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Institute of Condensed Matter and Nanosciences

Molecular Chemistry, Materials and Catalysis

**Non-Covalent Interactions for Directing Self-
assembly of Supramolecular Architectures
towards Nanocontainers**

Dissertation submitted for the Degree of Doctor in Sciences

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This thesis is dedicated to my parents, who always supported and chose to give me the best education they could.

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Authors' Contributions

The author and the supervisors Prof. Michael Singleton and Prof. Yann Garcia have designed this project.

The author carried out the experiments, recorded the analytical data and interpreted the results that are presented in this thesis with the following exceptions:

The mass spectroscopic experiments were recorded by Mr. Raoul Rozenberg (UCLouvain) and Mr. Eduard O. Bobylev (University of Amsterdam, The Netherlands).

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List of abbreviations

°	Degree
°C	Celsius degree
α	Alpha
β	Beta
Δ	Delta
ΔE_p	Peak to peak separation
δ	Delta
θ	Delta
Å	Ångström
d	Diameter
r	radius
Ac	Acetyl
AFM	Atomic force microscopy
AOF	Aromatic oligoamide foldamers
Bn	Benzyl
Boc	<i>tert</i> -Butyloxycarbonyl
B ₂ Pin ₂	Bis(pinacolato)diboron
BPO	Benzoyl peroxide
CD	Circular dichroism
COSY	¹ H- ¹ H correlation spectroscopy
CM	Classical mechanics
CSI-MS	Cold-spray ionization mass spectrometry
CD ₃ CN	Acetonitrile
CSE	Coordination sphere engineering
D	Diffusion coefficient
DA	Diels-Alder reaction
DOSY	Diffusion-ordered spectroscopy
DTE	Dithienylethenes

DCM	Dichloromethane
DIAD	Diisopropyl azodicarboxylate
DIPEA	Di-iso-propylethylamine
DMAD	Dimethylacetylene dicarboxylate
DMAP	4-dimethylaminopyridine
DMF	Dimethylformamide
DMSO	Dimethylsulfoxide
DFT	Density functional theory
DLS	Dynamic light scattering
Et	Ethyl
Et ₃ N	Triethylamine
Et ₂ O	Diethyl ether
ESI-TOF-MS	Electrospray ionization time-of-flight mass spectrometry
Equiv.	Equivalent
HATU	1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate
HRMS	High-resolution mass spectrometry
Hz	Hertz
<i>i</i> Bu	<i>iso</i> -butyl
kJ	Kilo Joule
M	Molar
MS	Mass spectrometry
MS 4 Å	Molecular sieves 4 Ångström
NBS	N-Bromosuccinimide
NMR	Nuclear magnetic resonance spectroscopy
NASAP	Numerical analysis of the self-assembly process
Ph ₂ O	Diphenyl ether
PyBOP	Benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate
PEG	Polyethylene glycol
QASAP	Quantitative analysis of the self-assembly process

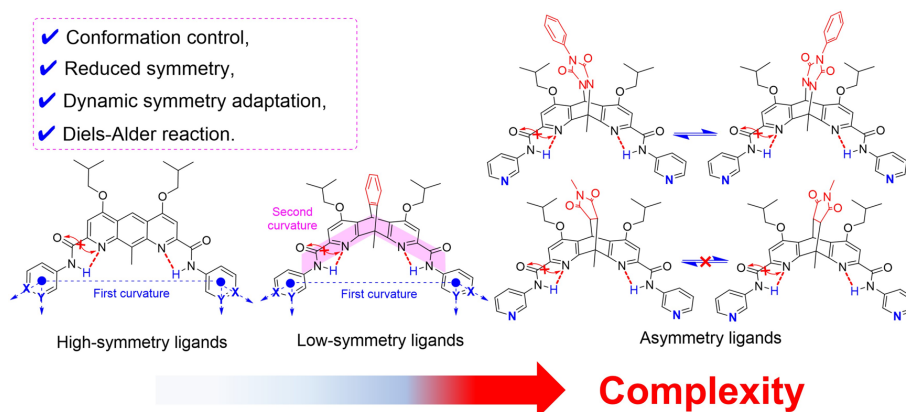
RT	Room temperature
SEM	Scanning electron microscopy
<i>t</i> Bu	<i>Tert</i> -butyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TEMPO	2,2,6,6-Tetramethylpiperidine-1-oxyl
TLC	Thin layer chromatography
UDCA	Ursodeoxycholic acid

Abstract

Self-assembly and folding with primary oligomers rely on various non-covalent interactions are important for generating higher-order secondary or tertiary structures of large biological molecules, from which emerge their sophisticated functions. Mimicking this approach for the self-assembly of complex artificial supramolecular structures is still challenging. Building blocks with characteristics like low symmetry and flexibility, while common in biological systems, pose numerous problems for synthetic self-assembly. In this thesis, the research aims to advance knowledge of how non-covalent interactions designed into aromatic amide based building blocks for self-assembly can be used to control conformation and generate complementary shapes for directing self-assembly of larger structures and through this to develop an approach that could allow the formation of more complex structures with interesting properties and reactivities. This work is divided into two different but complimentary approaches: 1) Metal-based self-assembly of aromatic amide units and 2) The use of multiple helix formation in aromatic oligoamides as a driving force for self-assembly of larger systems.

In chapter 3, a series of heteroaromatic amide-based ligands (**L1-L5**) were synthesized and used for coordination-driven self-assembly of M_nL_{2n} polyhedral cages. 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 giving access to $M_2(\mathbf{L1})_4$, $M_6(\mathbf{L2})_{12}$, and $M_{12}(\mathbf{L2})_{24}$ cages. Additionally, the multiple endohedral hydrogen bonding sites on the ligand were found to play a role in the binding and discrimination of neutral guests. The subsequent work in chapter 4 studied the more complex novel dual curvature ligands (**L6-L18**). These were obtained using a Diels-Alder reaction to break the symmetry of the ligands and incorporate additional steric constraints and complementary shapes for self-assembly. Mixing the dual

curvature ligands with Pd^{2+} ions demonstrates that these constraints could help direct self-assembly towards a single M_2L_4 cage or M_4L_8 double-walled metallomacrocycle out of hundreds of possible isomers. Moreover, this gives access to endohedrally functionalized M_4L_8 cages for different applications.



Next, using the idea of the Diels-Alder reaction, we studied covalent post-modification in chapter 5 as a shorter alternative pathway to achieve similar complex structural and functional diversity. Two dienophiles, 4-Phenyl-1,2,4-triazoline-3,5-dione and 1-Methyl-1H-pyrrole-2,5-dione used for the synthesis of ligands (**L19** and **L20**) and their self-assembly studied. Importantly, the ligand **L19**, due to the high dynamic exchange between its enantiomers, simplified the self-assembled mixtures, allowing easy NMR characterization and crystallization. Using this as a reference, we were able to covalently post-modify the metal-organic architectures at room temperature using 4-phenyl-1,2,4-triazoline-3,5-dione **5.01** and found that a new cage species could be formed. Although the nature of this cage species still requires further study, it demonstrates a rapid and facile approach to tune structures and functionalities of metal-organic architectures through covalent post-modification.

Finally, in chapter 6, we describe another important advance in this thesis, a proof of concept work on the use of multiple helix formation with aromatic oligoamide foldamers as a driving force for the self-assembly of higher-ordered architectures. Based on the results and experience from coordination-

driven self-assembly, two kinds of ligands were designed with central linkers differing in bend angles and rigidity. An optimized synthetic method was established and allowed us to obtain two foldamer-based ligands, **L22** and **L23**. Importantly, NMR and MS studies for ligand **L22** showed promising results suggesting it can assemble into larger structures, providing a proof of concept for our idea.

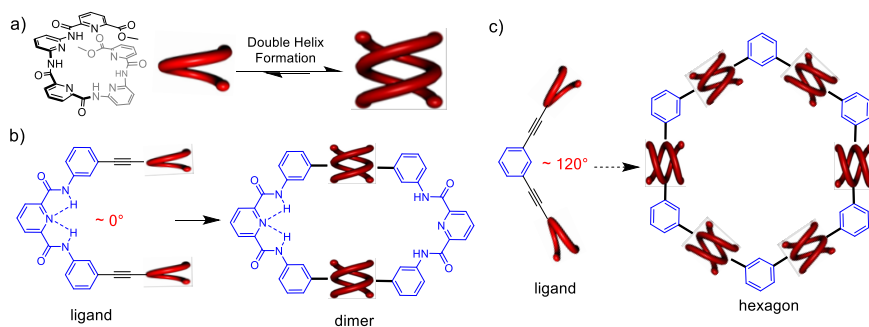


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Chapter I

Introduction

1. Design of metal-organic architectures

In nature, folding and self-assembly of supramolecules using a variety of weak, non-covalent interactions allows a small collection of simple building blocks to become extremely complex biomolecules that are vital for processes important for life, Figure 1.01. Impressive examples include DNA and RNA structures for transmitting genetic information or proteins, three-dimensional structures capable of selective catalysis and recognition resulting from the folding of peptides.^[1] The existence of life and the diversity of nature is heavily dependent on these large biological assemblies. A representative example of such processes is the formation of the iron storage protein, apoferritin.^[2] The sequence of covalently connected amino acids in the primary oligomers enables folding into monomeric proteins whose conformations are controlled by intramolecular non-covalent interactions. These monomeric proteins can spontaneously form 3-fold symmetry and 4-fold symmetry higher-order protein subunits benefitting from the intermolecular interactions between monomeric proteins. Moreover, these higher-order protein subunits then self-assemble into hollow clusters with octahedral symmetry as a result of non-covalent interactions and geometric matching of protein subunits. Importantly, the hollow clusters offer a well-defined cavity that functions for the storage and release of iron.

