^A)₂(L^C)₂](NO₃)₄, 2C·4NO₃; (v) [Pd₂(L^A)₂(L^D)₂](NO₃)₄, 2D·4NO₃; (vi) [Pd₂(L^A)₂(L^E)₂](NO₃)₄, 2E·4NO₃; (vii) [Pd₂(L^A)₂(L^F)₂](NO₃)₄, 2F·4NO₃.

the cages 2E·4NO₃ and 2F·4NO₃, we found more pronounced $\Delta\delta_{\text{Complex-Ligand}}$ for H_a (1.52 ppm and 1.58 ppm). Likewise, a similar observation was found for the proton H_d, which showed gradual upfield shifts from 2B·4NO₃ to 2F·4NO₃. This distinctive chemical shift change may be due to the

intramolecular hydrogen bonding between H_a/H_d and carbonyl oxygen. As the conformational switching progressively changes from *syn-syn* to *anti-anti* via *syn-anti* conformation, H_a/H_d could potentially move closer/away from C=O, respectively.



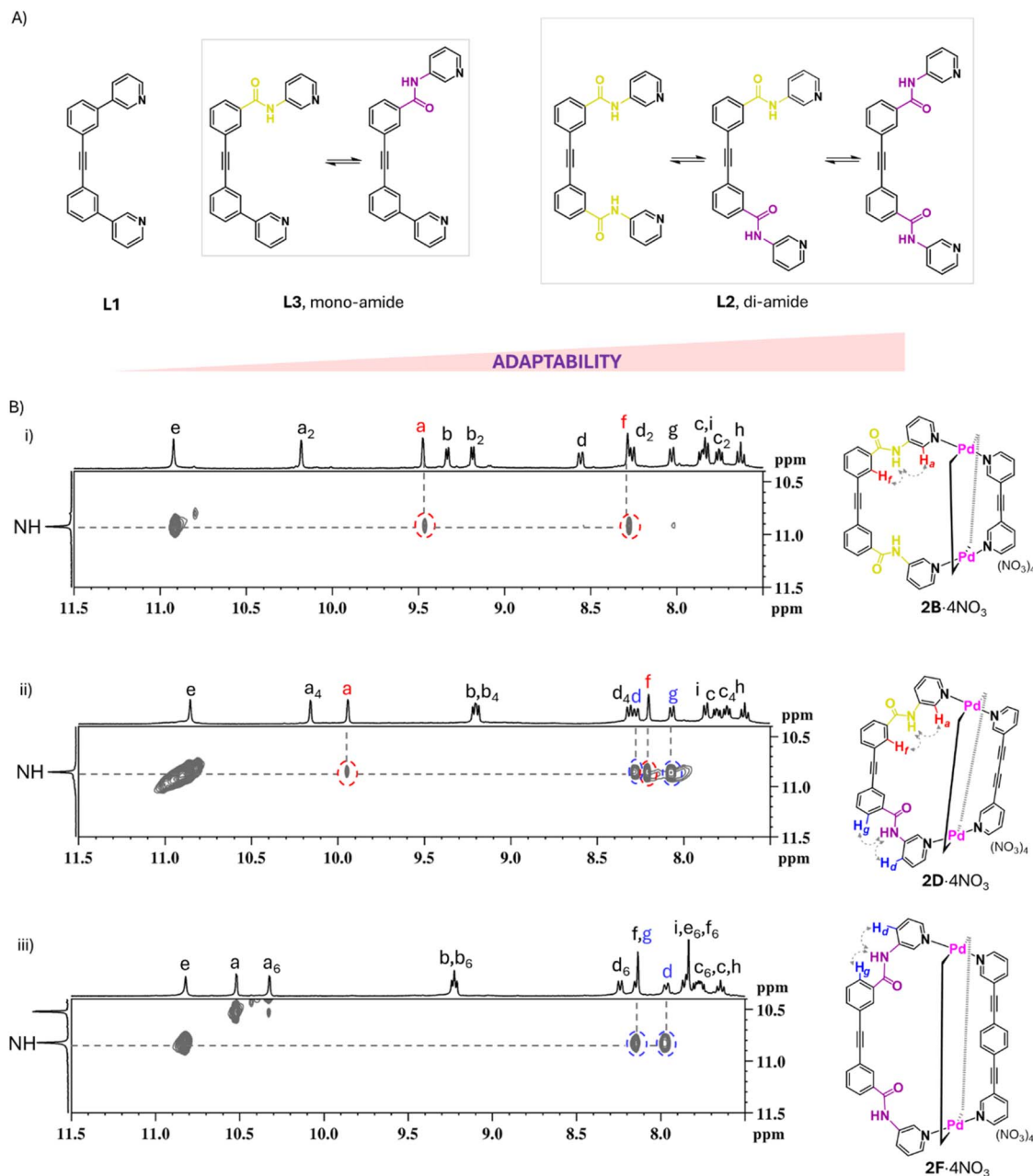


Fig. 5 (A) Conformational adaptability (with the chosen distinct conformations) trend for the ligands L1, L3 (mono-amide) and L2 (di-amide) towards the construction of *cis*-Pd₂L₂L₂^x-type mixed ligated assemblies; (B) expanded ¹H-¹H NOE spectra (400 MHz, 298 K, DMSO-*d*₆) showing intra-ligand cross peaks for strong correlation of the amide protons (N-H_e) with inward (*syn*) or outward (*anti*) pointing protons of the pyridine and phenyl groups in (i) 2B·4NO₃; (ii) 2D·4NO₃ and (iii) 2F·4NO₃, respectively.

After successfully achieving a series of cages 2B·4NO₃–2F·4NO₃ through integrative self-sorting of individual ligand components and Pd(II) using an adaptive shape-complementary approach, we were curious to inspect whether the self-assembled products are pathway-dependent or at the thermodynamic minimum. Hence, we performed the cage-to-cage transformations from the corresponding homoleptic assemblies. Mixing 2 equiv. of 2·4NO₃ with 1 equiv. of corresponding homoleptic assemblies of L^x (x = B–F), *i.e.*, B·8NO₃–F·8NO₃ (Pd₄L₈-type cages D·8NO₃, E·8NO₃ and F·8NO₃ exist along with the Pd₃L₆-type cages D'·6NO₃, E'·6NO₃ and F'·6NO₃),

