Design of catalytic metal–organic assemblies via shape complementarity and conformational constraints in dual curvature ligands

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ABSTRACT: Non-covalent interactions play an essential role in the folding and self-assembly of large supramolecular biological assemblies in nature. These interactions are not only a driving force for the formation of large structures but also control conformation and complementary shapes of subcomponents that promote the diversity of structures and functions of the resulting assemblies. Understanding how non-covalent interactions direct self-assembly and the effect of conformation and complementary shapes on self-assembled structures will help design artificial supramolecular systems with extended components and functions. Herein, we develop a strategy for controlling more complex self-assembly with lower symmetry and flexible building blocks that combine endohedral non-covalent interactions with a dual curvature in the ligand backbone to give additional shape complementarity. A Diels-Alder reaction was used to break the symmetry of the diazaanthracene units of the ligands to give dual curvature ligands with different shapes and endohedral groups (L1–L3). The self-assembly studies of these ligands demonstrated that non-covalent interactions and shape complementary effectively control the self-assembly and enable the design of cages for supramolecular catalysis.

Introduction

Self-assembly and folding play essential roles in the complexity and function of proteins. For example, these processes in enzymes lead to the formation of active site cavities lined with functional groups that promote the range of reactions necessary for life. Over the past decades, the possibility of generating synthetic molecules with similar complexity and functions has inspired significant progress in designing self-assembled cavities. While numerous strategies for the self-assembly of such structures have been developed, the combination of organic ligands and metal ions for the formation of metal-organic architectures has risen as a highly promising approach. Notably, the combination of Pd2+ or Pt2+ with ditopic ligands for the formation of M3L2 structures has attracted substantial attention and led to some of the largest well-defined systems. A wide range of applications related to their cavities has been reported, including sensing, catalysis, drug delivery, storage, and molecular recognition.

Unlike synthetic building blocks, folding of peptides leads to subunits for self-assembly that have not only complex electrostatic potential surfaces but also a wide diversity of shapes. The resulting high complementarity between different subcomponents allows for the selective self-assembly of different units into complex asymmetric architectures. By contrast, the majority of synthetic strategies for coordination-driven self-assembly rely on rigid ligands with high, often planar, symmetry. This can be readily seen in M3L2 assemblies. The ligands are most commonly curved organic molecules where N-heterocyclic donor groups are connected by flat aromatic or alkyne spacers, the rigidity of which allows the angle between coordination sites, the bend angle, to be well-defined. This offers numerous advantages, such as allowing good prediction of the final self-assembled structures and clean formation of single species. Still, the use of lower symmetry ligands could allow additional shape complementarity between ligands to help direct self-assembly, ultimately leading to new strategies and more complex structures. In the last decade, a number of elegant approaches relying on enhanced shape complementarity for controlling self-assembly have been described, such as combining two different ditopic ligands with compatible convergent and divergent bend angles or the use of coordination sphere engineering. The latter uses additional functional groups included near the coordination sites on the ligands to provide complementarity inter-ligand steric or electrostatic interactions.

Recently, we succeeded in using heteroaromatic amide-based ligands for the self-assembly of multiple Pd4L8 (n=2, 6, or 12) metal-organic cages capable of neutral guest discrimination. Despite the flexibility around the amide bonds, non-covalent interactions in the ligands lead to preferential curved conformational states that orient the coordination sites and allow sufficient control over the bend angles of the ligands to direct self-assembly. Nevertheless, these ligands are predominately flat and offer only limited
interactions between ligands for the self-assembly of metal-organic cages. In fact, this is seen in the majority of ligands used for the self-assembly of $M_n L_{2n}$ assemblies. Modification of the surface of the flat aromatic units to include perpendicular interactions is a challenge. However, this can be the fastest way to direct groups towards other ligands for designing interligand interactions and shape complementarity. We have recently shown that the large diazaanthracene units used for our ligands are amenable to modification via Diels-Alder reaction leading to diazaiptycene or triptycene units. These motifs are intriguing for incorporating additional shape complementary aspects, remote from the coordination sites, into heteroaromatic amide ligands for self-assembly. In effect, the reaction of the central ring in the diazaanthracene bends the attached N-heterocyclic rings towards each other, a change which, in the ligand structure, would add an additional curvature perpendicular to the curvature that defines the bend angle, Figure 1a. Herein, we demonstrate that this dual curvature, combined with the electrostatic interactions that dictate the bend angle, can direct self-assembly towards a single $M_2 L_4$ cage or $M_4 L_8$ double-walled metallomacrocycle out of the hundreds of possible stereoisomers that could result from different combinations of amide conformation and triptycene unit orientation, Figures 1 and S9. Using this strategy, we further show that the high modularity of the amide ligands allows ready access to deep endohedral functionalized cavitands capable of tandem catalysis.

