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Original

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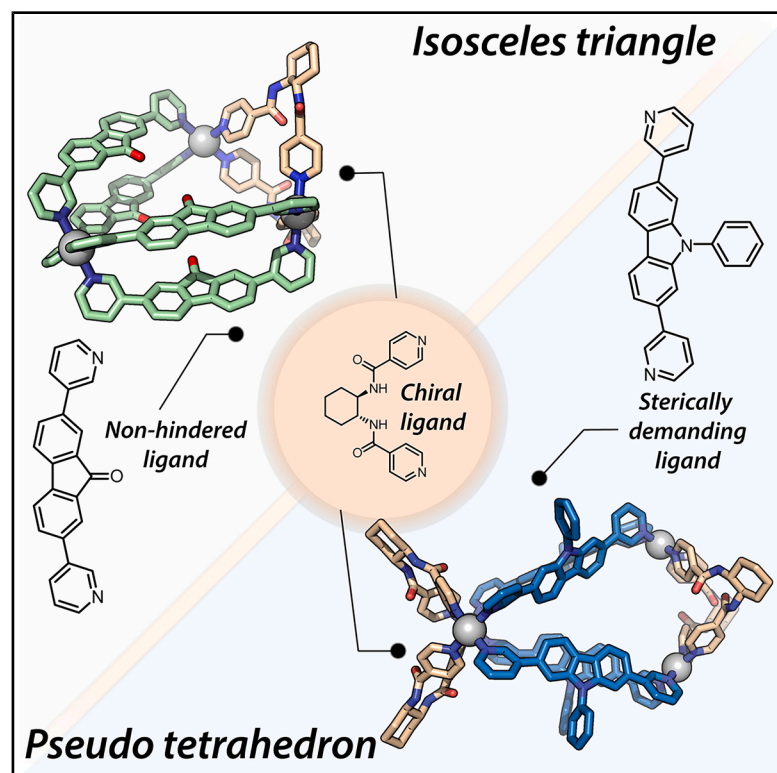
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Graphical abstract



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In brief

The precise formation of low-symmetry nanostructures from different building blocks is prevalent in nature but a major challenge in the lab. Recent advances in non-statistical assembly strategies have opened access to intricate structural motifs, combining multiple functionalities. As predicted by a computational toy model, Pd₃A₂B₄ isosceles triangles and Pd₄C₄D₄ pseudo-tetrahedra form under control of “adjacent backbone interactions” (ABIs). Assembled from four orthogonal ligands, they coexist under heteromeric narcissistic self-sorting conditions and have the ability to discriminate guest enantiomers.

Highlights

- Non-statistical self-assembly of heteroleptic Pd₃A₂B₄ isosceles triangles
- Heteromeric narcissistic self-sorting from a mixture of four different ligands
- Structure prediction using a computational toy model
- Selective discrimination of guest enantiomers in self-assembled chiral hosts

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Article

Adjacent backbone interactions control self-sorting of chiral heteroleptic Pd₃A₂B₄ isosceles triangles and Pd₄A₄C₄ pseudo-tetrahedra

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THE BIGGER PICTURE Life's molecular machinery is composed of a multitude of individual proteins and nucleic acids that selectively associate to larger complexes via a combination of weak interactions. Synthetic supramolecular chemistry takes inspiration from this structural and functional complexity, aimed at mimicking and understanding underlying concepts such as heterotopic interactions, non-statistical multi-component assembly, and dynamic interconversions. Gaining control over the self-sorting of a set of different building blocks to yield a discrete three-dimensional nano-object is not only a challenging goal for advancing synthetic methodology, but it is also crucial to bring multiple functionalities together within a single assembly. Mastering selective multicomponent assembly enables the emergence of sophisticated function, for example, in high-fidelity guest recognition, selective catalysis, or precise placement of photo-functional building blocks in chromophore aggregates. Low-symmetry multicomponent structures of increasing size can now be accessed by metal-mediated self-assembly when exploiting adjacent backbone interactions (ABIs) as a structure-guiding effect. Furthermore, modern computational methods help with predicting plausible assembly outcomes.

SUMMARY

Taking inspiration from biological structures, self-assembled nano-objects promise application potential, e.g., in selective catalysis, smart materials, and drug delivery. While integrating multiple different building blocks greatly enhances their versatility, it is a challenge to design low-symmetry multicomponent structures without generating statistical mixtures. Based on adjacent backbone interactions (ABIs), we introduce here a series of integratively self-sorted Pd_nL_{2n} (n = 3, 4) assemblies, each comprising two distinct, easily accessible ligands. In these Pd₃A₂B₄ isosceles triangles and Pd₄A₄C₄ pseudo-tetrahedra, one ligand is always chiral. Noteworthy, the triangular structures contrast previously described heteroleptic Pd₃L₆ assemblies in that the two differentiable ligands are not contained in equal stoichiometries. The chiral assemblies bind and strongly discriminate chiral guests. They can coexist orthogonally, leading to cage populations under heteromeric narcissistic self-sorting. We further present a computational toy model toward structure prediction of such assemblies, opening avenues for the rational design of discrete metallosupramolecular three-dimensional architectures.

INTRODUCTION

Coordination-driven discrete nanoarchitectures have attracted considerable attention and stand as appealing candidates for mimicking natural host systems such as enzymes. The direction-

ality of bonds between palladium(II) cations and nitrogen heterocycles, together with their dynamic nature, has allowed a myriad of homoleptic assemblies to be rationally constructed or serendipitously discovered. These have been employed in guest separation,^{1–6} catalysis under confinement,^{7–14} and as bases



for advanced materials.^{15–17} With the aim to bring their structural and functional complexity even closer to biological receptors and catalysts,^{18–21} supramolecular chemistry has recently intensified efforts in development of strategies to create non-statistical heteroleptic assemblies in which multiple components are brought together within a single low-symmetry cage structure.^{22–26} Just very recently, populations of such assemblies in which multiple homoleptic or heteroleptic Pd-based structures coexist in a controlled and orthogonal way have started to be described.^{27–29} We succeeded to establish a set of synergistic and rational approaches to target formation of such heteroleptic architectures, namely, shape complementary assembly (SCA),^{30–33} coordination sphere engineering (CSE),^{25,26,34,35} and more recently, adjacent backbone interaction (ABI).^{36,37} These proved to be highly instrumental in the design of a series of multifunctional dinuclear species, culminating in the synthesis of maximally self-sorted Pd₂ABCD cages.^{38–40}

Design strategies toward non-statistical cage assembly have recently been supported by computational workflows.^{22,41–43} However, existing approaches focus on predicting the stability of known structures.⁴⁴ Unbiased structure prediction from a set of given building blocks is an expensive task, requiring the evaluation of a large number cage structures (many of which end up as unreasonable, wasted computations).⁴⁵ Some of us recently developed an open-source, toy-model approach that can evaluate thousands of structures on ordinary computational hardware in a reasonable time (days), opening the possibility of rapidly predicting hard-to-intuit assemblies.⁴⁶