individually in DMSO-*d*₆, resulted in the mixed ligated assembly 2X·4NO₃ under thermodynamic control (Fig. 4A). The robustness of the mixed ligated cage 2B·4NO₃–2F·4NO₃ was further demonstrated by concentration variation studies (SI Section S8 and Fig. S151–S155).

Thereafter, we were curious to inspect the conformational preference of ligand L2 in the Pd₂L₂L₂^x-type cage assemblies. For this purpose, we performed ligand exchange reactions, in which to a chosen mixed ligated complex, a calculated amount of another ligand (from the series L^B–L^F) was added. In some cases, the bound ligand has been replaced partially or entirely



by the incoming ligand (SI Section S9, Scheme S32 and Fig. S156–S175). Based on these experiments, the relative ligand selectivity of **L2** to form mixed ligated cages was found to be $L^E > L^C > L^F > L^B \approx L^D$. Based on the electrostatic potential map analysis of the ligands L^B – L^F , we presume this outcome could possibly be due to the basicity of the rigid complementary ligands rather than the conformation of the **L2** (Fig. S185).

The striking difference in the adaptability of **L1** and **L2** to self-assemble into *cis*-Pd₂L₂²L₂²-type cages stems from the embedded amide moieties in **L2**. When **L1** was paired with a set of diverging ligands (L^X , N_{py}···N_{py} = 5.6–16.8 Å), an absolute integrative self-sorted product was obtained only for the case of L^B . Whereas integrative self-sorting of **L2** was successful for a series of five ligands, *i.e.*, L^B – L^F (N_{py}···N_{py} = 8.1–15.0 Å), resulting in a family of five *cis*-Pd₂L₂²L₂²-type assemblies (**2B**·4NO₃–**2F**·4NO₃). Thus, we were curious to study the adaptability of a converging ligand with a single amide moiety embedded. Hence, we chose a mono-amide functionalized ligand **L3**, for the complexation with L^A – L^G .