**Results and Discussion**

**Ligand design and synthesis** - Diazatriptycene ligands $L_1$ and $L_2$ were synthesized in three steps, Scheme 1, starting with a [4+2] cycloaddition between in situ generated benzyne and a functionalized 1,8-diazaanthracene-2,7-dicarboxylate ester. Subsequent saponification and amide coupling with either 3-aminopyridine or 4-aminopyridine gave ligands $L_1$ and $L_2$ in 68 and 87% yield, respectively. The Diels-Alder reaction with benzyne bends the ligands introducing the second curvature of $\sim 120^\circ$ between the planes of the amide groups based on the calculated structures, Figure 1a. Additionally, it adds a large benzene ring on one face of the ligand, which is expected to act as a source of steric bulk between ligands that can help control the self-assembly.

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**Figure 1** a) Design of aromatic amide-based dual curvature ligands for coordination-driven self-assembly via Diels-Alder reaction with diazaanthracenes. This breaks the ligand symmetry and introduces additional shape complementarity as seen in the density functional theory (DFT) calculated structures of b) flat versus dual curvature ligands. c-e) the structure of ligands $L_1$-$L_3$ and their self-assembled products that can act as catalysts for the tandem reaction sequence shown in the inset.
**Scheme 1. Synthetic procedures for ligands L1 and L2.**

**Self-Assembly with L1 and L2** – Complexation of L1 with Pd²⁺ (NO₃, BF₄, CF₃SO₃, or PF₆ salt) in a 2:1 molar ratio in CD₃CN or D₂O-DMF at 40 °C results in a clear yellow solution. The ¹H NMR spectrum shows after two hours a single sharp set of signals with the same number of resonances as the starting ligand, Figure 2a-b and Figure S4-S6. Compared to L1, significant shifts of several resonances are observed. Notably, protons H₃ and H₆ of the pyridine groups appear further downfield, implying coordination of pyridine to Pd(II). These observations suggest the formation of a single symmetric species derived from the complexation of L1 with Pd²⁺ ions. Based on the expected parallel coordination vectors of the ligand, this was proposed to be an M₂L₄ structure. Consistent with this, diffusion-ordered ¹H NMR (DOSY) showed that all the proton resonances had the same diffusion coefficient of \( D = 6.99 \times 10^{-10} \text{ m}^2/\text{s} \), which, based on the Stokes-Einstein equation, indicates a small structure with a radius of 8.3 Å, Figure 2c. Electrospray ionization time-of-flight mass spectrometry (ESI-TOF-MS) further supported this assignment; a series of isotopic patterns corresponding to \([\text{Pd}_2(\text{L1})_4(\text{BF}_4)_6]^{4+} (n=2-4)\) were observed, Figure 2d.

**Figure 2.** ¹H NMR spectra (500 MHz, CD₃CN, 298 K) of ¹H NMR spectra of a) L1 and b) its self-assembly product Pd₃(L1)₄. c) the DOSY spectra of Pd₃(L1)₄. d) ESI-TOF-MS for Pd₃(L1)₄ as its BF₄⁻ salt. Inset shows the comparison of the observed isotopic pattern with the simulated spectrum. e) X-ray crystal structure of Pd₃(L1)₄ with views perpendicular to (left) and along (right) the Pd-Pd axis. Protons, solvent molecules and counterions are omitted for clarity.