Most experimental systems reported to date have focused on dinuclear Pd₂L₄ heteroleptic assemblies. However, the employed principles can be translated to higher-order heteroleptic species, and while still scarce, some studies have reported the formation of multicomponent structures with nuclearities of three, four, and even six.^{24,36,37,47–49} Specifically, we demonstrated that SCA and ABI can be used to obtain Pd₃A₃B₃ and Pd₄A₄B₄ rings as well as a heteroleptic Pd₄A₄C₄ tetrahedra.^{36,37} The functionalization and application of such high-nuclearity heteroleptic architectures are still in their infancy.^{36,49} Herein, we report the formation of a family of chiral assemblies for which self-sorting is driven by the degree of steric demand (from small NH or C=O groups to bulky geminal alkyl substituents) installed on the non-chiral ligand component. On the one hand, non-bulky ligands display an unprecedented sorting behavior and assemble with chiral counterparts into isosceles triangular Pd₃A₂B₄ rings. On the other hand, the utilization of bulky groups on those ligands generates tetranuclear pseudo-tetrahedral Pd₄A₄C₄ architectures. All compounds display intra-assembly ligand-to-ligand chirality transfer, evidenced by chiroptical spectroscopies, as well as the ability to discriminate chiral guests. Eventually, we highlight the formation of cage populations by heteromeric narcissistic self-sorting, composed of either two distinct Pd₃A₂B₄ rings or of a Pd₃A₂B₄ ring and a Pd₄A₄C₄ tetrahedron.

RESULTS AND DISCUSSION

Synthesis of isosceles triangles

All ligands used in this study were synthesized through high-yielding one-step reactions from commercially available

reagents, following our established procedures (Figures S1–S3).^{23,37} Self-assembly of ligands with Pd(II) cations and formation of the corresponding homoleptic species have been previously reported, except for ligand **L7** (*vide infra*). In particular, enantiopure ligand **L1** (*R,R* enantiomer) leads to the formation of a mixture of homoleptic compounds with a general formula Pd_nL₁_{2n} when combined in a 1:1 ratio with [Pd(MeCN)₄](BF₄)₂ in acetonitrile.⁵⁰ Ligands **L2**, **L4**, and **L5** all generate mixtures of homoleptic Pd₄L₈ tetrahedra and Pd₃L₆ rings in acetonitrile, while **L3** leads to the tetrahedral assembly exclusively.^{23,37,38} We previously showed that the presence of steric bulk in ligands with such bent backbones results in an opposite orientation between the backbone substituent and the pyridine nitrogen in respective assemblies, with a consequent opening of the binding vectors to a ~90° angle.³⁷ Due to this effect, **L6** results in the formation of a homoleptic Pd₆L₁₂ octahedron when combined with Pd(II). The same principle applies to **L7**, for which we here observed the formation of a similar octahedral Pd₆L₁₂ structure with the phenyl groups on the carbazoles directed outside the cavity. **L7** and the octahedron were fully characterized by nuclear magnetic resonance (NMR), electrospray ionization mass spectrometry (ESI-MS), and a single-crystal X-ray structure (Figures S4–S8, S103, and S104). The introduction of steric bulk into this class of ligands has been shown to yield heteroleptic structures through ABI. Indeed, the combination of **L6** with **L2** yielded a discrete Pd₄A₄B₄ heteroleptic tetrahedron where the bulkier ligand **L6** occupies the single edges, while ligand **L2** occupies the doubly bridged ones.³⁷

Aiming at enhancing both the structural and functional complexity of such higher-nuclearity heteroleptic assemblies, we then extended the system by introducing an enantiomerically pure ligand **L1**. At first, we studied the self-assembly of Pd(II) with **L1** and **L2**, motivated by the fact that **L2** retains its emissive properties in Pd-based assemblies and that **L1** has been shown to successfully transfer its chiral information to another fluorenone-based ligand, resulting in circularly polarized luminescence (CPL).⁵⁰ By reacting the components in a 1:1:1 ratio, we obtained a mixture of homoleptic and heteroleptic species. Analyzing the NMR allowed us to identify signals related to the homoleptic species of **L1** as well as another signal set, where particularly four signals from Ha (Figure 2A) of equal intensities caught our attention. Further, DOSY NMR confirmed that all of these signals belonged to the same species with a hydrodynamic radius of 12.7 Å. ESI-MS allowed us to identify the stoichiometry of this compound, resulting in an unprecedented [Pd₃L₁₂L₂₄+n BF₄]^{(4–n)+} assembly. Thus, when Pd(II) cations and the same ligands **L1** and **L2** were then combined in a 3:2:4 ratio, we were able to exclusively obtain this species (Figures 2B and S9–S16).

While symmetric homoleptic and heteroleptic³⁶ trinuclear rings have been reported, in-depth analysis of the ¹H NMR splitting, helped by 2D NMR data, reveals the formation of a rather low-symmetrical isosceles triangular ring structure with a previously not reported ligand stoichiometry reminiscent, yet different, of a structure reported earlier by us with a backbone-bridged ligand.²³ The two chiral ligands connect two neighboring Pd(II) ions, while the four fluorenone ligands