The high control over the final structures, in terms of size, shape, and composition, as well as the functions and interactions possible with

Chapter I

biomolecules, has highly inspired chemists to attempt to mimic biological self-assembly with synthetic components. This has led to rapid developments in supramolecular synthesis in the last several decades, along with increased knowledge of both synthetic and characterization methods for complex systems.^[3] As shown in Figure 1.01, one representative example is the synthetic self-assembled M_6L_8 octahedral cavity derived from C_3 symmetric organic ligands with Pd^{2+} cations.^[4]

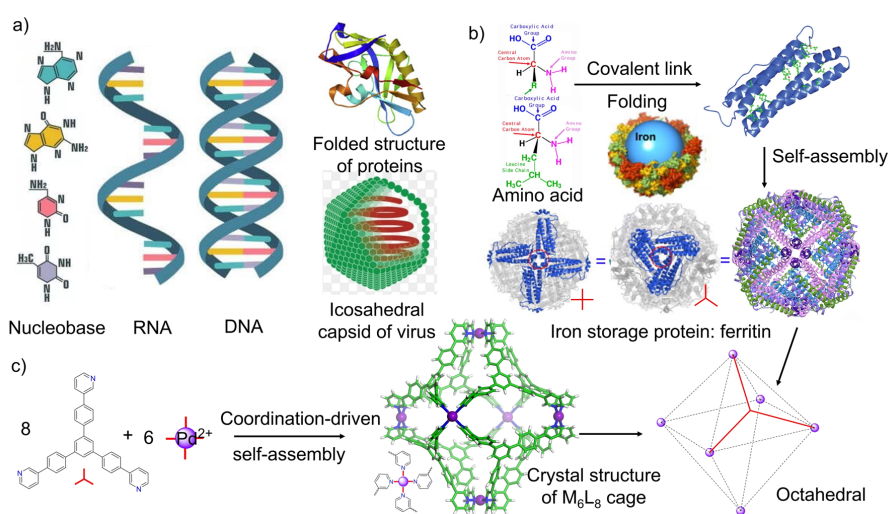


Figure 1.01 a) Representative examples of large supramolecular assemblies in nature,^[1] b) non-covalent interactions drive the folding of a ferritin protein and self-assembly of a higher-order cluster with octahedral symmetry in biology,^[2] and c) synthetic approach for the formation of an octahedral cage relying on coordination-driven self-assembly.^[3]

1.1 General concepts in self-assembly

Self-assembly is a process in which pre-existing disordered components in a system spontaneously form an organized structure or pattern as a result of specific and local interactions among the components themselves, without external direction, Figure 1.02. The term has been used in a broad sense to describe processes in a variety of areas, from the growth of seeds into plants

and the formation of organized human society. In chemistry, it most often describes ordered structure formation via interactions between molecular components resulting in large, complex systems that are often difficult to construct by normal synthetic means.^[5] This is most specifically referred to as “molecular self-assembly,” but in this thesis, we will most commonly use the shorter term “self-assembly” when referring to molecular systems. In almost all cases, self-assembly is based on solution chemistry between various types of molecules, particularly organic molecules with or without metal ions, that form weak chemical bonds/interactions with a strength that depends sensitively on molecular shape and orientation. Even still, the constitutive components used in self-assembly can be broad, ranging from specific molecules, macromolecules, polymers, colloids, or large particles and materials.^[6]

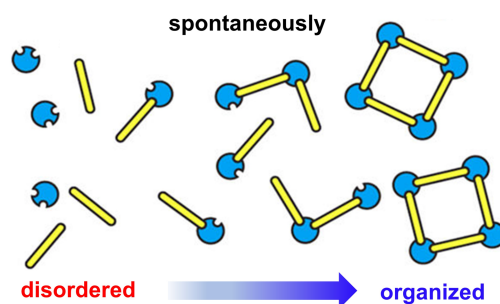


Figure 1.02 Schematical presentation of self-assembly.^[5-6]

Self-assembly features many advantages over traditional covalent synthesis, such as facile reaction conditions, self-correcting and defect-free assembly of the final products.^[5] The typical feature of self-assembly is a spontaneous organization under thermodynamic equilibrium conditions into a more stable species that is stabilized through the driving force of reversible non-covalent interactions, or for that matter, metal-ligands coordination bonds. This results in an additional property of most self-assembly for error correction, which is not normally available to fully covalent systems, thus resulting in increased overall structural complexity under thermodynamic equilibrium

because of the number of intermolecular contacts present. It needs to be noted that self-assembled systems can also be under kinetic control rather than thermodynamic. This is more likely to occur in complex supramolecular assemblies that contain many intermolecular contacts, especially when building blocks are moderately rigid. It may also happen when kinetically inert metal ions are incorporated in the framework of the resulting supramolecular structures. For example, the low solubility of the intermediate product in the assembly process leads to precipitates out of solution.

1.2 Coordination-driven self-assembly

Indeed, the self-assembly of discrete components through various interactions has become a crucial strategy for achieving high complexity and functionality in well-defined artificial supramolecular assemblies, which in turn has led to the emergence of novel artificial materials.^[6f, 7] The interactions used as driving forces in these systems include hydrogen bonding, van der Waals forces, π - π interactions, dipole-dipole interactions, metal-ligand interactions, and many more. Among these driving forces, metal-ligand interactions have been widely used to design supramolecular assemblies because of the highly directional and predictable geometric preferences of coordination bonds between the metal centers and ligands.^[8] Importantly, their self-assembly process also benefits from the intermediate energies of the metal-ligand bonds (15-50 kcal/mol) versus covalent bonds (ca. 60-120 kcal/mol) or weak non-covalent interactions (ca. 0.5-10 kcal/mol). This gives them suitable rigidity and reversibility depending on coordination kinetics. As a result, during self-assembly, a dynamic exchange between building blocks, intermediates and self-assembled architectures is established to allow self-correction in the assembly and disassembly processes. Ultimately this ability to break and reform that coordination bonds allow the system to progress to the most thermodynamically stable species with high yield in solution.

Over the past several decades, among various established synthetic strategies for creating supramolecular assemblies, coordination-driven self-

assembly of simple building blocks and metal cations into metal-organic architectures has evolved as one of the most powerful bottom-up strategies and the rapid development in this field provides access to a rich library of metal-organic supramolecular structures, Figure 1.03. Benefit from the large diversity of different ligands and metal coordination environments, countless metal-organic assemblies can be formed.^[8] These assemblies can be cationic or anionic polynuclear clusters with various topological structures of different sizes, shapes, and compositions. In order to simplify their classification, these discrete systems can be divided into two categories: two-dimensional structures (metal-organic macrocycles) and three-dimensional structures (polyhedra and polygons, referred to as metal-organic cages). The selective formation of these metal-organic structures results from several different factors that are important in their design. The following sections will look at these in more detail.

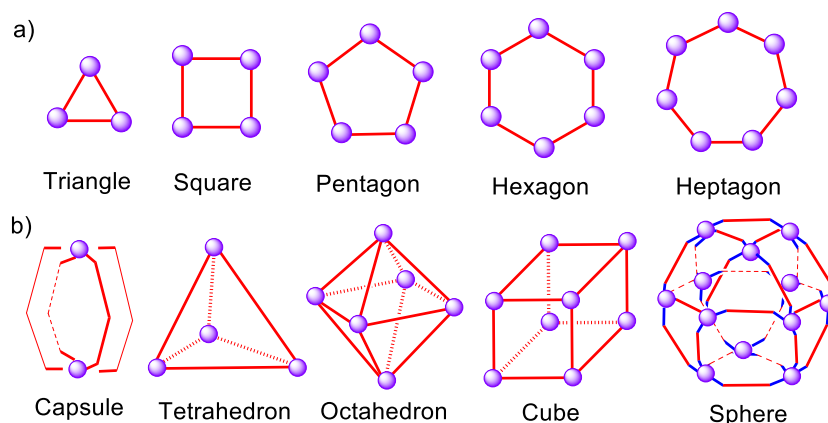


Figure 1.03 Examples of shapes of discrete supramolecular structures through coordination-driven self-assembly of organic ligands and metal ions, including a) metal-organic macrocycles and b) metal-organic cages.^[8]

1.3 Components of metal-organic architectures

The formation of metal-organic assemblies through coordination-driven self-assembly exploits coordination bonds to direct the overall structure, shape,

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and orientation of components in a system. Thus, the most important factors involved in the formation are the components: the metal ions and organic ligands. The coordination nature of the metal and the properties of the ligands are essential for directing the type of structure that will form. Important aspects include, for example, the coordination number and geometry of the metal center, and the donor sites, angles, and shapes of ligands.

The most frequently used cations in these systems are transition metal ions, such as Pd(II), Pt(II), Fe(II), Co(II), due in large part to their predictable coordination geometries, and more rarely with lanthanide and actinide ions, due to their inherent versatile coordination numbers/geometries and the lability of lanthanide complexes.^[9] Typically, the s, p, and d orbitals of the metal central accommodate 18 electrons contributed by interactions with s and p orbitals of the organic building blocks and the d orbitals of the metal ions. Thus, the coordination number, the number of ligands attached to the central ion, or more specifically, the number of donor atoms, is often from 2 to 9. Moreover, the coordination number also depends on the size, charge, and electron configuration of the metal ion and the ligands. For instance, large metal ions with small ligands can lead to high coordination numbers and small metal ions with large ligands lead to low coordination numbers. The large size of lanthanides, actinides, and early transition metal ions often leads to high coordination numbers. As shown in Figure 1.04, the most common coordination geometries of metal complexes with coordination numbers 6 and 4 are octahedral, tetrahedral, and square planar, the preference being related to electronic/orbital effects between the ligands and metal. For example, in Pd²⁺ and Pt²⁺ complexes, the metal orbitals are also more radially diffuse (i.e., bigger), and the pairing energy is also smaller in their complexes, leading to a stronger overlap with the orbitals of the ligands and as described by VSEPR dsp² hybridization that gives a square planar geometry. This geometry is also described by the high crystal field stabilization of the d⁸ configuration in square planar complexes. Indeed, the coordination number highly determines the geometry around the central metal ion. These common coordination

geometries with high symmetry and saturated coordination are also exactly what is needed in the design of metal-organic architectures.