For this species, the symmetry and single set of signals observed by NMR are interesting because the different orientations of the amides or ligand backbones could lead to hundreds of possible isomers, Figure 3 and Figure S8-S9. These nevertheless appear to converge to a single stable species, and time-dependent NMR studies of the self-assembly of L1 did not show any clear signs of other isomers forming as intermediates, Figure S5. Within ten minutes of mixing the ligand with Pd²⁺ ions, the ¹H NMR of the solution exhibited relatively broad signals with low intensity. ESI-TOF-MS analysis of the solution mainly found Pd₃(L1)₄(BF₄)₄ suggesting the composition of this mixture was predominately the M₂L₄ cage with possibly some oligomers and intermediates from the self-assembly. After one hour, only a single sharp set of resonances, as observed above, emerges and becomes the significant species by ¹H NMR.

**Figure 3.** Density functional theory (DFT) calculated structures and relative energies (B3LYP/6-31g* for ligands and B3LYP/def2SVP for cages) of a) three possible conformations of ligand L1 (L1A, L1B and L1C), b) Pd₃(L1)₄ cage with two representative ligand conformations, and c) four possible steric isomers of Pd₃(L1)₄ cage.

Relative to the possibility for different conformations, density functional theory (DFT) computational studies (B3LYP/6-31g*) support that the anti-conformation (L1A) between the amides of ligand L1 (possible ligand isomers, L1A, L1B, and L1C) should be favored by almost 30 kJ/mol in the self-assembly solvent (CD₃CN), Figure 3a. Similar studies (B3LYP/def2SVP) on the M₂L₄ cage also suggest that this preference should be maintained in the complex,
Figure 3b. Still, the lack of planar symmetry in the ligands could result in four different Pd₄(L₁)₄ isomers (A-D) with different cis/trans relationships between the 9,10-bridging groups, Figure 3c. However, the dual curvature designed into the ligands should allow for good shape complementarity that directs single isomer formation in order to avoid steric interactions between neighboring ligands. Indeed, additional DFT studies comparing the four isomers estimated that isomer A, where the curves of the ligands are oriented in the same direction, should be the most stable by ~40 kJ/mol. Based on the calculated structures, the higher energy for the three other isomers likely results from steric interactions between nearby benzene rings in the diazatriptycene backbones.

Further support for the formation of isomer A came from its solid-state structure. Single crystals of Pd₄(L₁)₄(BF₄)₄ could be obtained and were studied by X-ray diffraction, Figure 2e. The crystal structure of the complex shows two palladium ions, each in a square planar N₄ coordination environment, bridged by four units of L₁ with a Pd²⁺ to Pd²⁺ distance in the cage of 12.3 Å. In accordance with the solution observations and computational results, the benzene rings on the ligands are all oriented in the same direction around the four-fold symmetry axis, and the amide carbon–nitrogen pairs of a square. Each palladium has square planar coordination with a Pd²⁺ to Pd²⁺ distance in the cage of 12.3 Å. In accordance with the solution observations and computational results, the benzene rings on the ligands are all oriented in the same direction around the four-fold symmetry axis, and the amide carbon–nitrogen pairs of a square. Each palladium has square planar coordination with a Pd²⁺ to Pd²⁺ distance in the cage of 12.3 Å. Indeed, ad