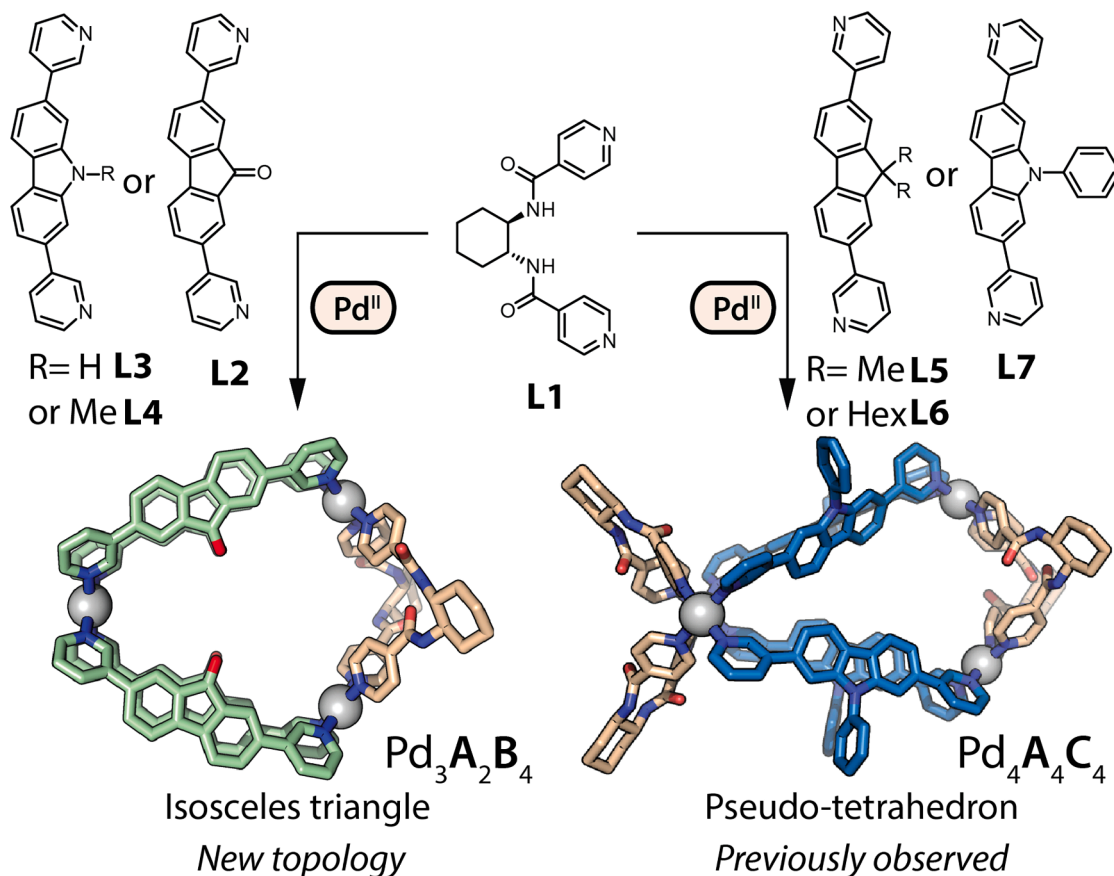


Figure 1. Adjacent backbone interactions drive integrative self-sorting

Adjacent backbone interactions (ABIs) between cyclohexane diamide ligand **L1** and a set of fluorene/carbazole-based ligands **L2–L7** allow control over the formation of chiral heteroleptic Pd₃L₁L₂L_x (x = 2,3,4) isosceles triangles or Pd₄L₁L₄L_x (x = 5,6,7) pseudo-tetrahedra.

L2 complete the ring by bridging those Pd(II) cations with the remaining one. This is evidenced by the ¹H-¹H ROESY cross-peaks between H1 and H1' from **L1** and Ha3, Ha4, Hc3, and Hc4 from **L2** (Figure S15). Two Pd(II) centers have therefore a heteroleptic *cis*-environment, while the third is only coordinated by pyridines of **L2**. Owing to the chirality of **L1**, the structure possesses a single C₂ axis passing through the middle of the void between the two ligands **L1** and the opposite Pd(II) center. All four pyridines of the two ligands **L2** on the same side with respect to the ring plane are thus inequivalent (highlighted by different colors in Figure 3C), creating a 4-fold splitting of **L2**, while **L1** protons split into two sets. This topology is further supported by two distinct sets of ¹H-¹H ROESY cross-peaks between Ha3 and Ha4 on one side and Ha1 and Ha2 on the other (Figure S15). To strengthen the reliability and versatility of this strategy to form unsymmetrical heteroleptic rings, we expanded the scope of non-chiral ligands to a series of other compounds, having a similar bent backbone but different steric bulk (**L3–L7**; Figure 1). **L3** and **L4**, having less or similar backbone hindrance, yielded the same Pd₃A₂B₄ structure (Figures S17–S30), while larger substituents (**L5–L7**) yielded a different outcome (*vide infra*).

Computational structure prediction using minimal models

Having experimental evidence for the formation of a structure with the unexpected stoichiometry Pd:**L1**:**L2** equal to 3:2:4 and indications of the building block configuration, we turned to computational approaches to better understand the structure of this assembly and to obtain insights into reasons why this is selected among the theoretically possible ones. We implemented a computational structure prediction algorithm that relies only on the input of building block structures and target stoichiometries (complete computational details are available in the supplemental information). Because many possible structures could be derived, we use low-cost toy-model simulations.⁴⁶ This new, open-source approach is built on the software *stk*⁵¹ and OpenMM⁵² for efficient geometry optimizations (Figures S91–S99; Section S6).

Our toy-model approach simplifies chemical complexity to a few key geometrical features. Here, we have mapped **L1** to a rigid ligand template (Figure 2C; note that this version of the model does not encode stereochemistry into the **L1** model and is inherently an approximation of that geometry) and a twistable ligand template (Figure 2C; Section S6); the distinction is necessary to represent rotations in the pyridine groups. This mapping

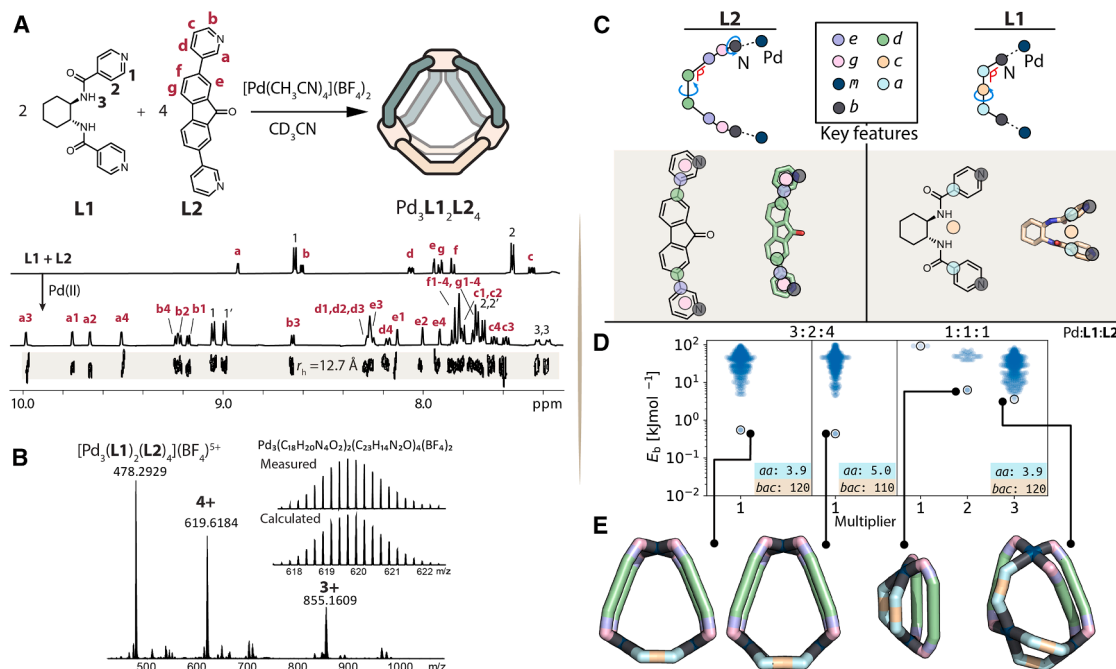


Figure 2. Assembly of the low-symmetry $\text{Pd}_3\text{L}_1\text{L}_2\text{L}_4$ three-membered ring and its toy-model prediction

(A) Self-assembly of **L1** and **L2** with Pd(II) yields a $\text{Pd}_3\text{L}_1\text{L}_2\text{L}_4$ ring. ^1H NMR (trideuteroacetonitrile [CD_3CN], 500 MHz) stack of both ligands mixed and after the addition of Pd(II). Assignment and ^1H DOSY NMR traces are given on the spectra.
 (B) HR-ESI-MS of an acetonitrile solution of $\text{Pd}_3\text{L}_1\text{L}_2\text{L}_4$. The inset highlights the measured and calculated isotopic pattern.
 (C) Mapping between atomistic and toy models for first-pass structure prediction.
 (D) Energy per building block (E_b) of all generated structures with **L1** and **L2**. Different multipliers of the stated stoichiometry (above the plot) are shown as columns in (D), and a bee-swarm spread is applied in the x axis position to avoid overlap. The lowest energy is highlighted by a black circle.
 (E) Lowest-energy structures from each stoichiometry study (including *cis*- $\text{Pd}_2\text{L}_1\text{L}_2\text{L}_2$); lines mark position in (D); bead colors as in (C).

is a first-step approximation for large-scale structure prediction that does not consider the building block fluctuations due to environmental and assembly effects. We explore the strain energy per building block (E_b), arising from the placement of these toy-building blocks into arbitrary cage graphs (Section S6.3). For **L1** + **L2**, our method automatically builds 489 systems with stoichiometry 3:2:4 (multiplier of 1) and 531 with stoichiometry 1:1:1 (multipliers of 1, 2, and 3). Figure 2D shows that the lowest-energy topology for **L1** and **L2** is a double-walled isosceles triangle topology with an arrangement of the building blocks as expected from the experimental results. With a 1:1:1 ratio, we see that a double-walled triangle with a non-symmetric arrangement of building blocks (one edge bridged by two different ligands) is also the lowest in energy, however, still highly strained. The common $\text{M}_2\text{L}_2\text{L}'_2$ structure is shown to be also of rather high energy for the **L1** + **L2** combination. This structure prediction approach agrees with the experimental data derived above and provides a platform for further exploration.