In our previous report,⁸ we utilized **L3** (a structurally-constrained ligand) along with suitable symmetrical/unsymmetrical diverging ligands and Pd(II) to develop two highly anisotropic binuclear mixed ligated cages. However, the conformational adaptability of **L3** was unexplored. To investigate the full extent of adaptability of **L3** in the presence of suitable diverging ligands, we attempted the complexation of Pd(NO₃)₂ with **L3** and L^A – L^G . We previously obtained the mixed ligated cage, *i.e.*, [Pd₂(**L3**)₂(L^B)₂](NO₃)₄, **3B**·4NO₃ as the minor product upon complexation of **L3** and L^B with Pd(II). Whereas in the case of L^C , an exclusive formation of [Pd₂(**L3**)₂(L^C)₂](NO₃)₄, **3C**·4NO₃ was achieved. Among the newly attempted cases (*i.e.*, L^A , L^D – L^G), we successfully obtained discrete mixed ligated assembly [Pd₂(**L3**)₂(L^D)₂](NO₃)₄, **3D**·4NO₃ from the combination of **L3**, L^D and Pd(NO₃)₂, as indicated by ¹H NMR spectroscopy and ESI-MS data (Fig. S82 and S112). Since **L3** is unsymmetrical in nature, the mixed ligated cage was obtained as an isomeric mixture of two possible isomers of cage **3D**·4NO₃ (Fig. S186). For all the other cases, the mixed ligated assembly of **L3** and the diverging ligands (L^A , L^E – L^G) were unsuccessful. So, the mono-amide ligand **L3** can adapt to two different diverging ligands (L^C and L^D), producing the desired *cis*-Pd₂L₂²L₂²-type cages (where **L3** is in *anti*-conformation in the cage structures, Fig. S85); while the rigid **L1** yielded only one *cis*-Pd₂L₂²L₂²-type cage through integrative self-sorting. Hence, we infer that the conformational adaptability of **L3** falls somewhere between **L1** and **L2**. This showcases that the extent of conformational adaptability is proportional to the number of embedded amide units in the ligand backbone (Fig. 5A).

In the Pd₂L₂²L₂²-type assembly, the identical ligands coordinate to the Pd(II) centres in a *cis* fashion, where **L2** can adapt to any of the three conformations such as *syn*–*syn* ($L2^{SS}$), *syn*–*anti* ($L2^{SA}$) and *anti*–*anti* ($L2^{AA}$) in the cage structure. Earlier, we postulated the existence of three conformations based on the complexation-induced chemical shift changes in protons H_a and H_d, presumably due to possible intramolecular hydrogen bonding interactions with carbonyl oxygen (Fig. 4B). Next, we used ¹H–¹H NOE spectroscopy to verify the existing

conformations of **L2** in all five mixed-ligated cages. In the NOE spectrum of **2B**·4NO₃, the amide proton (N–H_e) shows strong cross-peak correlations with H_a and H_f, indicating that the **L2** is present in a *syn*–*syn* conformation ($L2^{SS}$) (Fig. 5B(i)). Similarly, we found NOE correlations for the amide protons (N–H_e) of **2E**·4NO₃ and **2F**·4NO₃ with H_d and H_g, no correlations were found with H_a/H_f, indicating the ligand conformation to be *anti*–*anti* ($L2^{AA}$) in the cage (Fig. 5B(iii) and S73). Understandably, the cages **2C**·4NO₃ and **2D**·4NO₃ showed multiple NOE correlations for the amide N–H_e with H_a, H_d, H_f, and H_g suggesting a *syn*–*anti* ($L2^{SA}$) conformation of **L2** in the cage (Fig. 5B(ii) and S60). In addition to the intra-ligand contacts, the NOE spectrum of all the cages also showed several cross-peaks for the inter-ligand through-space contacts between **L2** and L^X (x = B–F).

The *syn*–*syn* ($L2^{SS}$) and *anti*–*anti* ($L2^{AA}$) conformation of **L2** in **2B**·4NO₃ and **2E**·4NO₃/**2F**·4NO₃ contributes to the overall higher symmetry of the cages. On the other hand, though the *syn*–*anti* ($L2^{SA}$) conformation of **L2** in **2C**·4NO₃ and **2D**·4NO₃,