Motivated by the high selectivity observed with ligand L₁, we next looked to see if the self-assembly of larger structures using the reduced symmetry ligands could still be controlled by the dual curvature effects. Ligand L₂ was reacted with 0.5 equivalents of PdCl₂(NO₃)₂, CF₃SO₃PF₆ or PdCl₂(BF₄)₂ in D₂O–DMSO or D₂–DMF. Similar to self-assembly with L₁, the ¹H NMR spectrum showed a single set of resonances distinct from the starting ligand, Figure 4a-b and Figure S10-S12. As expected, DOSY studies on this species suggested the formation of a larger structure (D = 7.32×10⁻¹¹ m²/s; r = 13.8 Å), Figure 4c. However, as opposed to the M₄L₁₂ or M₄L₂₄ cages obtained previously with the analogous planar ligand, L₃. ESI-TOF-MS analysis showed isotopic patterns consistent with the formation of an M₄L₈ assembly with the formula Pd₄(L₂)₈(BF₄)₈, Figure 4d. This composition was further confirmed by X-ray diffraction studies. The crystal structure shows a deep crown-like double-walled metallo-macrocycle, Figure 4e. The four palladium ions are found in the same plane and can be seen as occupying the four corners of a square. Each palladium has square-planar coordination, with two ligands, one above and one below the plane, bridging between each pair of adjacent metal ions. This gives a structure with cavity dimensions of 20.5 Å between opposite palladiums and 23.8 Å between the top and bottom faces. All of the ligands are oriented in the same way, with the benzene ring of the diazatriptycene units in each bridging pair pointing away from each other towards either the top or bottom of the structure. This also results in the 9-position group on the diazatriptycene units of the ligands converging towards the center of the cavity.

Interestingly, the bend angle for the ligands in the crystal structure of Pd₄(L₂)₈ is ~70°, while the same bend angle in the DFT optimized structure of the free ligands was found to be ~60°. Previously, we observed that the partial flexibility in the amide bonds could allow changes of almost 30° in the bend angle, making it possible to transition from a smaller cage structure to a larger one. For example, M₄L₁₂ and M₄:L₄₄ structures, which require ideal bend angles of 90° and 120° respectively, could be formed with the same aromatic amide ligand in a step-wise manner. With this in mind, we attempted to push the self-assembly of Pd₄(L₂)₈ towards a larger Pd₄(L₂)₁₂ octahedron. However, even after extending the time for self-assembly up to two weeks or increasing the temperature to 120 °C, no other apparent species were observed by NMR nor ESI-TOF-MS analysis. The cube-like structures in most M₄L₁₂ octahedra contain eight adjacent 3-fold symmetry axes. With the dual curvature ligand L₂, it is impossible for the ligands to be arranged in a way where they are all pointing away from each other, something that can occur with Pd₄(L₂)₈, Figure 4e. Interestingly, no close contacts of the complementary shapes, as seen in the isomers of Pd₄(L₁)₄, are observed in a PM6 model of a Pd₄(L₂)₁₂ octahedron, Figure S13. Thus, it is suspected that a combination of unfavorable ligand orientation and significant distortions in the torsion angles around the amides necessary to form the M₄L₁₂ structure may limit its stability.
Self-Sorting Studies - To look at how strongly the non-covalent interactions present in the ligand structures control their bend angle, self-sorting studies were performed. In theory, changes in the torsion angles around the amides, at the expense of weakening the non-covalent interactions, should permit both ligands to achieve the same bend angle. While this could potentially allow the self-assembly of structures containing both ligands L1 and L2, this does not appear to be favored. Indeed, upon reacting a 1:1 mixture of L1 and L2 with Pd(CH3CN)4(BF4)2 in D2O-DMSO, two distinct sets of signals, as verified by the COSY and DOSY spectra, were observed by 1H NMR, corresponding to the M2(L1)4 and M4(L2)8 species as described above, Figure 5 and Figure S17. ESI-TOF-MS analysis also showed only a mixture of M2L4 and M4L8 species. These observations indicate that, despite the weak nature of the non-covalent interactions that direct the ligand conformation, they still provide sufficient control to allow self-sorting based on bend angle, something only previously reported for more ridged ligands.14

Cage functionalization and catalysis - While the smaller cavity in Pd4(L1)4 limits the potential for having both endohedral functionalization and guest binding, the larger M4L8 structure is an intriguing scaffold for designing functional group lined cavities for catalysis. From the structure, the large openings in the top and bottom faces of the host can easily allow substrate and product diffusion in or out of the deep cavity. Moreover, the defined orientation of the diazaanthracene 9-position and modularity of the ligand design can facilitate the endohedral functionalization of the structure. To this end, ligand L3 bearing a carboxylic acid function of high interest for self-assembly of functional supramolecular catalysts was synthesized as shown in Scheme 2. Following reported procedures, the 9-methyl in the precursor 1,8-diazaanthracene-2,7-dicarboxylate ester could be easily functionalized into a Boc-protected 9-methylamino diazaanthracene derivative.15 Next, triptycene formation and installation of the pyridine coordination sites were performed in a manner analogous to L2. Subsequent amine deprotection and reaction with succinic anhydride allowed the incorporation of the carboxylic acid group in L3.