One key benefit of the toy-model approach is that we can scan multiple “configurations” or “mappings” between models to derive structure-property relationships. First, we performed a one-dimensional scan of the stability of the $\text{M}_3\text{L}_4\text{L}'_2$ structure from the **L1** parameters *aa*, *dd*, *de*, *bac*, and *dde* (Figure S96; as we focus only on one topology, we performed more costly geometry optimizations in this case). From there, we found

that only the angles *bac* and *dde* led to significant changes in energy. Hence, we scanned these parameters (and others; Section S6) in two dimensions. The angle *bac* directly determines the ligand binder angles, while *dde* has this effect by altering the position of the rotatable pyridine ring. From this analysis, we see that the range of stable *bac* angles is limited to around 110° – 130° (depending on the variable on the other dimension). We also see a twisting of the twistable ligand in these maps (Figures 3B and S98), but the $\text{M}_3\text{L}_4\text{L}'_2$ topology cannot support the convex binding mode seen in the other examples.

To further support the robustness of the experimental and computational approaches, we employed another chiral ligand **L1b** (*R,R* enantiomer) that upon combination with **L2** yielded the same type of ring with the formula $\text{Pd}_3\text{L}_1\text{b}_2\text{L}_4$. Indeed, **L1b** and **L1** are roughly similar in shape concerning binding angles and distances (Figure S95); both align within the stable regions of the grid-based scan (Figures S95–S99). That a comparable structure is formed was confirmed by observing the same splitting in the ^1H NMR of the assembly, as well as by evident ROESY cross-peaks (Figures S59–S64). At the same time, high-resolution (HR)-ESI-MS shows only peaks corresponding to the expected species. Eventually, we obtained single crystals suitable for X-ray synchrotron diffraction from benzene vapor diffusion in acetonitrile (Figures 3D, S105, and

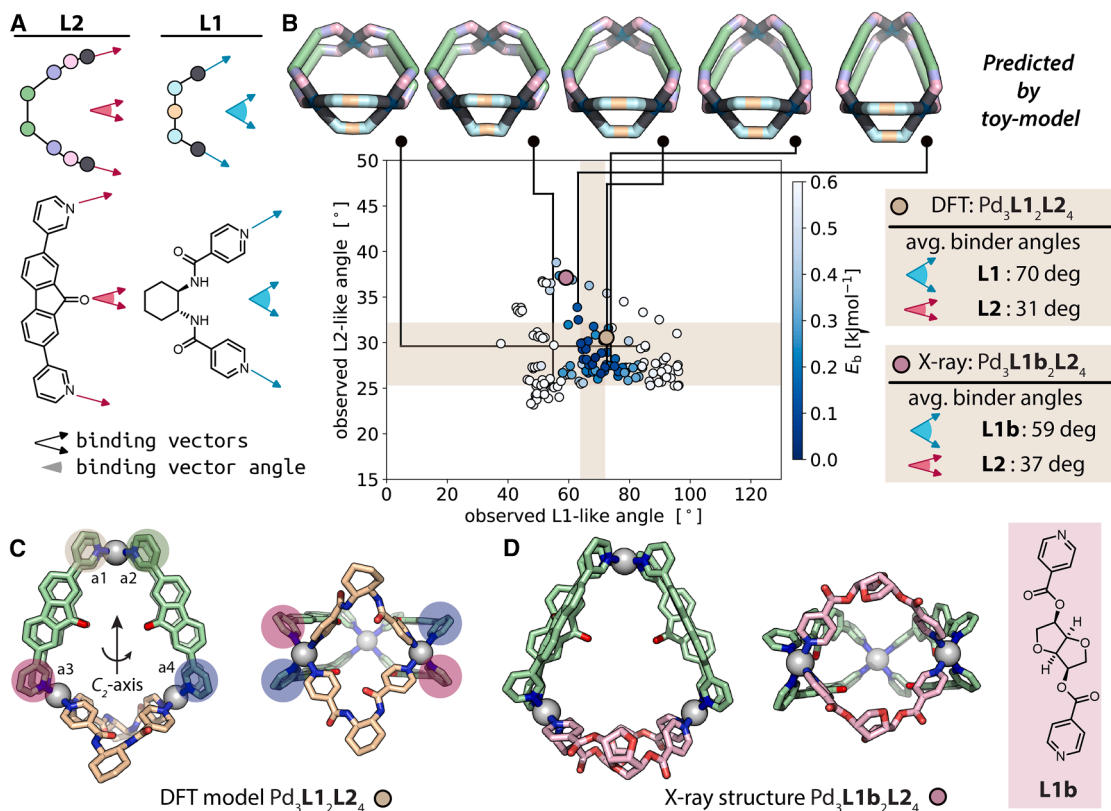


Figure 3. Geometric parameters extracted from toy model and comparison with DFT modeling and single-crystal X-ray structure

(A) Relationship between the binder-vector angles and the atomistic and toy models.

(B) A map of the measured L1-like and L2-like angles of toy-model cage structures obtained from a scan of the *bac* and *dde* angles. Beige regions highlight the limit of angles where stable structures are found ($E_b < 0.1$ kJ mol⁻¹). Some toy models covering this space (of various stability) are shown at the top. The parameters corresponding to the atomistic structures presented in (C) and (D) are highlighted in beige boxes and marked on the map to visualize the model adequacy with experimental and higher computational data.

(C) Top and side view of DFT model (ω B97X-D/def2-SVP) of Pd₃L₁₂L₂₄, with the different chemical environments of L2 highlighted.

(D) Top and side view of the X-ray structure of Pd₃L_{1b}₂L₂₄, with L1b structure shown in the pink box.