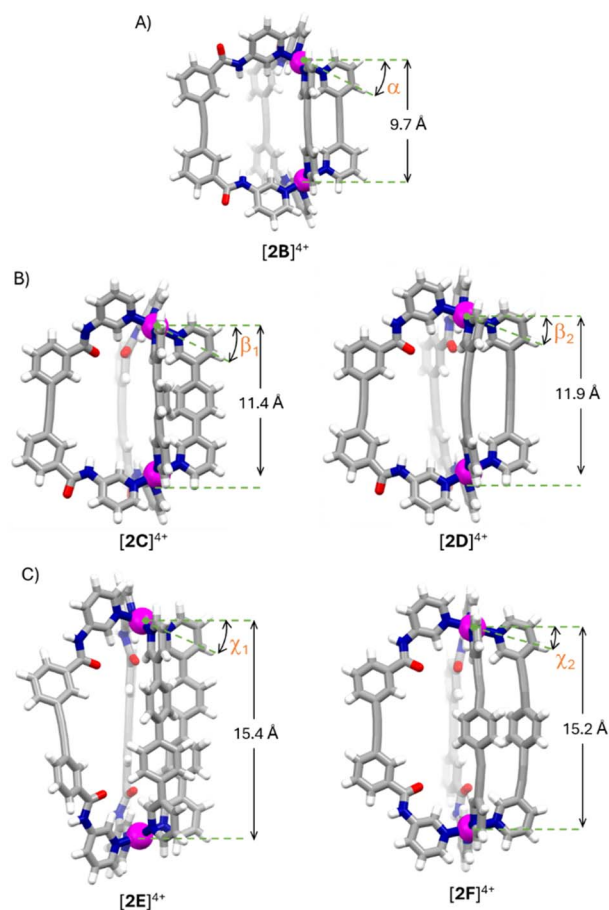


Fig. 6 (A) DFT optimized structure of $[2B]^{4+}$ showing *syn*–*syn* conformation of **L2**; (B) SC-XRD structure of $[2C]^{4+}$ and $[2D]^{4+}$ showing *syn*–*anti* conformation of **L2**; (C) DFT optimized structure of $[2E]^{4+}$ (left) and SC-XRD structure of $[2F]^{4+}$ (right) showing *anti*–*anti* conformation of **L2**. $\alpha = 38^\circ$; $\beta_1 = 35^\circ$; $\beta_2 = 32^\circ$; $\chi_1 = 25^\circ$; $\chi_2 = 19^\circ$. Angle α , β_1 , β_2 , χ_1 and χ_2 represent the angle of deviation from the parallel Pd(N_{py})₄ planes seen in typical Pd₂L₄²-type cages. Solvents and counteranions are not shown for clarity.