Figure 5. a) Narcissistic self-sorting of M2L4 and M4L8 architectures from mixed ligands. b) 1H NMR spectra (500 MHz, DMF-d7, 298 K), c) the DOSY spectra and d) ESI-TOF-MS of self-sorting outcomes showing a mixture of M4(L1)4 and M4(L2)8 species.

Scheme 2 Synthetic procedures for ligand L3.
self-assembly with L2, i.e., a single set of signals shifted relative to the free ligand, are seen by $^1$H NMR, Figure 6a-b and Figure S14-S16. Given the similar bend angles expected for L2 and L3, self-assembly with the functionalized ligand should also lead to an M4L8 structure. This was supported by DOSY studies (D = 7.55×10$^{-11}$ m$^2$/s; r = 13.4 Å), which suggested the formation of a complex with a size similar to parent Pd$_4$(L2)$_8$, Figure 6c. The Pd$_4$(L2)$_8$(BF$_4$)$_8$ formula was further confirmed by ESI-TOF-MS, though some low-intensity signals for an M$_3$L$_{10}$ structure could also be observed, Figure 6d. The presence of the more bulky group on the 9-position of L3 relative to L2 may lead to this minor formation of some of the larger macrocycles.17 Still, the X-ray crystal structure of the product showed Pd$_4$(L3)$_8$ and was highly similar to the M$_4$(L3)$_8$ structure, Figure 6e. The 9-position substituents are still found pointing into the cavity and oriented towards each other such that they occupy the cavity windows formed by the pairs of bridging ligands. This also leads to short distances between neighboring carboxylic acid groups (O-O distances of 2.3 - 2.7 Å), suggesting potential hydrogen bond formation between these groups. Such interactions might be expected to lead to some preference for self-sorting. However, self-assembly with mixtures of L3 and L2 resulted in statistical mixtures of M$_4$L$_8$ species with different ratios of the two ligands, though similar studies using L3 and L1 still showed self-sorting into M$_2$(L1)$_4$ and M$_4$(L3)$_8$ based on the different bend angles, Figure 7 and Figure S18-S21.

![Figure 7](image-url)

**Figure 7.** Mixed ligands self-assembly with ligand L3, mixed with a) L1 leads to narcissistic self-sorting of M$_3$(L1)$_4$ and M$_4$(L3)$_8$ assemblies and b) L2 formed non-sorted scrambled dynamic mixtures of Pd$_4$(L2)$_8$(L3)$_8$ and M$_3$L$_{10}$ structures.

Metal-organic architectures offering defined microenvironments for specific host-guest interactions are of interest for developing enzyme active site mimics. The confined spaces in these structures have been reported to give significant rate enhancements and product selectivity for a range of organic reactions.56,18 Based on the carboxylic acid functions in ligand L3, we were interested in studying the reactivity of the endoedral functionalized M$_4$L$_8$ structures. For this, we chose to look at a tandem reaction sequence involving hydrolysis of the dimethyl acetal of benzaldehyde followed by aminal formation with anthranilamide to give 2,3-dihydroquinazolinones. This class of molecules is a useful privileged scaffold in medicinal chemistry due to their range of pharmacological activities.19 Importantly, both steps of the reaction sequence can be catalyzed by Lewis or Bronsted acids, and the latter step was also reported to be highly efficient with rate enhancements inside the cavity of metal-organic cages.20 These make the endoedral acid functionalization in the Pd$_4$(L3)$_8$ and the parent Pd$_4$(L2)$_8$ structures highly interesting as potential supramolecular catalysts for promoting product formation, Table 1.