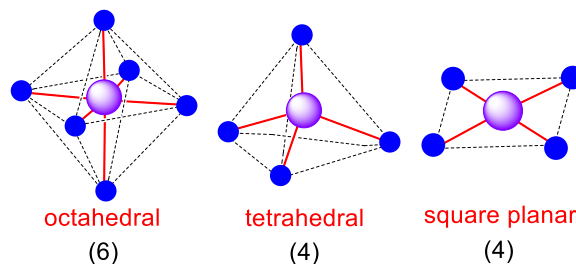


Figure 1.04 The most common coordination geometries and coordination numbers of the complexes: octahedral, tetrahedral, and square planar.

Another important factor in the design is the organic ligand. Different from the inherent properties in metal ions, the repertoire of synthetic chemistry can be used to make a vast collection of ligands with diverse structures and properties. As shown in Figure 1.05, the coordination sites of ligands can vary between monodentate to polydentate coordination, such as pyridyl coordinators, aminopyridine, bipyridine, pyridyl triazoles, pyridyl pyrazoles and acyclic chelating ligands.^[8d] The metal cations are coordinated by these coordination sites, which act as the driving force for forming the larger structure. Moreover, in order to enable the formation of 2D and 3D metal-organic architectures, the ligands used for self-assembly should at least include two coordination sites. Thus, the central link between coordination sites essentially determines the ligand shapes and can also significantly impact the outcomes of self-assembly. Examples of the forms of linear ligands, bent ditopic ligands, tritopic ligands, and more complex ligands with three-dimensional geometries are shown in Figure 1.05. A more detailed discussion on the role of ligand shape will be given in section 1.4.

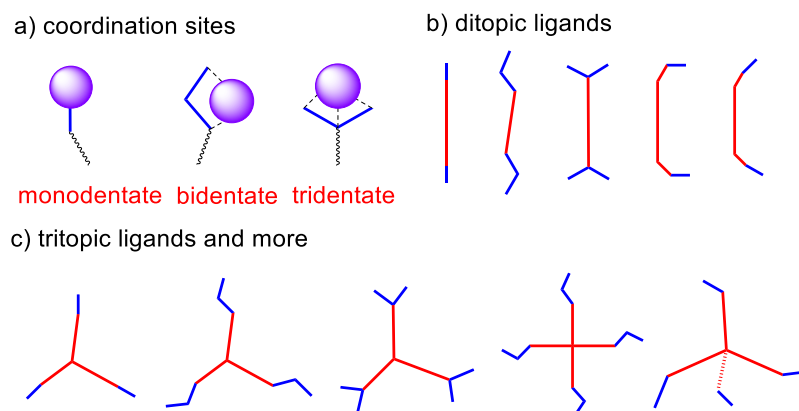


Figure 1.05 Examples of different coordination sites and the shapes of organic ligands from simple ditopic to three-dimensional geometry.

Careful control of reaction conditions and monitoring of the self-assembly process is also an important aspect. For this reason, as can be seen from many of the reported examples, the general procedure for metal-based self-assembly relies on using a polar solvent (e.g., DMSO, CH₃CN and DMF) and controlling the time and temperature to promote the formation of metal-organic architectures. In most cases, assembly formation is monitored using a series of characterization techniques, including NMR, MS, DOSY, DLS, TEM, AFM and X-ray diffraction to determine the nature of self-assembled species. Still, directing the metal and ligand to a single desired species requires more planning, and several strategies have been devised. In order to permit the rational design and preparation of metal-organic architectures, several design principles, such as the directional bonding method, the symmetry interaction strategy, the molecular paneling approach, and the weak link strategy, were developed by the groups of Fujita, Stang, Raymond, Mirkin, Newkome, Nitschke and others.^[8a, 9b, 10]

1.4 Strategies for combining ligands and metal ions

The directional-bonding approach is based on the use of metal centers with directing or blocking ligands that control which of the remaining coordination sites are available to incoming ligands.^[10c, 11] Through proper choice of these

coordinatively inert directing ligands, the angle or stereochemical relationship between open coordination sites on the metal can be controlled. In many cases, this fits well with the principle of maximal site occupancy in that the preferred assemblies tend to be the smallest structures where all coordination sites are occupied and where strain is minimized. For instance, cis-protected Pt(II) complexes leave two free coordination sites with a 90° relationship between them, Figure 1.06. This allows the metal to be considered as a spacer or building unit with known geometric parameters.^[12] Next, control over the shape (bend angles, topicity) of the ligands can be achieved by organic synthesis. This gives rigid components with pre-designed relationships between interaction sites. With this idea, the final self-assembled structures should result from the combined angular information programmed into the metal and ligand components. This has allowed a series of target metal-organic architectures ranging from 2D macrocycles to 3D cages to be achieved based on simple geometric principles. For example, self-assembly of a coordinatively unsaturated metal complex with a 60° angle between the coordinatively labile sites and a rigid ditopic ligand with a bend angle of 120° leads to the formation of a rhomboid macrocycle. Interestingly, using the same metal precursor but simply changing the angle of ditopic ligand from 120° to 180° lead to the construction of a molecular triangle.

This directional-bonding approach has since become a general and high-yielding synthetic strategy, allowing a wide range of more complicated polygons and polyhedra to be accessed through rational choices of metal starting complexes and rigid ligands based on their angles and shapes. However, the defined angles are essential to the closure of the appropriate geometric shape. Thus, the limitations of this approach are the ligand systems must be rigid, highly directional multibranched monodentate ligands to have the predictability of the final structure and preclude the formation of mixtures of products. This rigidity limits the use of flexible ligands for self-assembly that can be interesting for applications. The rigidity also limits the possibility of inducing conformational changes in metal-organic architectures for molecular

switches or other applications. Additionally, as the coordination sites on the metal centers should all be occupied in these metal-organic architectures, there are limited possibilities for metal-based catalysis.

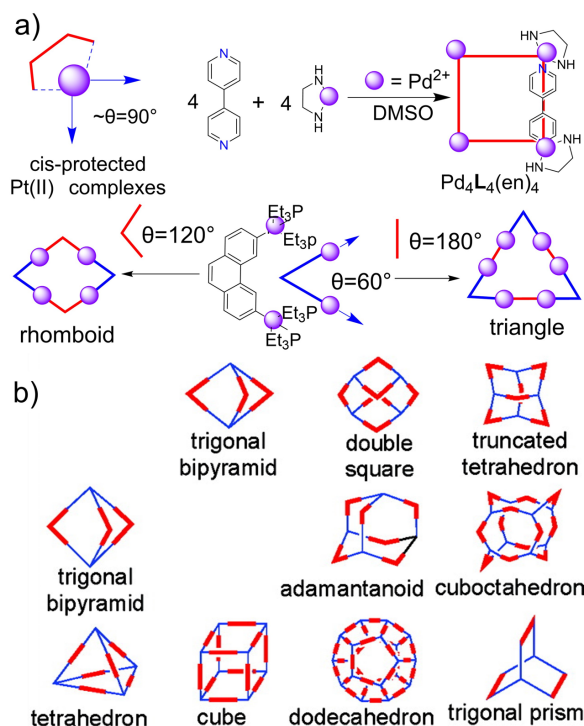


Figure 1.06 Example of directional-bonding approach for a) angle-directed macrocyclic polynuclear complex and c) three-dimensional architectures formed by the combination of ditopic and tritopic subunits.^[10c, 11-12]

Another important principle frequently used in the rational design of metal-organic architectures is the symmetry-interaction approach, which is based on the orientation of multi-branched chelating ligands fixed in rigid backbones in conjunction with transition or main group metals ions, Figure 1.07. Similar to the directional bonding approach, rigid backbones are often used to improve the selectivity for a molecular geometry and avoid the formation of oligomers and polymers.^[10c, 13] However, due to the use of chelating ligands, more weakly coordinating groups are preferred to maintain

coordinative lability. With the rigid structure, this targets thermodynamic control and kinetic reversibility for error checking in self-correction of the final assemblies. In this approach, the structures that form are predicted based on the geometric relationship between the coordination mode of the chelating ligands and the inherent symmetry of pairs of coordination sites available on the metal center. The shapes of self-assembled supramolecular architectures should be largely dependent on the symmetry of their metal coordination environments. Obviously, this approach is more complicated because it must balance multiple symmetry interactions of metal geometry, ligand orientation, and ligand-ligand steric interactions, etc.