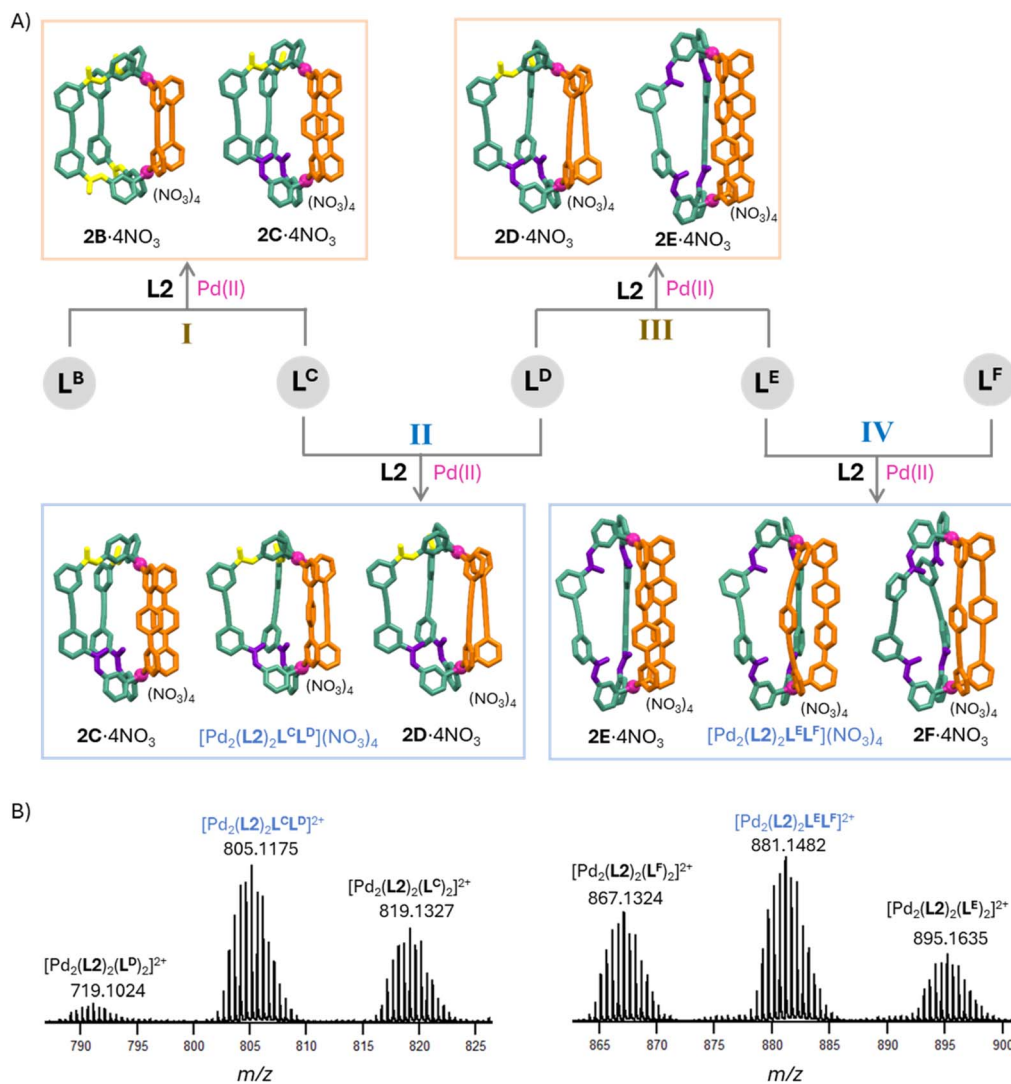


Fig. 7 (A) Selected self-sorting scenarios for the self-assembly of three ligand components with Pd(II). I and III: 2-fold heteromeric complete self-sorting; II and IV: mixed self-sorting; (B) partial ESI-MS for self-sorting scenarios in case II and IV showing mixed self-sorting products.

could lower the symmetry of the cage, we obtained a single set of signals in the ^1H NMR spectrum, presumably due to the fast exchange between the conformations at room temperature. To restrict the ligand conformation in the cage assembly, we attempted a variable temperature NMR study (lowering the temperature up to $-30\text{ }^\circ\text{C}$) using $2\text{C}\cdot 4\text{BF}_4$ and $2\text{D}\cdot 4\text{BF}_4$ in CD_3CN . However, we could not observe any significant splitting of the ^1H NMR signals, suggesting the existence of fast exchange process even at $-30\text{ }^\circ\text{C}$ (Fig. S176 and S180). Further, the two units of L_2 in cages $2\text{C}\cdot 4\text{NO}_3$ and $2\text{D}\cdot 4\text{NO}_3$ can have either a parallel/antiparallel arrangement in the $\text{Pd}_2\text{L}_2\text{L}_2^\lambda$ -type structure (Fig. S187 and S188). DFT calculation of the two possible isomers at the B3LYP/LanL2DZ, 6-31G(d) level in gas and implicit solvent (DMSO) phase suggested a lower energy for isomer-I, *i.e.*, parallel arrangement of L_2 in both the cages (SI Section S11, Table S1 and S2).

To further corroborate the conformational control in five *cis*- $\text{Pd}_2\text{L}_2\text{L}_2^\lambda$ -type cages, $[\text{Pd}_2(\text{L}_2)_2(\text{L}^\lambda)_2]^{4+}$ by single crystal X-ray diffraction (SC-XRD) analysis, concerted efforts were made to

crystallize the cages. We used different solvents and solvent mixtures as well as varied the counteranions. After numerous attempts, we could get crystal data suitable for SC-XRD analysis of $[2\text{C}]^{4+}$ and $[2\text{D}]^{4+}$ with NO_3^- as counteranion by vapour diffusion of benzene:acetonitrile and toluene:*t*-butanol in DMSO solution of $2\text{C}\cdot 4\text{NO}_3/2\text{D}\cdot 4\text{NO}_3$, respectively. SC-XRD analysis confirmed *syn-anti* conformation of L_2 in both the cage structures (Fig. 6). Subsequently, we collected the crystal data for $[2\text{F}]^{4+}$ with BF_4^- as counteranion. The single crystals were obtained by vapour diffusion of THF in a mixture of DMSO: CH_3CN (2:1) solution of $2\text{F}\cdot 4\text{BF}_4$. Structural analysis reiterated the existence of L_2 in *anti-anti* conformation in $[2\text{F}]^{4+}$ (Fig. 6C). In cages $[2\text{B}]^{4+}$ - $[2\text{F}]^{4+}$, the angle of intersection of the $\text{Pd}(\text{Npy})_4$ planes (usually parallel for typical $\text{Pd}_2\text{L}_4^\lambda$ -type cages) gradually decreased when we progressively increased the length of rigid complementary ligands.

We successfully introduced conformational adaptability in *cis*- $\text{Pd}_2\text{L}_2\text{L}_2^\lambda$ -type systems with embedded amide moiety in L^λ -type ligand and suitable rigid diverging ligands (L^λ -type), which



could dictate the requisite conformation of L^a in the cage. The control over the choice of conformations based on the length of rigid diverging ligands opens the possibility of exploring the higher-order self-sorting processes using $Pd_2L_2^aL_2^x$ -type cages. We presume that three distinct conformations of L_2 (where L_2 can be used as a common ligand) could enable up to an unprecedented 3-fold heteromeric complete self-sorting (*i.e.*, three co-existing mixed ligated assemblies) in coordination cages.