**Table 1. Supramolecular catalysis at room temperature**

<table>
<thead>
<tr>
<th>Reactions</th>
<th>Catalysts</th>
<th>Initial rate, $\times 10^{-4}$ mM/min</th>
<th>TOF$^{\text{init}}$</th>
<th>Yield$^c$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) A→B</td>
<td>Pd$_4$(L3)$_8$</td>
<td>1016</td>
<td>5.08</td>
<td>93</td>
</tr>
<tr>
<td></td>
<td>Pd$_4$(L2)$_8$</td>
<td>366</td>
<td>1.83</td>
<td>56</td>
</tr>
<tr>
<td>L3</td>
<td>50</td>
<td>0.03</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>L2</td>
<td>0.2</td>
<td>0.01</td>
<td>&lt;2</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>0.2</td>
<td>0.01</td>
<td>&lt;2</td>
<td></td>
</tr>
<tr>
<td>2) B+D→C</td>
<td>Pd$_4$(L3)$_8$</td>
<td>5933</td>
<td>29.6</td>
<td>92</td>
</tr>
<tr>
<td></td>
<td>Pd$_4$(L2)$_8$</td>
<td>4600</td>
<td>2.3</td>
<td>90</td>
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<tr>
<td>L3</td>
<td>1466</td>
<td>0.92</td>
<td>74</td>
<td></td>
</tr>
<tr>
<td>L2</td>
<td>n.d.</td>
<td>n.d.</td>
<td>&lt;2</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>n.d.</td>
<td>n.d.</td>
<td>&lt;2</td>
<td></td>
</tr>
<tr>
<td>3) A+D→C</td>
<td>Pd$_4$(L3)$_8$</td>
<td>733</td>
<td>3.66</td>
<td>93</td>
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<tr>
<td></td>
<td>Pd$_4$(L2)$_8$</td>
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<td>84</td>
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<td>L3</td>
<td>50</td>
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<td>n.d.</td>
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</table>

$^a$ [substrate] $=$ 40mM; $^b$ 3.1 mol% Pd$_4$(L3)$_8$ or Pd$_4$(L2)$_8$ or 24.8 mol% L3 or L2 as a catalyst; $^c$ NMR; Yield determined at t = 24h.; n.d. = not able to be determined due to no visible product signals; Initial rates and TOF$^{\text{init}}$ were calculated based on the first four hours of reaction.

The assemblies, Pd$_4$(L3)$_8$ or Pd$_4$(L2)$_8$, or the free ligands L3 or L2 as controls, were used as catalysts for the tandem 2,3-dihydroquinazolinones synthesis (reaction 3, Table 1) as well as the individual acetal hydrolysis (reaction 1, Table 1) and aminal formation steps (reaction 2, Table 1) separately. In all cases, the reactions were performed in wet DMSO using the substrates at concentrations of ~40mM in the presence of either 3.1 mol% Pd$_4$(L3)$_8$ or Pd$_4$(L2)$_8$, or 24.8 mol% L3 or L2 as a catalyst and product formation was followed by $^1$H NMR using an internal standard. The initial
rates and TOF, as well as the yields for the reactions are summarized in Table 1 and Figures S22-S26.

In the absence of a catalyst or with only unfunctionalized L2, there is no appreciable reaction for any of the steps. Only for the acetal hydrolysis was minor product formation observed within the first four hours of reaction. Expectedly, the presence of the carboxylic acid group on L3 leads to a minor improvement in reaction rates, with initial rates of 50, 1466, and $50 \times 10^{-4}$ mM/min calculated for reactions 1, 2, and 3 respectively. By contrast, more remarkable rate enhancements are observed with the self-assembled structures. Acetal hydrolysis to benzaldehyde in wet DMSO occurs rapidly with Pd$_4$(L3)$_8$ at room temperature. The initial rate, $1016 \times 10^{-4}$ mM/min, with the assembly represents an almost 2000% increase over the free L3. The same reaction with Pd$_4$(L2)$_8$, while also faster than the ligands is still about 2.8 times slower than the acid functionalized assembly. The stark difference between the two otherwise similar cages highlights the importance of the endohedral functionalization in Pd$_4$(L3)$_8$ for this initial hydrolysis step. Nevertheless, the reactivity with Pd$_4$(L2)$_8$ suggests that the Pd$^{2+}$ ions in the two structures can potentially act as Lewis acids to catalyze the reaction. Indeed, this also appears to be the case for the aminal formation step, both Pd$_4$(L2)$_8$ and Pd$_4$(L3)$_8$ performed similarly, with rates = 4600 and $5933 \times 10^{-4}$ mM/min respectively, Table 1 and Figure S27-S31. L3, while moderately active for this step, was substantially slower than either Pd$_4$(L2)$_8$ and Pd$_4$(L3)$_8$.