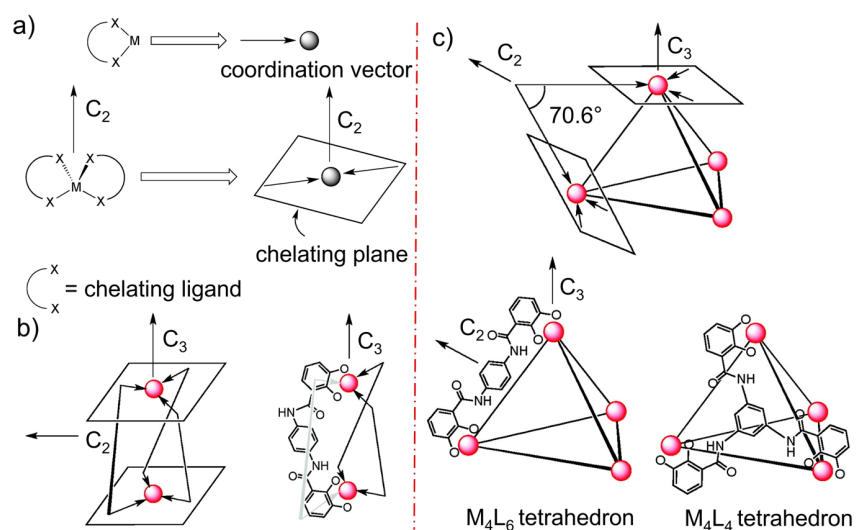


Figure 1.07 Symmetry-interaction approach a) Coordination vector and chelate plane for the symmetry interaction approach, design of b) D_3 -symmetrical triple helicate and c) tetrahedra.^[10c, 13]

Raymond and coworkers have simplified the description of the multiple binding sites using coordination vectors that represents the interaction between the ligand and metal, Figure 1.07. The coordination vector of a bidentate ligand can be described as a vector that bisects the angle between the two donor atoms and the metal.^[10c, 13] For the metal, the chelating plane

will be the plane perpendicular to one of the major symmetry axes. In tetrahedral complexes, this is the C_2 axis and in octahedral complexes, this is the C_3 symmetry axis. The combination of the metal ions and the ligand should lead to structures where the coordination vectors of the ligands can be coplanar with the chelating plane of the metal. Then based on the angle between the coordination vectors in the ligand, different structures can form. For example, suppose the coordination vectors in a C_2 symmetric ligand are parallel to each other. In that case, coordination to an octahedral metal should lead to an M_2L_3 triple helicate. If the angles of coordination vectors are around 70.6° , self-assembly can give an M_4L_6 tetrahedral cage. Based on this symmetry-interaction approach, a variety of elegant architectures have been accessed using the predictable coordination chemistry of multibranched chelating ligands with transition and main group metal centers. Computer modeling has also improved the prediction of target architectures in these complex systems based on theoretical knowledge of coordination modes between metals and ligands. As one of the pioneering examples, Raymond and coworkers designed O-donors catechol-based ligands and synthesized a family of anionic metal-organic architectures, which are rarer than their positively charged analogs. They further demonstrated that these systems could have interesting host-guest interactions or be used for supramolecular catalysis.^[14] However, the cavities of most metal-organic architectures formed through the symmetry-interaction approach have relatively small dimensions that limit the encapsulation of large guest molecules.

The molecular paneling approach accessed metal-organic architectures with large accessible interior cavities, which reduces the polyhedra resembling platonic solids to combinations of molecular components with simple shapes, such as equilateral triangles, squares, and pentagons.^[15] For example, a tetrahedral cage can be accessed by stitching together four triangular panels and eight triangular panels can be used to form an octahedral cage in a similar method, Figure 1.08. Square-planar Pt(II) or Pd(II) metal centers with *cis*-blocking ligands are usually used in these systems to make the coordination

geometry around the metal center convergent for the formation of discrete metal-organic architectures rather than oligomeric products.^[11a, 16] Similarly, other 2D molecular paneling, such as squares and pentagons, can span all or some of the faces of the resulting platonic architectures, giving a variety of 3D metal-organic structures, including the M_6L_4 truncated tetrahedral cage, the M_6L_4 square pyramidal cone, M_8L_4 tetrahedra, and $M_{18}L_6$ hexahedra.^[17] One of the prime advantages of this strategy is the large interior cavities in the resulting complexes that have been exploited for reversible guest inclusion, molecular recognition, and cavity-driven catalysis.^[16d, 18] It should be noted that, for the above approaches, other structures can potentially be accessed through the use of guest molecules as templates during the self-assembly process.^[19] For example, aromatic π -stacked molecules have been used as templates for the stabilization of prism-like cages, Figure 1.08. Indeed, template-directed self-assembly is an important supplement to the typical design principles for metal-organic architectures that are unstable or not readily available.

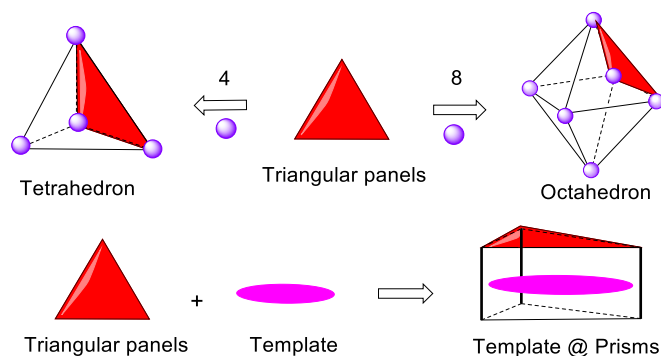


Figure 1.08 Representative examples of designing the tetrahedral and octahedral cage using triangular panels.^[15, 19]

Next to the above design approaches based on rigidity and symmetry, the weak-link synthetic strategy allows the self-assembly of metal-organic architectures incorporating flexible units through the use of hemilabile directing ligands. This weak-link synthetic approach also offers the ability to

prepare supramolecular structures with available coordination sites for further application.^[20] As an example shown in Figure 1.09, hemilabile ligands are usually used to bond to transition metal centers in a bidentate fashion, in such a way that one of the metal-ligand bonds is stronger than the other. Incorporating two of these groups onto a spacer that favors the formation of a binuclear complex rather than a mononuclear complex, i.e., a rigid unit or long-chain, can permit a discrete macrocyclic structure to be formed. In the example, additional stacking interaction in the spacer also helps direct the assembly of this structure. Once formed, the addition of stronger monodentate ligands to the solution can replace the hemilabile group, opening up the structure to generate a larger cavity. This weak-link approach grants access to sophisticated structurally flexible supramolecular architectures through control over the coordination environment of transition metal centers with hemilabile ligands. The remaining dynamic structural properties and active coordination sites of the supramolecular structures are of interest for potential applications in host-guest chemistry and catalysis.

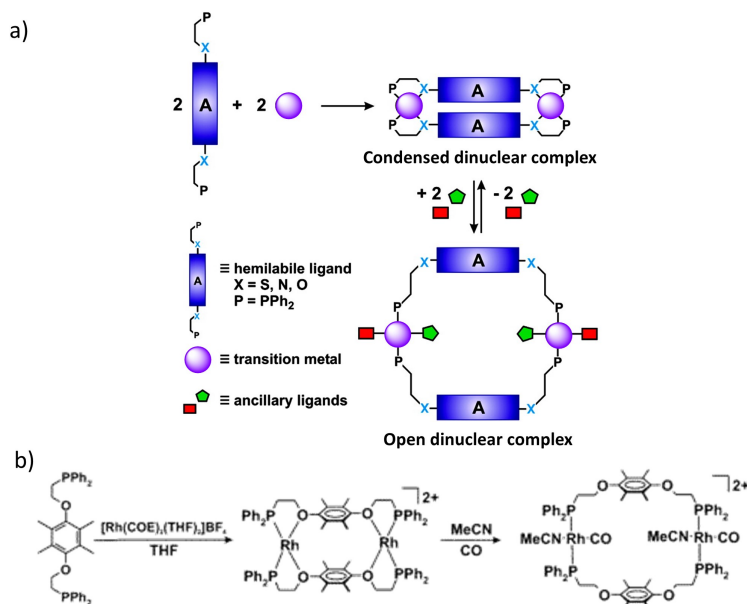


Figure 1.09 a) General role of weak-link synthetic strategy, b) representative examples of the formation of the dinuclear complex via weak-link synthetic

strategy.^[20]

Some other less commonly used strategies have also been developed,^[21] such as the dimetallic building block approach has been used in conjunction with various organic linkers to construct a wide array of neutral supramolecules, Figure 1.10.

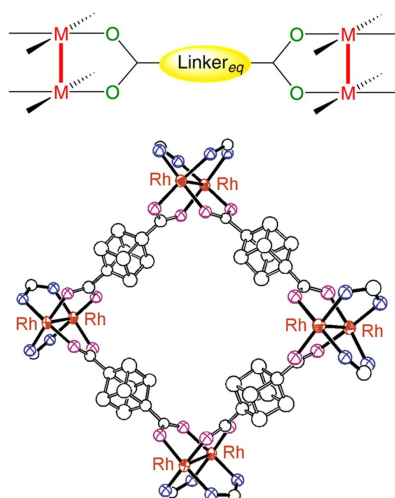


Figure 1.10 One of the basic modes of dinuclear units and its example in the formation of the Rh₂ cubanededicarboxylate square.^[21]

In the past several decades, the above design strategies have become well-established for the formation of discrete structures. As shown in Figure 1.11, some representative examples of self-assembled discrete metal-organic architectures were achieved using some of the strategies described above. Still, this is only a handful of the different possibilities. Indeed, it is unrealistic for this thesis to comprehensively review all the examples in the broad and rapidly developing field of metal-organic assemblies. Herein, we will focus on the self-assembly of Pd(II) ions and ditopic ligands into M_nL_{2n} complexes ranging from simple capsules or macrocycles to large spheres and use selected examples to understand the key design principles for increasing structural complexity and diversity.