We set out to explore the conformationally adaptive nature of ligand L_2 to demonstrate the self-assembly of three different ligands and Pd(II), targeting the assembly of two co-existing $Pd_2L_2^aL_2^x$ -type cages, also known as 2-fold heteromeric complete self-sorting.^{6,7} In the co-existing mixed ligated assemblies, we take the conformationally adaptive L_2 as a common ligand, while we use the combination of any two rigid ligands from a set of five ligands, L^B-L^F . For all the experiments, we treated $Pd(NO_3)_2$ with L_2 and two chosen ligands amongst L^B-L^F in a 2 : 2 : 1 : 1 ratio in $DMSO-d_6$ and stirred at room temperature. In the cases where 2 consecutive ligands (*i.e.*, $L^B:L^C$, $L^C:L^D$, $L^D:L^E$ and $L^E:L^F$) were selected alongside L_2 and $Pd(NO_3)_2$ (Fig. 7A), we observed two different scenarios: (i) 2-fold

heteromeric complete self-sorting outcome for the cases **I** and **III**, where a mixture of co-existing mixed-ligated cages ($2B \cdot 4NO_3 + 2C \cdot 4NO_3$ and $2D \cdot 4NO_3 + 2E \cdot 4NO_3$, respectively) was observed; (ii) mixed self-sorting (both integrative and heteromeric) outcome for the cases **II** and **IV**, where we observed an additional tripleptic mixed-ligated assembly^{5c,d} ($[Pd_2(L_2)_2L^C L^D](NO_3)_4$ and $[Pd_2(L_2)_2L^E L^F](NO_3)_4$, respectively), along with heteromeric products ($2C \cdot 4NO_3 + 2D \cdot 4NO_3$ and $2E \cdot 4NO_3 + 2F \cdot 4NO_3$) (Fig. S125, S129, S132 and S134). Also, in case **II** the tripleptic cage $[Pd_2(L_2)_2L^C L^D](NO_3)_4$ was observed as the dominating species in the mixture of assemblies. ESI-MS analysis for case **II** confirmed the existence of three co-existing assemblies, $2C \cdot 4NO_3$, $2D \cdot 4NO_3$ and $[Pd_2(L_2)_2L^C L^D](NO_3)_4$. Likewise, a combination of $2E \cdot 4NO_3$, $2F \cdot 4NO_3$ and $[Pd_2(L_2)_2L^E L^F](NO_3)_4$ was supported by ESI-MS data for case **IV** (Fig. 7B). However, all the other diverging ligand combinations (*i.e.*, $L^B:L^D$, $L^B:L^E$, $L^B:L^F$, $L^C:L^E$, $L^C:L^F$ and $L^D:L^F$) apart from the cases **I-IV**, displayed 2-fold heteromeric complete self-sorting outcome. So, it is understandable that the heteromeric assembly using two different diverging ligands together with L_2 and $Pd(NO_3)_2$ yielded a 2-fold heteromeric complete self-sorting outcome, where the two diverging ligands could induce two different