S106). The compound crystallizes in a monoclinic C_2 space group, being one of the 65 Sohncke space groups where chiral compounds can crystallize. In the obtained ring structure, the expected ligand arrangement can be observed with the two ligands L1b sitting on the same edge while the four ligands L2 bridge to the third Pd(II). When considering that the fluorenone ligands are able to freely rotate in solution, the mentioned C_2 axis through the middle of the space between the two chiral ligands and the opposite Pd(II) center can be anticipated. In the X-ray structure, however, two fluorenone ligands on one side with respect to the ring plane are rotated by about 90° to this plane and face the backbones of their neighboring ligands, similar to what we previously observed in the solid-state structure of the Pd₃L₂₆ homoleptic assembly. The binding angles between pyridines of the same L2 range between 31.5° and 37.0°, while for L1b, the binding vectors are more divergent with angles of ~60°. This results in a cone-shaped structure with the two chiral ligands bulging slightly outward from the triangle. Based on this X-ray structure, we constructed a density functional theory (DFT) geometry-optimized model for Pd₃L₁₂L₂₄ and observed that both species are similar in shape (Figures 3C and S100). We stress, however, that

while both L1 and L1b take comparable positions in assemblies Pd₃L₁₂L₂₄ and Pd₃L_{1b}₂L₂₄, the edge occupied by L1 (based on the Pd-Pd distance in the corresponding DFT model) measures about 85% of the respective Pd-Pd distance in the X-ray structure of the L1b-containing assembly (12.3 Å). A closer look at the structures reveals that ligand L1, having amide linkages installed in vicinal positions on the aliphatic ring, allows for H-bonding between the amides of both ligand arms, thus rather contracting the edge (and also bending ligands L2 slightly inward), while L1b, carrying the donor arms in positions separated by three bonds on the aliphatic core (and featuring non-H-bonding esters instead of amides), possesses a more extended geometry. Similar structural features are also seen in the toy models.

Formation of a pseudo-tetrahedron by ABIs

In line with our strategy to obtain higher-nuclearity heteroleptic structures such as Pd₄A₄B₄ rings, saddles,³⁶ or tetrahedra,³⁷ we were curious to test the effect of using bulkier fluorenone or carbazole-type ligands in combination with L1. We thus expanded the scope of ligands by employing L5, featuring a

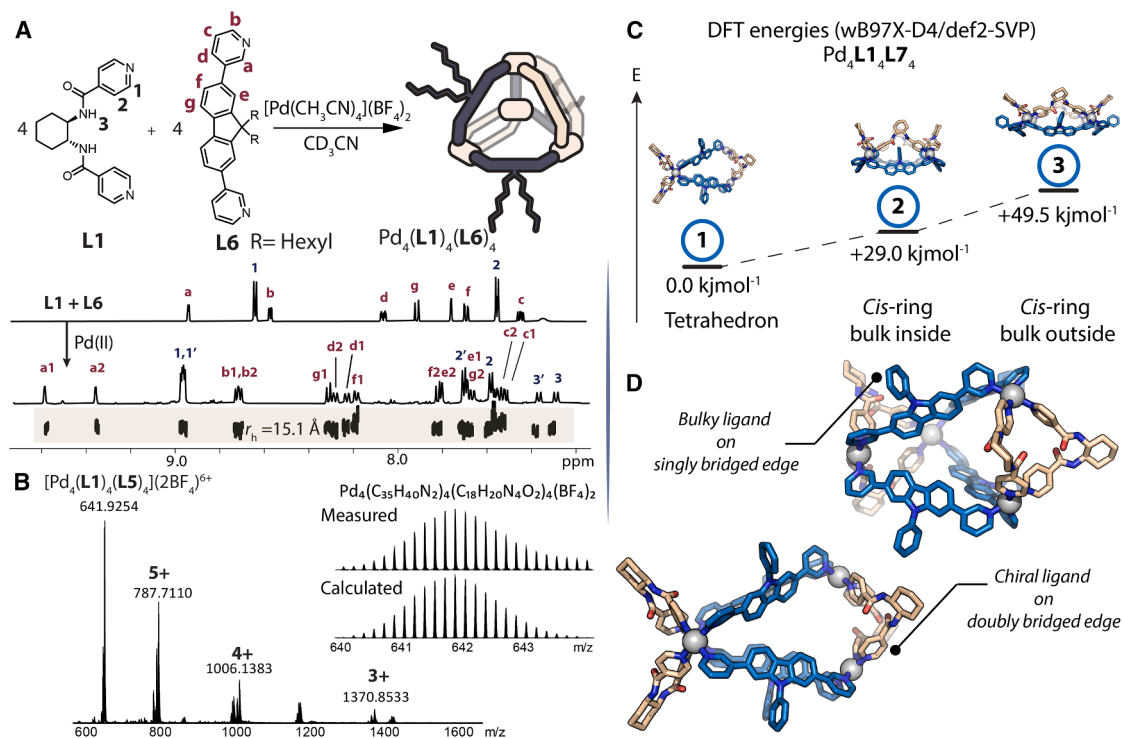


Figure 4. Assembly of a $\text{Pd}_4\text{L}_1\text{L}_6\text{L}_4$ architecture and DFT modeling of the lowest-energy isomer for $\text{Pd}_4\text{L}_1\text{L}_7\text{L}_4$

(A) Self-assembly of **L1** and **L6** with Pd(II) yields a $\text{Pd}_4\text{L}_1\text{L}_6\text{L}_4$ tetrahedron. ^1H NMR (CD_3CN , 500 MHz) stack of a mixture of both ligands and after addition of Pd(II). Assignment and ^1H DOSY NMR trace are given on the spectra.

(B) HR-ESI-MS of an acetonitrile solution of $\text{Pd}_4\text{L}_1\text{L}_6\text{L}_4$. The inset shows measured and calculated isotopic patterns.

(C) Energy diagram of three plausible $\text{Pd}_4\text{L}_1\text{L}_7\text{L}_4$ isomers obtained through DFT modeling ($\omega\text{B97X-D/def2-SVP}$).

(D) Side and top views of the $\text{Pd}_4\text{L}_1\text{L}_7\text{L}_4$ lowest-energy structure.

slightly more sterically demanding structure, as well as **L6** and **L7**, comprising significantly larger steric hindrance.

When combined in a 1:1:1 ratio with a Pd(II) source, **L1** and **L5–L7** lead to the emergence of new ^1H NMR signals that do not correspond to the respective homoleptic species (Figures S31–S58). As the three obtained assembly products share the same characteristics, we will only describe exemplary cases. For the combination of **L1** with **L6**, a DOSY experiment indicated that all the signals belong to the same species with a hydrodynamic radius $r_{\text{H}} = 15.1 \text{ \AA}$ (Figure 4A). In this assembly, all protons from ligands **L1** and **L6** split into two sets of signals of equal intensities, indicating a higher symmetry than the isosceles triangular rings introduced above. Further, ESI-MS analysis revealed a stoichiometry of $[\text{Pd}_4\text{L}_1\text{L}_6\text{L}_4+n\text{BF}_4]^{(4-n)+}$ ($n = 2\text{--}5$; Figure 4B). This sum formula would allow for several possible topologies, including a rectangular or cone-shaped four-ring (or saddle) or a doubly bridged tetrahedron. NOESY analysis provided a first insight into the structure. The set of cross-peaks between Ha and Hf, as well as Hd and He, evidences an **L6** orientation where the backbone substituent is pointing in the opposite direction to the coordination vectors. This is compatible with a binding angle of $\sim 90^\circ$ and therefore should favor the formation of tetrahedral or octahedral assemblies. At the same time, cross-peaks between the pyridine protons of both **L1** (H1) and **L6** (Ha,b) confirm the *cis*-arrangement of the ligands per square-planar Pd(II) center.