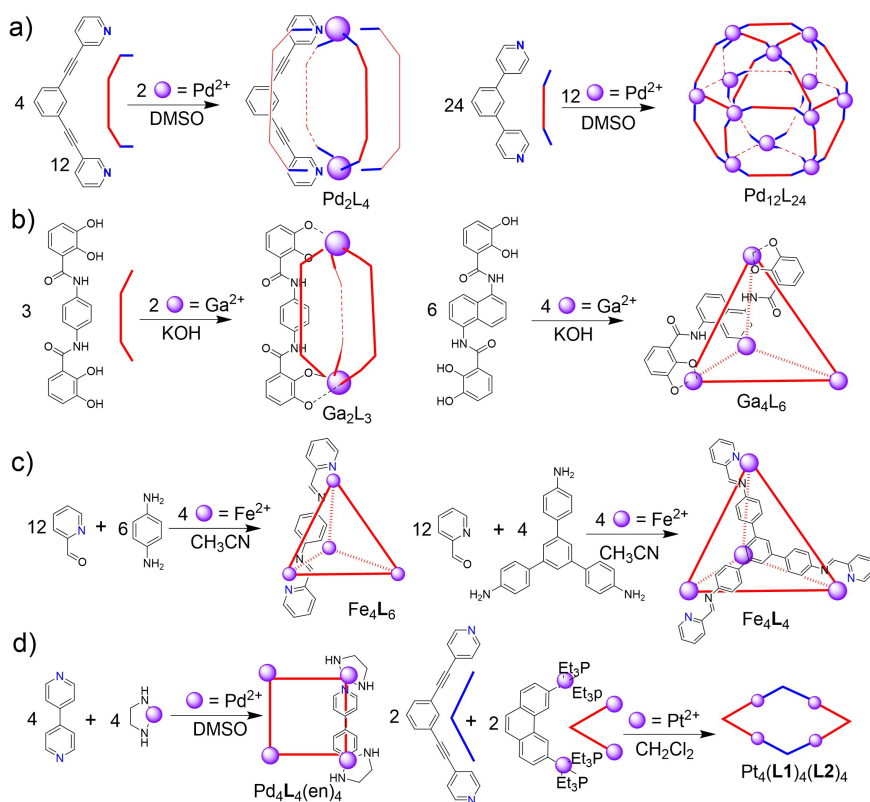


Figure 1.11 Representative examples of self-assembled discrete metal-organic architectures, a) M_2L_4 capsule and $\text{M}_{12}\text{L}_{24}$ sphere, b) anionic M_2L_3 helicate and M_4L_6 tetrahedral cage, c) subcomponent self-assembly of M_4L_6 and M_4L_4 tetrahedral cage, d) ligands angle-directed macrocyclic polynuclear complex.

2. Self-assembly of M_nL_{2n} assemblies

Coordination-driven self-assembly has been established to be a simple and efficient method for the construction of a wide range of well-defined discrete metal-organic architectures, such as macrocycles, helicates, capsules, grids, spheres, knots and cages.^[8d, 22] As one class of assemblies using rigid and highly symmetric building blocks, the synthesis of M_nL_{2n} type metal-organic assemblies through the complexation of coordinated metal centers, most

commonly square planar or octahedral metal cations, e.g., Pd(II), Pt(II) and Cu(II), with rigid, bent and ditopic ligands has emerged as a promising area of self-assembly.^[8c, 10a, 23] Based on the design strategies described in section 1, this system allows high predictability of the overall shape and nuclearity of the final self-assembled structures.^[8c, 10a] From the simplest M_2L_4 capsule to the more complex M_nL_{2n} hollow spheres ($n=2, 6, 8, 9, 12, 24, 30, 48$) and M_nL_{2n} ($n=3, 4, 5, 6, 7 \dots$) double-walled macrocycles, numerous structures have been described based on the ratio of metal and ligands, the shape and size of the ditopic ligands, Figure 1.12. This section will review these structures separately.

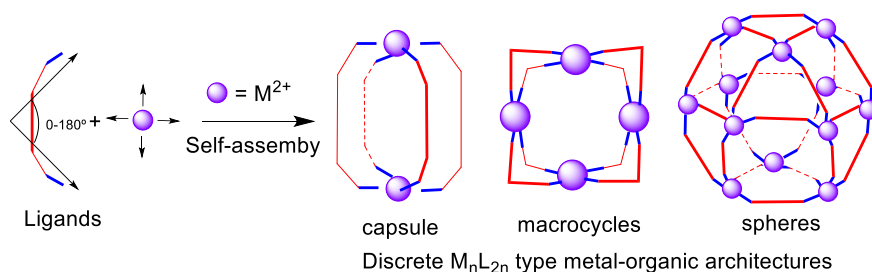


Figure 1.12 Overview of coordination-driven self-assembly of M_nL_{2n} assemblies with internal cavities using bent ditopic ligands for the formation of capsules, double-walled macrocycles and polyhedral spheres.

2.1 M_2L_4 capsule

M_2L_4 capsules are one of the simplest cages with the lowest nuclearity of M_nL_{2n} type metal-organic assemblies, but they are also the most studied cages and an important growing family, Figure 1.13. This is because of their simple composition, highly symmetric structures, well-defined internal cavities, and applicability in various fields such as molecular recognition, catalysis and drug delivery.^[24] Similar to the general procedure for self-assembly, M_2L_4 capsules can be simplified to mixing bent ditopic ligands ($\theta \sim 0^\circ$) and metal cations in a polar solvent (e.g., DMSO, CH_3CN and DMF). The quantitative formation of possible single species is expected in solution, and the counter anions can be used to tune the solubility of the outcomes in most cases. Generally, self-

assembled M_2L_4 cages feature a simple composition and highly symmetric structures. However, even in such a simple self-assembled system, the formation of mixtures has been frequently observed. Thus a careful design and selection of solvent system, concentration, temperature and potential guest templates are required to promote the self-assembly of a single product. It should be noted that for these structures, there is the potential for the ligands to twist, leading to right-handed (*P*) and left-handed (*M*) helical structures. As a result, many studies in the literature refer to these helical M_2L_4 structures as quadruple-stranded helicates, Figure 1.13. However, the more general term cage is frequently used interchangeably to describe both helical and non-helical M_2L_4 structures containing a cavity.

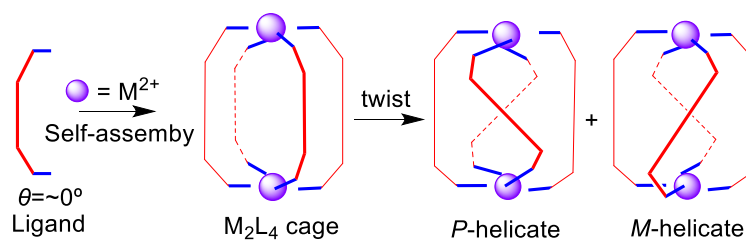


Figure 1.13 Schematic representation of coordination-driven self-assembly of a prototypical M_2L_4 cage and its potential right-handed (*P*) helicate and left-handed (*M*) helicate structures.

The first example of an M_2L_4 capsule was reported by Steel and coworkers in 1998.^[25] Four bent ditopic ligands and two Pd(II) metal ions self-assembled to give an M_2L_4 structure. It was characterized in solution by NMR and mass, and unambiguously confirmed in the solid-state by single-crystal X-ray structure. In the crystal structure, two square planar geometry Pd(II) metal cations were bridged by four bent ditopic ligands leading to a cavity within which resides a well-ordered PF_6^- anion. This is the first example of the encapsulation of a complex anion (PF_6^-) that was reported to be facilitated through weak $Pd \cdots F$ interactions, Figure 1.14. In the same year, a Cu(II) based M_2L_4 cage was reported using bent ditopic ligands, which were found to coordinate in an equatorial fashion (square planar arrangement) around the

octahedral Cu(II) metal cations, Figure 1.14. Two water molecules further stabilized the self-assembled cage in the axial positions of the two Cu(II) centers.^[26]

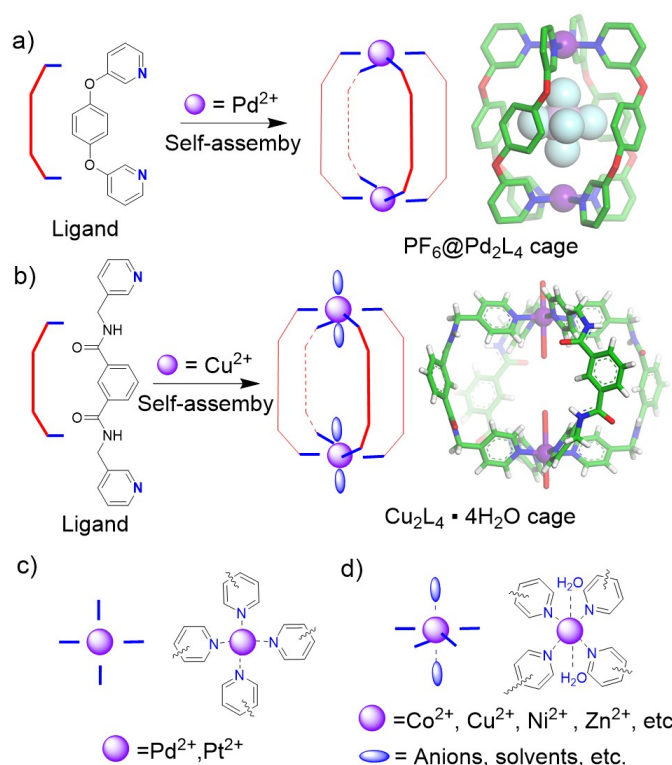


Figure 1.14 Examples of M_2L_4 cage a) square-planar $Pd(II)$ cations and b) $Cu(II)$ cations with the square planar arrangement of pyridine and axial water. Self-assembly of M_2L_4 metal-organic cage using c) square coordinated metal cations and d) octahedral coordinated metal cations. ^[25-27]