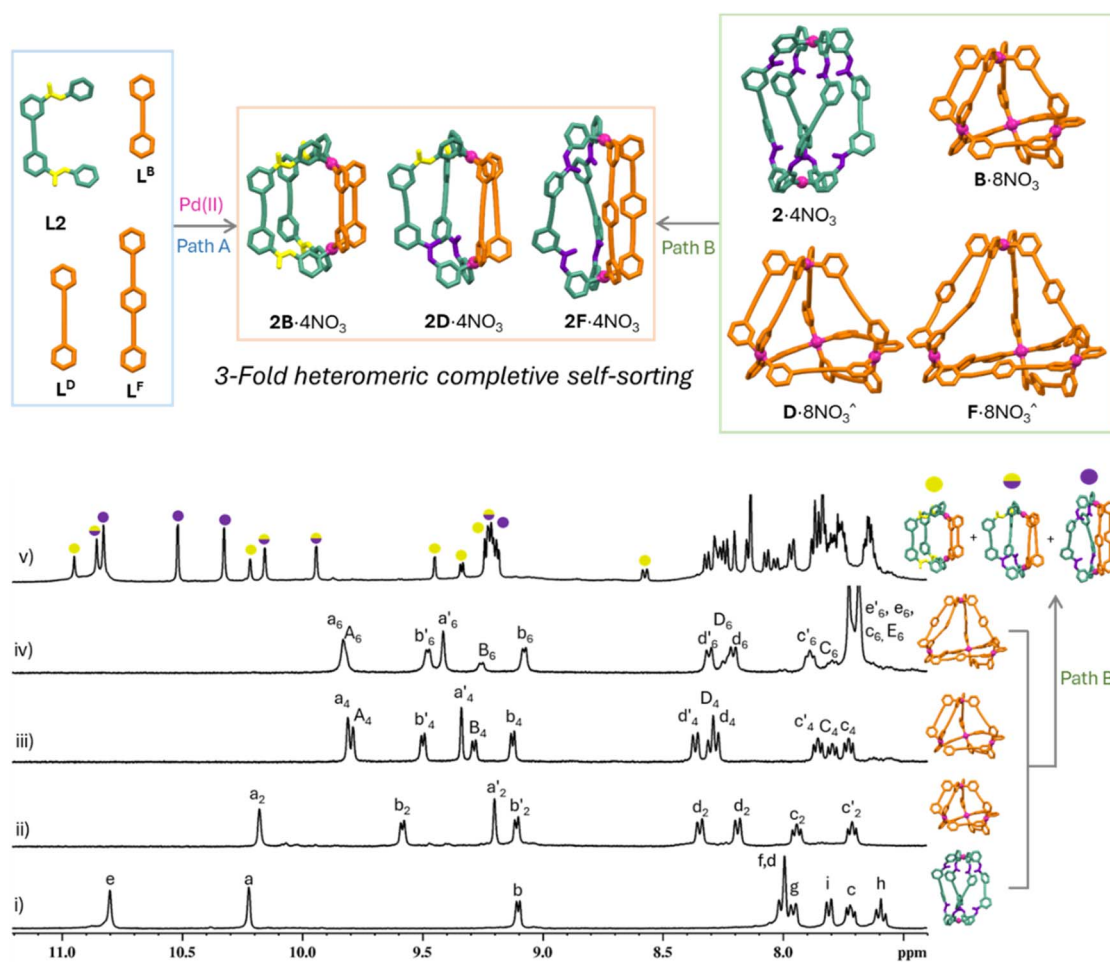


Fig. 8 3-Fold heteromeric complete self-sorting showing co-existence of three different $Pd_2L_2^aL_2^x$ -type assemblies; Partial 1H NMR spectra (400 MHz, 298 K, $DMSO-d_6$) of (i) $2 \cdot 4NO_3$; (ii) $B \cdot 8NO_3$; (iii) $D \cdot 8NO_3$ (Major product) + $D' \cdot 6NO_3$; (iv) $F \cdot 8NO_3$ (Major product) + $F' \cdot 6NO_3$; (v) co-existing mixture of $2B \cdot 4NO_3$, $2D \cdot 4NO_3$ and $2F \cdot 4NO_3$.



conformations of **L2**. On the other hand, when two different diverging ligands that can induce the same conformations produce mixed self-sorting (a combination of integrative and heteromeric) outcomes. A similar self-sorting outcome was observed for cage fusion reaction (case **I–IV**) of the three homoleptic assemblies, *i.e.*, $2 \cdot 4\text{NO}_3$ and the two chosen $\text{X} \cdot 8\text{NO}_3$ ($\text{X} = \text{B–F}$). The ^1H NMR spectra of all the cage mixtures obtained through 2-fold heteromeric complete self-sorting are comparable to that of the respective mixed-ligated $\text{Pd}_2\text{L}_2^{\text{X}}\text{L}_2^{\text{X}}$ -type cages (Fig. S125–S134).