Finally, the lack of cross-peaks between **L6** alkyl chain protons and either signals from **L1** or from the second set belonging to **L6** is evidence of a topology where the fluorene-based ligands singly bridge edges between neighboring Pd(II) centers, thus supporting the formation of a heteroleptic pseudo-tetrahedron. As we could not obtain single crystals suitable for X-ray diffraction analysis, we employed modeling (GFN2-xTB/ALPB (acetonitrile) and DFT $\omega\text{B97-D4/def2-SVP}$; Figure 4C) to support and better understand the structure (Figures S101 and S102). For this, we constructed the tetrahedron as well as tentative *cis*-rings, both with bulky substituents pointing inside or outside the cavity. We built the tetrahedron so that the bulky ligands occupy singly bridged edges, while the chiral ones sit in pairs on the remaining ones. This arrangement was previously observed for other $\text{Pd}_4\text{A}_4\text{C}_4$ heteroleptic tetrahedral Pd(II)-cages³⁷ and is supported by 2D NMR analysis, with the notable exception that the chirality of the here used ligand **L1** leads to an additional splitting of the signal sets of **L6**. To avoid lengthy calculations because of alkyl chain flexibility, but still considering the effect of the backbone bulk, we modeled structural isomers of related, phenyl-substituted compound $\text{Pd}_4\text{L}_1\text{L}_7\text{L}_4$. Indeed, the calculations indicate that the tetrahedral assembly is lower in energy as compared with its ring analogs, with a respective difference of 29.0 kJ mol^{-1} for the ring with the bulk inside and 49.5 kJ mol^{-1} for the least favored structure with bulk pointing

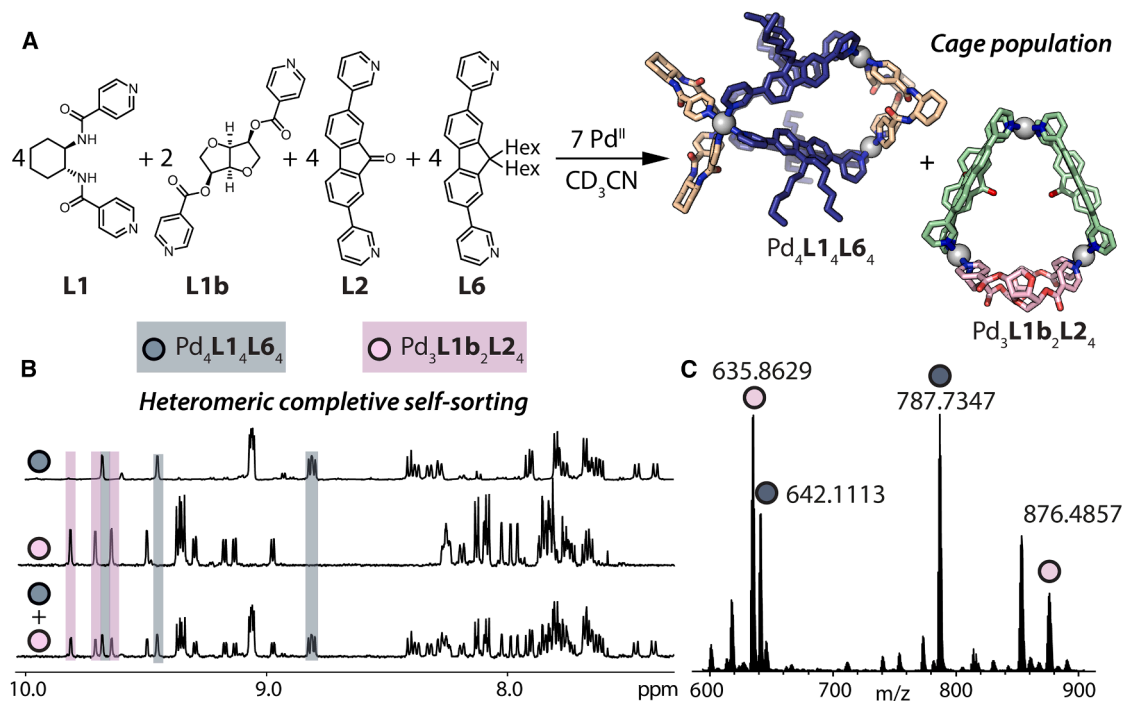


Figure 5. Formation of a cage population from four different building blocks through heteromeric narcissistic self-sorting

(A) The one-pot, yet orthogonal, self-assembly of **L1b**, **L1**, **L2**, and **L6** with Pd(II) cations in a 2:4:4:4 ratio leads to the concomitant formation of a Pd₄L₁₄L₆₄ pseudo-tetrahedron and a Pd₃L_{1b}₂L₂₄ ring.

(B) ¹H NMR (CD₃CN, 500 MHz) stack of (top, dark blue highlighted) Pd₄L₁₄L₆₄, (middle, pink) Pd₃L_{1b}₂L₂₄, and (bottom) the outcome of the heteromeric narcissistic self-sorting, leading to a defined cage population.

(C) HR-ESI-MS of the cage population showing the formation of the two separate species, marked by blue and pink dots.

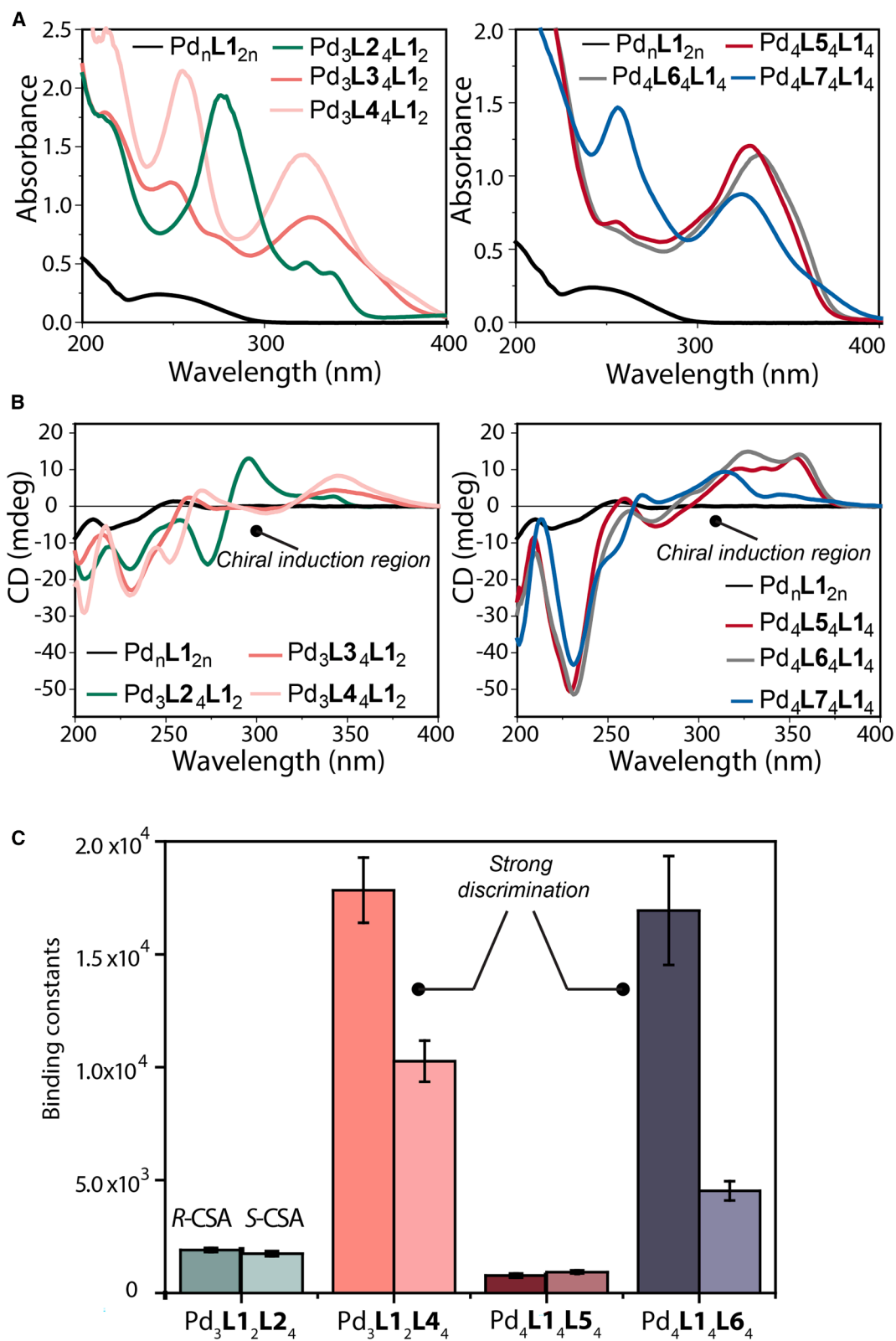
outside (Figure 4C). These results match our 2D NMR analysis (Figures S31–S58) and are in accordance with the DOSY-derived hydrodynamic radius (Figure 4B). The ABIs prevent the formation of ring structures in which bulky ligands would sterically clash if they were arranged next to each other on the same edges bridging neighboring Pd(II) centers. These interactions enable the formation of tetranuclear heteroleptic pseudo-tetrahedra in all cases when **L5–L7** are combined with **L1**.