After these early works, more transition metal cations have been successfully used in the self-assembly of the M_2L_4 metal-organic cage, Figure 1.14. Commonly, square planar geometry metal cations, $Pd(II)$ and $Pt(II)$, were used as a prominent role of central metals due to their predictable coordination geometries with convenient and dynamic metal-ligand interactions. On rare occasions, $Cu(II)$, $Zn(II)$, $Ni(II)$, $Mn(II)$ and $Co(II)$ cations have also been shown to allow the square planar arrangement of the ligands to enable the formation

of M_2L_4 capsules.^[27] Of note, even metal cations with similar coordination geometry will have obvious effects on self-assembly. For example, the clip-type ligand shown in Figure 1.15 was reported to self-assemble into M_2L_4 cages with remarkable thermodynamic stability using both Pd(II) and Pt(II) in DMSO. These metals have similar preferences for square planar geometries. However, higher reaction temperatures and longer times are necessary for self-correction when Pt(II) is used for cage formation. This is because the Pt-N bonds are more inert compared to Pd-N bonds.^[28] Moreover, the metal center can also have an important role in the reactivity of the cages on host-guest chemistry. For instance, the Pt(II) Pt_2L_4 metal-organic cage exhibits an adequate cavity for guest encapsulation of an Au(III) metal complex, Figure 1.15. By contrast, the analogous Pd(II) cage failed to host the gold complex, though the reason behind this difference was not established in the paper.^[29]

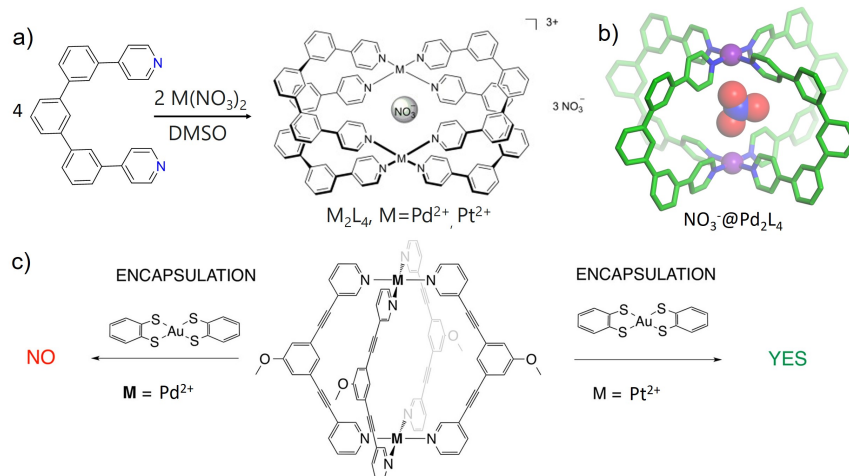


Figure 1.15 a) Self-assembly of Pd_2L_4 and Pt_2L_4 capsule,^[28] b) crystal structure of $NO_3^-@Pd_2L_4$, c) the Au(III) complex was successfully captured inside the cavity of the Pt_2L_4 in contrast to no encapsulation in Pd(II) cage.^[29]

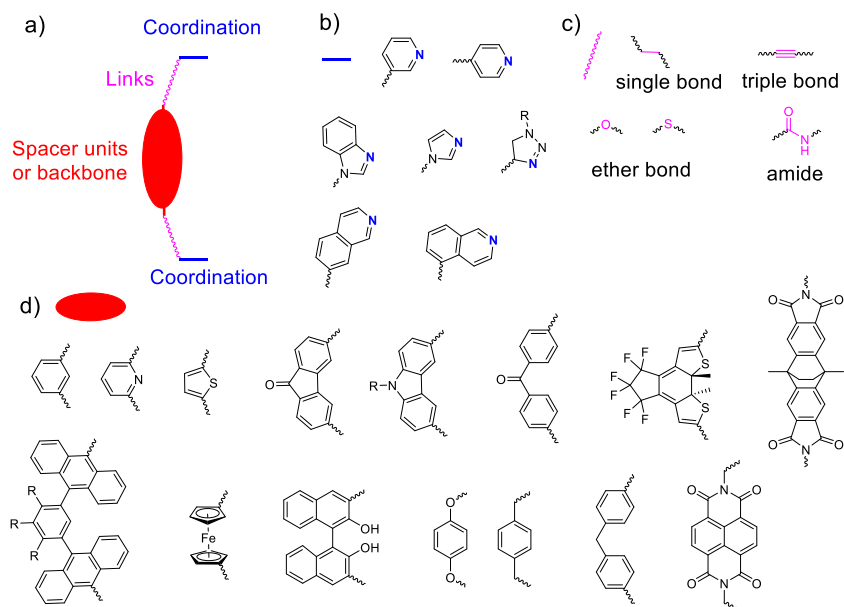


Figure 1.16 a) Sketch of components in bent ditopic ligands used for M_2L_4 cage, the chemical structure of commonly used b) coordination sites, c) organic links and d) the spacer units or backbones.

As discussed in the general design strategy of metal-organic architectures, the choice of central metal ions and organic building blocks are two important aspects of coordination-driven self-assembly. However, the great tunability of the organic building blocks in contrast to the inorganic metal salts leads to most of the works focused on the design and modification of organic ligands. The design of suitable ditopic ligands used for self-assembly of M_2L_4 cages requires at least three main components: the coordination sites, the spacer units or backbones, and the chemical bonds for the formation of overall bent ligands, Figure 1.16. Among the ligands reported in the literature for M_2L_4 -type cages, pyridine-appended compounds are most often used with $Pd(II)$ ions. Other commonly used coordination sites include carboxylates, imidazoles, benzimidazoles, and quinolines.^[30] In order to form well-defined M_2L_4 -type cages, the donor atoms in the coordination sites must be able to point in a common direction. Thus, the central spacer units or backbones in the bent ditopic ligands are often composed of rigid aromatic units and

covalently connected coordination sites, such as by single bonds, alkyne struts, amide linkers, etc.

Based on the above design strategy using metal ions with predictable coordination spheres and bent-shaped ligands, the self-assembly of M_2L_4 -type cages has been rapidly developed. Further and more detailed examples of this type of cage and related structures were summarized in recent reviews.^[8c, 24, 31] Of note, rigid and high-symmetry ditopic ligands have attracted widespread attention. Notably, using ligands consisting of rigid aromatic backbones connected through single bonds or linear alkyne spacers has been particularly well studied and shown to provide reliable access to M_2L_4 complexes through the pre-defined ligand geometries. Importantly, such rigidity in ligands offers a general means for self-assembly with larger building blocks to create bigger complexes for binding more complex guests. More generally, it helps to circumvent the void problem of the cavity and stabilizes the assemblies in highly polar solvents. For example, depending on the size of ligands, the self-assembly of M_2L_4 cages in size of 1-2 nm is commonly achieved. However, an attractive and simple strategy for bigger-sized assemblies is possible through the use of larger ligands, Figure 1.17. Simply replacing chemical bonds or connecting more aromatic backbones will allow tuning host properties in size while keeping the simple M_2L_4 cage motif in overall shape. Recently, Severin and coworkers have described a noteworthy example using rigid bent metalloligands, the largest crystallographically characterized M_2L_4 metal-organic cage up to 3 nm was achieved.^[32] A simple one-step protocol by self-assembly of two aromatic boronic acids with Fe(II) cations allowed the formation of large bipyridyl ligands. These ligands were subsequently reacted with Pd(II) metal cations, resulting in M_2L_4 cages of unprecedented size.

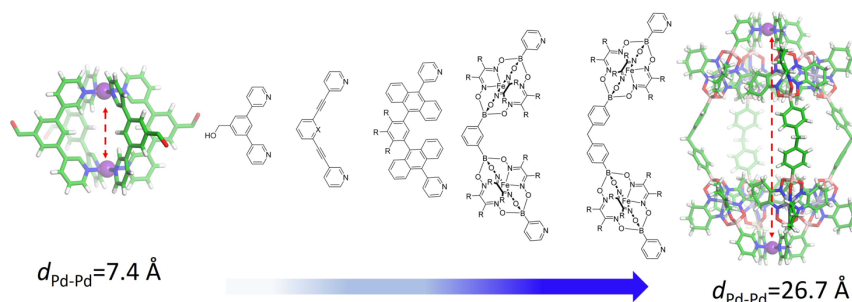


Figure 1.17 Example of the utilization of larger building blocks to create the bigger size M_2L_4 cage.^[32]

Moreover, the properties of the cage cavity are highly dependent on the physicochemical properties of their initial building blocks. Thus, slight modifications of the organic building blocks can easily alter or impart unique properties. Synergistically combining incorporated functional groups and hollow supramolecular structures, for example, can give significant changes in host-guest interactions relative to the unfunctionalized materials, Figure 1.18.