Next, we intend to extend the self-sorting processes to a more intricate level, *i.e.*, 3-fold heteromeric complete self-sorting. Achieving three discrete co-existing mixed-ligated assemblies *via* the self-assembly of four distinct ligands could be a fascinating study. We deduced that using the diverging ligand pairs inducing two different conformations in **L2** is essential for attaining orthogonality in the coordination cage systems to achieve 2-fold heteromeric complete self-sorting. Hence, we decided to pick a mix of three diverging ligands that induce three distinct conformations of **L2** (*i.e.*, L2^{SS} , L2^{SA} and L2^{AA}) to achieve 3-fold heteromeric complete self-sorting. Firstly, we have chosen diverging ligands L^{B} , L^{D} and L^{F} , such that **L2** would adapt to L2^{SS} , L2^{SA} and L2^{AA} conformations in their respective mixed ligated cages. A mixture of **L2**, L^{B} , L^{D} , L^{F} and $\text{Pd}(\text{NO}_3)_2$ (3 : 1 : 1 : 1 : 3) in $\text{DMSO-}d_6$ was stirred at room temperature for 12 hours (path A). Very interestingly, the ^1H NMR spectrum showed clean formation of three different $\text{Pd}_2\text{L}_2^{\text{X}}\text{L}_2^{\text{X}}$ -type assemblies, $2\text{B} \cdot 4\text{NO}_3$, $2\text{D} \cdot 4\text{NO}_3$ and $2\text{F} \cdot 4\text{NO}_3$ co-existing in the solution (Fig. S142). Here, the three different mixed-ligated assemblies share a common ligand (**L2**). However, they differ in the relative orientation of the amide moiety in the cage structures, where the ligand **L2** is locked in *syn-syn*, *syn-anti* and *anti-anti* conformations. Alternatively, the cage fusion of the four high-symmetry homoleptic assemblies $2 \cdot 4\text{NO}_3$, $\text{B} \cdot 8\text{NO}_3$, $\text{D} \cdot 8\text{NO}_3$ and $\text{F} \cdot 8\text{NO}_3$ (both $\text{D} \cdot 8\text{NO}_3$ and $\text{F} \cdot 8\text{NO}_3$ exist alongside a minor product (Pd_3L_6)) also resulted in the simultaneous formation of three low-symmetry mixed ligated assemblies (path B) representing the 3-fold heteromeric complete self-sorting as shown in Fig. 8. Though the system involves simultaneous utilization of multiple metal–ligand interactions, full orthogonality within the $\text{Pd}_2\text{L}_2^{\text{X}}\text{L}_2^{\text{X}}$ -type cages was achieved by geometric complementarity and conformational adaptability of **L2** in the presence of other rigid diverging ligands (L^{X}). A similar 3-fold heteromeric self-sorting process was also observed for the other combinations of the diverging ligands ($\text{L}^{\text{B}}:\text{L}^{\text{C}}:\text{L}^{\text{F}}$, $\text{L}^{\text{B}}:\text{L}^{\text{C}}:\text{L}^{\text{E}}$ and $\text{L}^{\text{B}}:\text{L}^{\text{D}}:\text{L}^{\text{E}}$) with **L2** and $\text{Pd}(\text{NO}_3)_2$. In all the cases, the ^1H NMR spectrum showed clean formation of the desired co-existing mixed ligated assemblies (Fig. S139–S141).

Conclusions

In summary, we have demonstrated a substantial change in the mixed ligand complexation behavior of a converging ligand by incorporating di-amide functionality on its backbone. While **L1** undergoes absolute integrative self-sorting with only one ligand from a series of diverging ligands ($\text{L}^{\text{A}}\text{–}\text{L}^{\text{G}}$) to form a *cis*- $\text{Pd}_2\text{L}_2^{\text{X}}\text{L}_2^{\text{X}}$ -type cage. On the other hand, the integration of amide moieties

on both sides, *i.e.*, **L2**, enables a family of five *cis*- $\text{Pd}_2\text{L}_2^{\text{X}}\text{L}_2^{\text{X}}$ -type architectures *via* self-assembly of the conformationally adaptive ligand and complementary ligands of varied lengths ranging from 8.1 to 15 Å. Fascinatingly, adaptability of **L2** with three distinct switchable conformational states enabled us to explore the higher order 2-/3-fold heteromeric complete self-sorting. An unprecedented, cage fusion of four different homoleptic assemblies resulted in a 3-fold heteromeric complete self-sorting, where three distinct *cis*- $\text{Pd}_2\text{L}_2^{\text{X}}\text{L}_2^{\text{X}}$ -type assemblies were found to co-exist in solution. The error-free orthogonality in the coordination cage system involving multiple metal–ligand interactions was a result of the ability of the conformationally adaptive ligand **L2** to attain three different conformations (L2^{SS} , L2^{SA} and L2^{AA}) in the *cis*- $\text{Pd}_2\text{L}_2^{\text{X}}\text{L}_2^{\text{X}}$ -type cages. This work illustrates that the introduction of switchable conformational states in the ligand backbone paves the way for constructing new architectures with modulable cavity size, shape and functions.

Author contributions

M. P., V. S., and D. K. C. designed the project. M. P. and V. S. carried out the research and analyzed the data. M. P., V. S., and D. K. C. wrote the manuscript. V. R. refined the SC-XRD data and contributed to the preparation of the manuscript. D. K. C. is the principal investigator and managed the project. All the authors reviewed the manuscript and have approved the final version of the manuscript.

Conflicts of interest

There are no conflicts to declare.

Data availability

CCDC 2466372 (**L2**) and 2466383–2466385 ($2\text{C} \cdot 4\text{NO}_3$, $2\text{D} \cdot 4\text{NO}_3$, and $2\text{F} \cdot 4\text{BF}_4$) contain the supplementary crystallographic data for this paper.^{23a–d}

The data supporting this article have been included as part of the supplementary information (SI). Supplementary information is available. See DOI: <https://doi.org/10.1039/d5sc05568g>.

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