It is worth mentioning that the methyl groups in **L5** represent the borderline case to direct the formation toward one or the other structure. As previously mentioned, the bulky substituents on **L6** and **L7** lead to the formation of homoleptic Pd₆L₁₂ octahedral species. Therefore, it is not surprising to obtain the tetrahedron when they are combined with **L1**. Homoleptic assembly of **L5** with Pd(II) cations yields a mixture of Pd₄L₈ and P₃L₆ species analogous to those obtained with **L2**. However, the slight increase in backbone steric hindrance from **L2** (C=O) to **L5** (C(CH₃)₂) is enough to dictate the formation of a Pd₄L₁₄L₅₄ heteroleptic tetrahedron rather than an isosceles triangular ring as observed for **L2**.

Formation of cage populations

We recently reported the formation of heteroleptic cage populations through *heteromeric complete self-sorting*, which allowed us to observe orthogonally coexisting dinuclear Pd(II)-based structures.²⁹ This was quickly followed by a report

from Chand and coworkers, where they observed the coexistence of heteroleptic species obtained from unsymmetrical ligands,²⁷ as well as a further paper where we reported guest segregation in a multi-cage heteromeric system.²⁸ Above, we demonstrated that **L1** and **L1b** both associate with **L2** to form an unprecedented Pd₃A₂B₄-type ring motif. We also observed that **L1b**, differing from **L1** by its chemically distinct backbone structure, does not readily assemble with any of the other **L3–L7** ligands. We were therefore curious about the possibility of orthogonally assembling multiple species in the same reaction vessel (Figures S85–S88). First, we mixed **L1**, **L1b**, and **L2** with Pd(II) in a 2:2:8:6 ratio in acetonitrile. After stirring the solution overnight, we observed the concomitant formation of the two rings Pd₃L₁₂L₂₄ and Pd₃L_{1b}₂L₂₄, independently coexisting in the same mixture. While the two chiral ligands are structurally similar, subtle differences lead to clean narcissistic sorting of the two rings without shuffling of components. Even more interesting observations were made by mixing the four different ligands **L1**, **L1b**, **L2**, and **L6** in a 4:2:4:4 ratio with Pd(II) (Figure 5A). Here, it was possible to obtain a population composed of the Pd₄L₁₂L₆₄ tetrahedron and the Pd₃L_{1b}₂L₂₄ ring, as confirmed by the perfect overlay of the ¹H NMR traces of the two separate assemblies, as well as the identification of these assemblies as the major components of the population by ESI-MS (Figures 5B and 5C). We phrase this heteromeric narcissistic self-sorting. The outcome here is not trivial as we



(legend on next page)

also reported before that **L2** and **L6** can associate into an heteroleptic tetrahedron Pd₄L₂L₄L₆.³⁷ Because **L1b** can only pair with **L2**, forming Pd₃L_{1b}L₂L₄ as the assembly of smallest possible nuclearity, it depletes the mixture from this ligand in a way that the remaining **L1** and **L6** must associate into Pd₄L₁L₄L₆.

No other species, i.e., Pd₄L₂L₄L₆ or Pd₃L₁L₂L₄, were observed, indicative of a highly selective sorting process. We assume that subtle geometrical differences, combined with entropic factors and the given stoichiometry, are at the origin of a precise sorting outcome of the ligands into a defined population, rather than the formation of a statistical mess. This now not only extends the concept of gaining control over cage populations to higher-nuclearity assemblies but also to coexisting heteroleptic species with different nuclearities and chiral building blocks. Eventually it is worth noting that in reference to our previously reported integratively self-sorted Pd₂ABCD cage,³⁸ this is the first observation of combining four different building blocks leading to two coexisting structures, each based on two distinguishable ligands.

Intra-assembly chiral induction

In light of the use of a homochiral ligand, we asked whether its chiral information is transmitted onto the region occupied by the fluorene or carbazole-type backbones, detectable by chiroptical spectroscopies.⁵⁰ Consequently, we proceeded with the (chiro)optical characterization of these rings and cages (Figures 6A, 6B, S89, and S90). As previously documented, chiral ligand **L1** only exhibits weak absorbance below 300 nm, characterized by a broad band centered at 250 nm. For the rings (Figure 6A, left), Pd₃L₁L₂L₄ displayed a strong absorption maximum at 275 nm, accompanied by smaller absorption bands centered at 325 and 335 nm, and a weaker broad band around 400 nm, characteristic of the fluorenone moiety. Notably, these latter three bands resided within a spectral region where **L1** exhibits no absorption, thereby facilitating the clear attribution of their origin to **L2**. Pd₃L₁L₂L₃ and Pd₃L₁L₂L₄ similarly showed absorption bands at 250 and 255 nm, respectively, which therefore overlap with the absorption of **L1**. However, both structures revealed a second absorption maximum with $\lambda > 300$ nm with the bands centered at 325 and 320 nm. The latter features arise from the sole contribution of the carbazole-based cores of **L3** and **L4**. A similar trend is observed for the tetrahedral assemblies (Figure 6A, right) obtained from **L5**, **L6**, and **L7**, with one band overlapping with **L1** around 255 nm and the second distinctive band centered at 330, 335, and 325 nm, respectively.