The trends for the individual steps are also seen for the tandem reaction of benzaldehyde dimethyl acetal with anthranilamide, Table 1 and Figure S32-S36. When Pd$_4$(L3)$_8$ was used as the catalyst, the starting acetal disappears rapidly. The initial rate was calculated to be $733 \times 10^{-4}$ mM/min, representing a 1400% increase versus the free ligand. The same reaction with the Pd$_4$(L2)$_8$ assembly lacking the carboxylic acid groups also leads to significant product formation. However, the initial reaction rate, $516 \times 10^{-4}$ mM/min, is moderately slower than for Pd$_4$(L3)$_8$, consistent with the results obtained for the individual steps of the reaction. Interestingly, for both cages, only minor amounts of the aldehyde were ever observed. While this can correspond with the slower kinetics of the hydrolysis step and formation of the aldehyde as being rate-limiting, the oxonium intermediate generated from loss of a methoxy group in the starting acetal can also react directly with anthranilamide, bypassing the aldehyde. As shown in Figure S37, spiking the reaction with excess water does not substantially increase the reaction rate relative to controls without the additional water, suggesting the mechanism may indeed pass through direct anthranilamide addition onto the oxonium, something that may be facilitated by the cavity of the structures.

In order to further examine the efficiency of the catalyst, the reactions with Pd$_4$(L3)$_8$ were set up with different ratios of catalyst to the substrate. Increasing or decreasing the substrates by 10-fold leads to different relative catalyst loadings of 0.31%, 3.1% and 31% versus substrate. For the acetal hydrolysis, as shown in Figure S38-S41, even with the lowest catalyst ratio, by $^1$H NMR the starting acetal disappears almost completely within 24 h, coinciding with >90% formation of the product. For the tandem reaction of benzaldehyde dimethyl acetal with anthranilamide, the lower catalyst:substrate ratio (0.31%) expectedly leads to a decrease in the reaction rate. Nevertheless, >90% product yield is still observed within 48 h.

Conclusions

In summary, we have provided an effective strategy for controlling self-assembly in more complex systems by combining endohedral non-covalent interactions in aromatic amides with additional shape complementarity brought by dual curvature ligands. A straightforward Diels-Alder strategy was used to break the symmetry of the ligands and incorporate additional steric constraints and complementary shapes. This allowed three dual curvature ligands (L1-L3) to be obtained. The self-assembly studies of the ligands showed the designed constraints are able to highly control the self-assembly of the ligands with Pd$_{2+}$ towards a single $M_4L_4$ cage or $M_4L_3$ double-walled metallamacrocycle out of hundreds of possible isomers. Moreover, the non-covalent interactions provide sufficient control to allow narcissistic self-sorting based on bend angle in mixtures of the flexible ligands. Finally, we show that this strategy can be used to generate endohedrally acid-functionalized $M_4(L_3)_n$ structures with deep cavities that are able to perform tandem catalysis with significant rate enhancements. These results give promising new design strategies for coordination-driven self-assembly and the formation of diversely functionalized cavities of interest for catalytic applications.

ASSOCIATED CONTENT

Supporting Information. Complete experimental procedures, additional spectra figures, and tables of NMR, ESI-TOF-MS, CIF and crystal data are described in the text.

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The authors declare no competing financial interest.

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REFERENCES

✓ Conformation control
✓ Shape complementarity
✓ Isomer selectivity of cages
✓ Tandem reactivity

Steric bulk

Second curvature

First curvature

Product

Substrate

 prêt