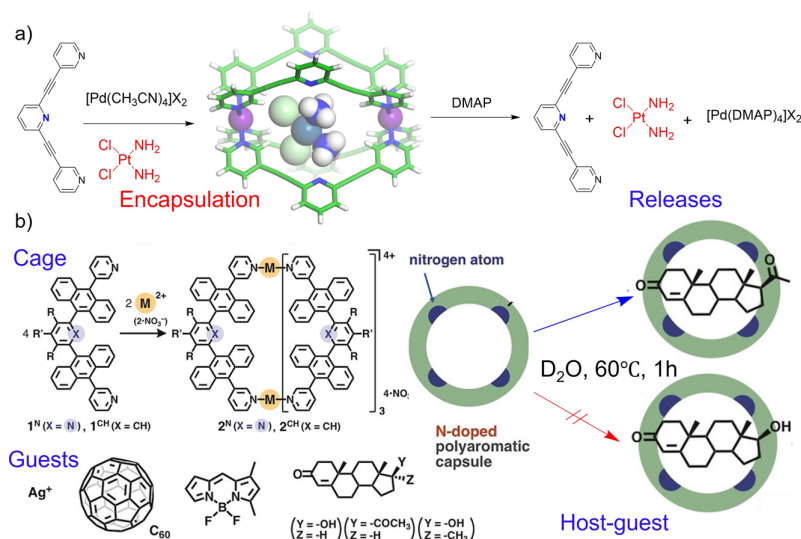


Figure 1.18 Example of a) stimuli-responsive dis- and reassembly of nitrogen-doped M_2L_4 cage towards targeted cisplatin drug delivery,^[33] b) N-doping of

polyaromatic capsules display unique host-guest interactions for selective guest encapsulation.^[35]

Crowley and coworkers designed a rigid tripyridyl ligand using a pyridyl unit instead of the benzene backbone that does not affect metal-ligand coordination during the self-assembly of cages but gives novel stimuli-responsive host-guest properties in their M_2L_4 cage.^[33] The assembly and disassembly of the cage are possible to control by the addition of competitive ligands, such as the addition of DMAP or Cl^- ions which lead to disassembly and using acid for protonation or silver cations for complexation to recover their assembled cages. This property opens the door to reversible encapsulation and release of the anticancer drug *cis*-platin from the cavity, supporting the idea that metal-organic structures have high potential as drug delivery agents. The cavity of the same N-doped Pd_2L_4 capsule has also been shown to catalyze Diels–Alder reactions with efficient turnover alongside enzyme-like hallmarks.^[34] Similarly, Yoshizawa and coworkers successfully synthesized nitrogen-doped polyaromatic M_2L_4 cage by pyridine-embedded, bent anthracene-based ligands.^[35] These new cages display unique host-guest interactions, the inclusion of Ag^+ ions, produce large absorption changes of fullerene C_{60} , altered emission of a BODIPY dimer, and the specific binding ability to distinguish highly similar guests (progesterone and methyltestosterone) in water.

A more effective strategy for functional M_2L_4 cages can be the incorporation of functional groups or properties into the organic building blocks combined with carefully selected metal coordination ions, Figure 1.19. Yoshizawa and coworkers developed a new kind of anthracene fluorophore-based ligands. It can self-assemble with $Pd(II)$, $Zn(II)$, $Cu(II)$ and $Ni(II)$ metal cations into M_2L_4 molecular capsules. Interestingly, the $Zn(II)$ capsules exhibited strong blue emission with a high quantum yield of 81% in contrast to the non-emission of the $Pd(II)$ capsules.^[27, 31a] These results on the emissive properties indicate that exterior functional groups can also be readily modified and elaborated by the central metal ions. An exo-functionalized Pd_2L_4 cage

with attached Ru(II) pyridine complexes was prepared via coordination-driven self-assembly and exhibited an exceptionally high quantum yield of 66%.^[36] Indeed, light-harvesting is another essential aspect of photochemistry in addition to light emission. Most recently, Clever and coworkers reported a new family of organic chromophore-based ditopic ligands for the construction of light-harvesting M_2L_4 cages.^[37] A key feature in their dye-based ditopic ligands is the implementation of piperazine linkers instead of typical linkers such as alkynes or arenes between the chromophore and two distinct coordinating moieties. Thus, the piperazine can mimic typical characteristics of dialkyl amines in the parent chromophores, Michler's ketone, crystal violet, methylene blue and rhodamine B. Based on these ligands, nine dye-functionalized M_2L_4 cages were achieved and were shown to control chromophore arrangement leading to strong absorption in the visible spectrum from yellow to deep violet. Moreover, CD spectroscopy of these cages discloses different degrees of chiral induction by enantiomerically pure guests, which was used for chiral recognition of small anions. More representations of functions were achieved by functionalized rigid backbone ligands containing, for example, redox-active groups.^[38]

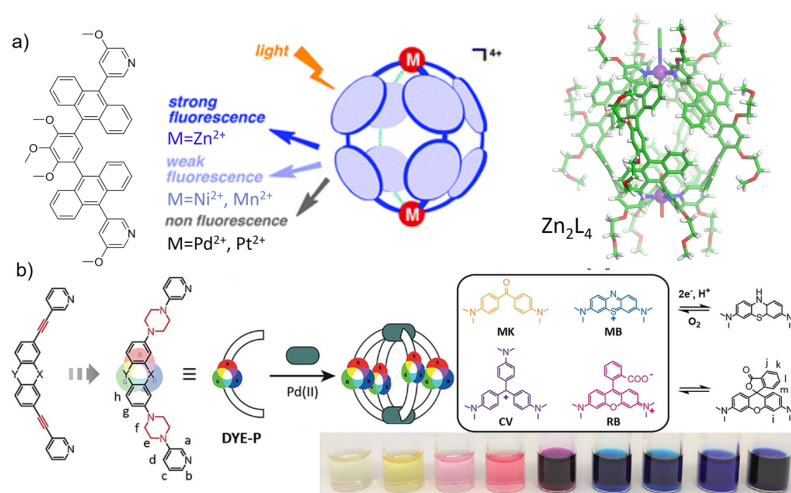


Figure 1.19 Design of a) ligands and highly fluorescent $Zn(II)$ -linked M_2L_4 capsule, b) dye-based and colored Pd_2L_4 cages by integration of organic

chromophores, Michler's ketone **MK**, crystal violet **CV**, methylene blue **MB** and rhodamine B **RB**.^[27, 31a, 37]

Interestingly, although most self-assembled M_2L_4 cages contain ligands featuring rigid backbones with defined geometries, self-assembly of M_2L_4 cages with ligands containing flexible units is also readily accessible. Flexible building blocks are usually known to reduce control on the final architecture that will be generated after coordination-driven self-assembly. When flexible building blocks were introduced into the ligands for M_2L_4 cages, the main competition generally came from the formation of mononuclear products. However, mainly due to the relatively simple M_2L_4 structure and few possible intermediate species, careful balancing of flexibility versus rigidity of ligands offers access to M_2L_4 cages and enables novel properties in terms of structures and functions. The flexibility of ligands often originates from the use of flexible sp^3 or amide linkers and less commonly from flexible spacer units or backbones.^[25, 39] Some novel properties such as enabling the adaption of their cavities for encapsulation of different sizes of guests, facilitating the formation of more complex mechanically interlocked cages, and potential allowing chirality changes of right-handed (*P*) and left-handed (*M*) structures have been reported.^[40] For example, the introduction of ligands possessing a conformational flexibility character due to the twisting of the amide moieties can still give self-assembly of the M_2L_4 cage.^[39b, 39c] The ligands can adopt different conformations resulting in changes to the electrostatic cavity surface that allows interaction with anions, neutral molecules, and cations, Figure 1.20. Another classic example is that Clever and coworkers have used photo-switchable dithienylethenes (DTE) as the backbone of a synthetic ligand as a controlled way to switch between flexible open or rigid closed forms. Both forms of the ligands can generate Pd_2L_4 cages that display interesting light-driven switching behavior and open up exciting guest uptake and release of large anionic $[B_{12}F_{12}]^{2-}$.^[41] The follow-up study by the same group on these DTE-based M_2L_4 cages with quinoline moieties as the coordination sites has demonstrated chirality transfer from the guest to the host.^[42]

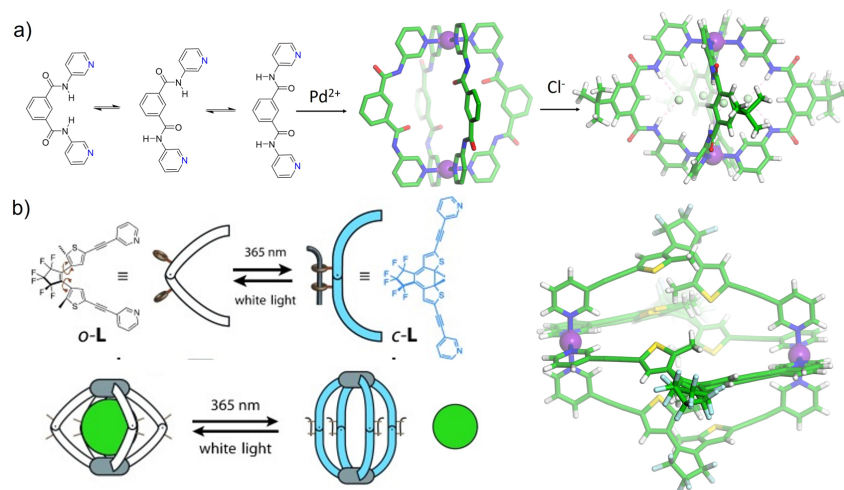


Figure 1.20 a) Conformations of amide-based ligands and crystal structures of self-assembled M_2L_4 cages that can act as adaptable receptors for guests,^[39b, 39c] b) Light-switchable conformationally flexible and rigid ditopic pyridyl ligand and its M_2L_4 cages used for guest $[B_{12}F_{12}]^{2-}$ uptake and release.^[41]

Although there have been only a few reports on quadruple-stranded helicates of Pd_2L_4 cages, the potential chirality is of special interest because of their structure and host properties.^[25, 43] For example, the complexation of an amide functionalized ligand with $Pd(II)$ ions resulted in single Pd_2L_4 quadruple-stranded helicates, Figure 1.21. The crystal structure analysis revealed both enantiomers, right-handed (P) and left-handed (M) helicates, simultaneously exist with an azimuthal angle of about 45° .^[43a] Homochiral M_2L_4 cages have been synthesized from enantiomerically pure chiral ligands.^[44] The chiral ligands and $Pd(II)$ ions self-assemble to homochiral M_2L_4 cages through high-fidelity narcissistic self-sorting due to self-recognition. Additionally, homochiral M_2L_4 cages can also be achieved by chirality transfer from guests to the host.^[42a]