L1 in enantiopure form has previously been shown to impart chirality onto the overall structure of a heteroleptic Pd₂A₂B₂ cage, yielding a CD signature for the originally achiral counter ligand.⁵⁰ We therefore expected similar observations for the herein studied higher-nuclearity rings and tetrahedra (Figure S89). Indeed, the characteristic UV-vis absorptions of

the achiral chromophores occurred as features in the CD spectra above 300 nm for all examined species (Figure 6B). These results validated that the chirality of **L1** is imparted onto the overall assembly and thus to the counter ligands **L2**–**L7**. This chirality transfer was further probed for assembly Pd₃L₁L₂L₄ by CPL spectroscopy, as **L2** retained some luminescent properties even after coordination to Pd(II). Given that **L1** is not luminescent, any CPL signals would show that the initially achiral fluorenone cores have been brought into a chiral arrangement. Although the measured luminescence was relatively weak, a CPL signal with a low dissymmetry factor $g_{lum} = 10^{-4}$ centered at 505 nm could be detected (Figure S90), a typical region of emission for the fluorenone chromophore (supplemental information). In contrast, for all other assemblies, the luminescence was entirely quenched.

Chiral guest discrimination

As we obtained a family of chiral assemblies (containing the *R,R* enantiomers of the respective ligands) with an accessible cavity, we examined whether they can differentiate between two enantiomers of a chiral guest (Figure 6C). We studied the binding of *R/S*-camphor sulfonate inside the rings and tetrahedra by NMR-based titrations (Figures S65–S84). For Pd₃L₁L₂L₄, guest addition resulted in a shift of inward pointing protons, indicating binding inside the host cavity. However, the 1:1 binding constants of the two enantiomers *R* and *S* were both small and comparable, with values of 1,900 and 1,742 M⁻¹. Binding was also supported by ESI-MS (supplemental information). On the other hand, Pd₃L₁L₂L₄ led to a chiral discrimination with a factor of 1.7 between *R* and *S* and binding constants 10 times higher than those for Pd₃L₁L₂L₄, with 17,839 and 10,268 M⁻¹, respectively. This discrimination value is rather good and in line with literature-reported examples.⁵³ The differing binding abilities of these rings may relate to the inward pointing groups. In Pd₃L₁L₂L₄, four carbonyl moieties are directed with their negative partial charges inside the cavity (disfavoring binding of the anionic guest), while in Pd₃L₁L₂L₄ four methyl groups occupy those positions (probably favoring guest binding by enhancing the hydrophobic character of the cavity). Noteworthy, we have recently described a discrimination factor close to 3 for another chiral Pd-based host binding the same guest.⁵⁴ For tetrahedron Pd₄L₁L₄L₅L₄, NMR titration yielded binding constants of 772 and 922 M⁻¹ for *R* and *S* camphor sulfonate. In the case of Pd₄L₁L₄L₆L₄, we also observed shifting, accompanied by broadening, of some proton signals. Here, the binding constant for the *R* enantiomer was determined to be 16,938 M⁻¹, while the one for the *S* enantiomer is only 4,523 M⁻¹, leading to a remarkable discrimination factor of 3.75. As observed in the crystal structure of a similar tetrahedron³⁷ and the model in Figure 5, the hexyl chains of the ligands on the singly

Figure 6. Chiral induction and guest discrimination

(A) UV-vis spectra overlay of (left) the different Pd₃L₁L₂L_x (x = 2, 3, 4) rings and (right) Pd₄L₁L₄L_x (x = 5, 6, 7) tetrahedra.

(B) Overlay of CD spectra of (left) the different Pd₃L₁L₂L_x rings and (right) Pd₄L₁L₄L_x tetrahedra. The intra-assembly chiral induction is observable through CD bands present in regions where only ligands **L2**–**L7** are absorbing.

(C) Bar chart comparing the binding constants for *R* and *S* camphor sulfonate among the different hosts. Strong discrimination is observed for *R,R*-Pd₃L₁L₂L₄ and *R,R*-Pd₄L₁L₄L₆ along with high binding constants. Error bars represent the standard fitting error estimations by the bindfit software.

bridged edges in Pd₄L₁₄L₆₄ partially cover the faces of the tetrahedron, leading to a better enclosed cavity, as compared with Pd₄L₁₄L₅₄, and hence stronger guest binding. Guest addition to Pd₃L₁₂L₃₄ and Pd₄L₁₄L₇₄ resulted in turbid solutions and precipitation, and it was therefore not possible to determine binding constants. All results are summarized in Figure 6C.

Conclusions

Based on readily accessible chiral and luminescent ligands, a family of heteroleptic metallocsupramolecular structures with nuclearities of three and four was obtained, and among them were the first Pd₃A₂B₄-type structures of isosceles triangular ring topology. A sequential increase in steric bulk results in ABIs, leading to the formation of heteroleptic pseudo-tetrahedra Pd₄A₄C₄. Experimentally observed assembly results could be rationalized and supported using low-cost computational toy models. Based on only some key structural and geometrical parameters of the building blocks, this algorithm affords the prediction of the most stable assemblies, hence considerably advancing the rational and guided design of low-symmetry coordination cages. While the software is freely available, improvements to the structure prediction algorithm are currently in progress. We further demonstrated the controlled formation of cage populations through heteromeric narcissistic self-sorting, where discernable species coexist orthogonally. This extends the toolbox of cage-based self-sorting schemes to chiral assemblies as well as higher-nuclearity species, opening new avenues to create structural complexity and functional applicability. We further showed that the chirality of one ligand is transmitted to the overall assembly, resulting in chiral induction on otherwise non-chiral chromophores. On the other hand, formed hosts could encapsulate and discriminate the enantiomers of a small chiral guest with selectivity factors up to 3.75.

Our study demonstrated how a collection of a few chemically simple but meticulously designed building blocks can lead to structurally complex assemblies and self-sorted mixtures, thus progressing the control over tailored nano architectures. We just started to apply the herein reported compounds and principles in dynamic systems with life-like properties, capable of dissipative transient species formation, competition in populations held under restrictive supply of limiting components, and molecular information propagation. They may further find application in chemical separation tasks, catalysis under confinement, and porous materials.

METHODS

All the experimental procedures and data are detailed in the [supplemental information](#).

RESOURCE AVAILABILITY

Lead contact

Requests for further information and resources should be directed to and will be fulfilled by the lead contact Prof. Guido H. Clever (guido.clever@tu-dortmund.de).

Materials availability

Synthetic procedures, NMR, MS, single-crystal X-ray diffraction (SCXRD) results, and calculation data are included in the [supplemental information](#) PDF

file. Data sets CCDC: 2429500, 2429501, 2406153 contain the crystallographic data.

Data and code availability

Software is freely available at <https://github.com/andrewtarzia/starships> (<https://zenodo.org/records/15205588>), with minimal model data available at <https://zenodo.org/records/14909754> and explorable at https://cgmodels.readthedocs.io/en/latest/starships_mar2025.html.

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AUTHOR CONTRIBUTIONS

E.B., J.T., and G.H.C. conceived the project. E.B. and J.T. performed the experiments and analyzed the data. A.T. created the toy model and performed calculations. A.J. and M.W.H. provided the chiral ligands. H.L. and J.T. refined the X-ray structures. E.B., J.T., and A.T. drafted the manuscript, revised by G.H.C., M.W.H., and G.M.P. All the authors have seen the manuscript and agreed on its content.

DECLARATION OF INTERESTS

The authors declare no competing interests.

SUPPLEMENTAL INFORMATION

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