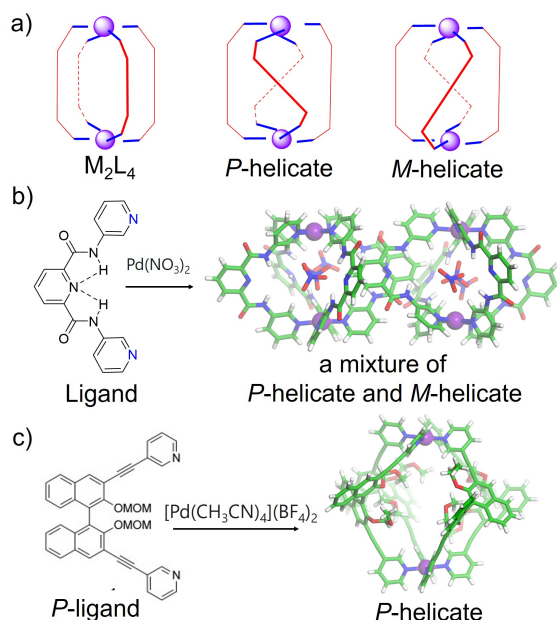


Figure 1.21 a) Graphics of simplified M_2L_4 cages, non-helicate (left), right-handed (*P*) helicate (middle) and left-handed (*M*) helicate (right). b) Selected conformers of amide-based ligand self-assembly into a mixture of both left-handed (*M*) and right-handed (*P*) helicate,^[43a] c) Chiral ligand and metal ion self-assembly of homochiral M_2L_4 cages.^[44]

2.2 Hollow M_nL_{2n} polyhedral spheres

Beyond the small structures described above, another challenge in coordination-driven self-assembly of metal-organic architectures is the controlled formation of larger assemblies, especially the self-assembly of well-defined multicomponent architectures. For self-assembly of large metal-organic cages, two approaches can be used: 1) self-assembly of a small number of large building blocks, such as the examples discussed above that using larger and longer ligands to achieve M_2L_4 capsules with the larger cavity, or 2) self-assembly of a large number of small building blocks as will be discussed in this section. Impressive examples of the latter have been described in Figure 1.22, such as a giant polyhedral $M_{48}L_{96}$ sphere with a

remarkable diameter of 5 nm that is assembled from 144 components, including 48 Pd(II) cations and 96 bent ditopic ligands.^[10a] The multicomponent self-assembly of the discrete spherical structure is undoubtedly a more complex system than the examples described in the previous section. These large structures often display dynamic properties with complex solution chemistry. Still, typical examples of controlled self-assembly of M_nL_{2n} polyhedral spheres have provided insight into multicomponent self-assembly for the design of large supermolecular systems.

Self-assembly of multiple components into ordered assemblies is essentially hampered by the fact that it should be entropically disfavored. Thus careful design and choice of the components based on kinetic and thermodynamic control is required. Indeed to avoid alternative structures or insoluble precipitates, balancing the geometry, solubility, and flexibility of the ligand are important. As the ligands and metals occupy the edges and corners of the polyhedra, one of the main strategies for the construction of this higher nuclear M_nL_{2n} ($n \geq 6$) polyhedra and spheres is a directional bonding strategy relying on controlling edges of the structure by ligand shape.^[23b] As for the M_2L_4 capsule, bent ditopic ligands and square planar metal cations, such as Pd(II) and Pt(II), are often used in these systems. However, the rigidity of the ligands is of much higher importance. With square planar metal cations, four ligands can be accommodated around the metal cations. These ligands will then bridge to adjacent metals in the structure dictating the spatial relationship between different metal atoms. Based on this, the size and nuclearity of the self-assembled structures should mainly depend on the angular variation between the two coordinating sites of the ditopic ligands, Figure 1.22. For instance, this angular dependence was supported across numerous early examples of M_nL_{2n} polyhedral spheres with the symmetry of Platonic or Archimedean solids and later extended to Goldberg polyhedra with the same general formula M_nL_{2n} ($n \geq 6$) that were designed and synthesized by Fujita and coworkers.^[8c, 10a, 23]

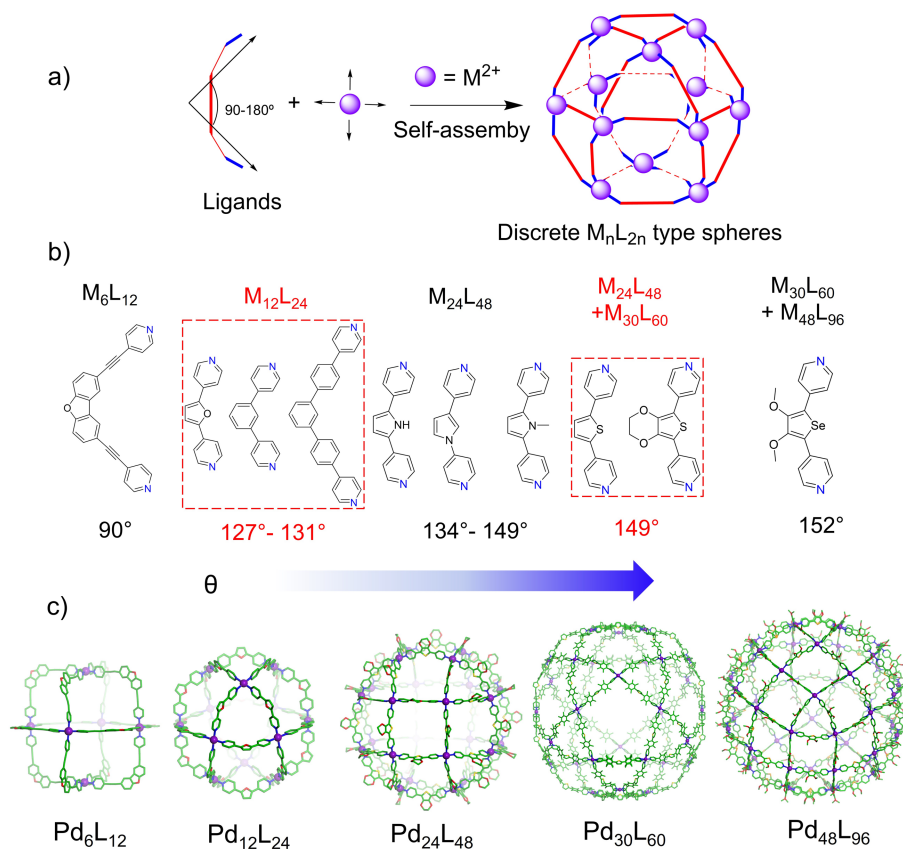


Figure 1.22 a) Schematic representation of bent ditopic ligands and square planar geometry metal ions self-assembling to M_nL_{2n} -type spheres, b) Influence of bend angle (θ) of divergent ditopic ligands on the formed cage derivative, c) crystal structures of M_nL_{2n} -type spheres from Pd_6L_{12} up to $Pd_{48}L_{96}$.^[8c, 10a, 23]

The first example of M_nL_{2n} ($n \geq 6$) spherical polyhedra based on the symmetry of Platonic or Archimedean solids was synthesized in 2004.^[45] Fujita and co-workers found that a highly spherical $M_{12}L_{24}$ cuboctahedron could be self-assembled from 36 components (24 bent ditopic bis(pyridine)ligands and 12 Pd(II) ions) when the bend angle between the ligand donor atoms was close to the ideal value of 120°. The formed assemblies were well characterized in solution and solid-state by NMR, mass, and single-crystal X-

ray measurements. Impressively, the simplicity of the NMR for this structure (one set of signals with the same number of resonances as the starting ligand) well highlighted the high symmetry of the assembly.

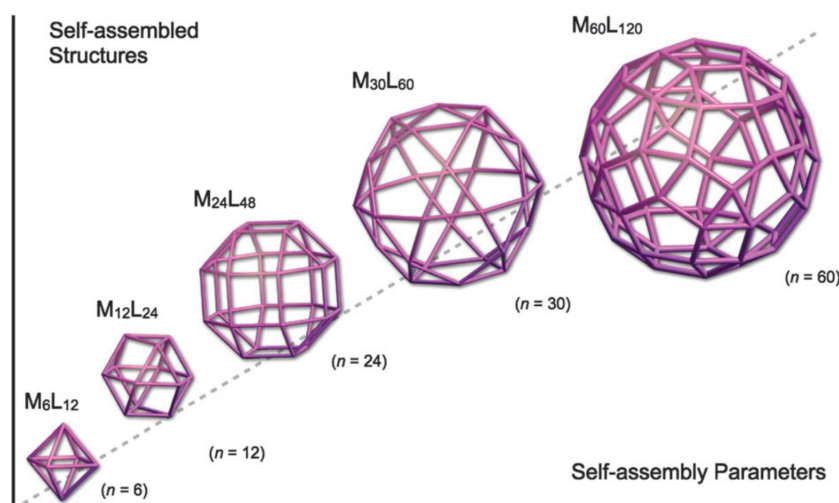


Figure 1.23 Schematic representation of M_nL_{2n} spherical polyhedra with the symmetry of Platonic or Archimedean solids, where metals (M) and bridging bis(pyridine) ligands (L) are mapped onto the vertices and edges, respectively.^[23b]

Based on the same design principles (angular variation of ligands), a decrease of the bend angle from 120° to 90° in the ligand leads to the preferred self-assembly of an M_6L_{12} complex with an octahedral arrangement of the six metal centers.^[46] Similarly, based on angles required by Archimedean and Platonic solids, increasing the bend angle can also result in the formation of higher nuclearity $M_{24}L_{48}$ and $M_{30}L_{60}$ cages.^[23a, 47] In these giant spheres with the composition M_nL_{2n} ($n \geq 6$), metal cations are regarded as vertices and the ligand as edges, Figure 1.22-1.23. The limitation of four coordination sites with square planar geometry of the metal center and polyhedra are consequently limited to equilateral and tetravalent polyhedral, and these geometrical constraints lead to the possible values of n being theoretically limited to 6, 12, 24, 30, and 60 in Archimedean and Platonic

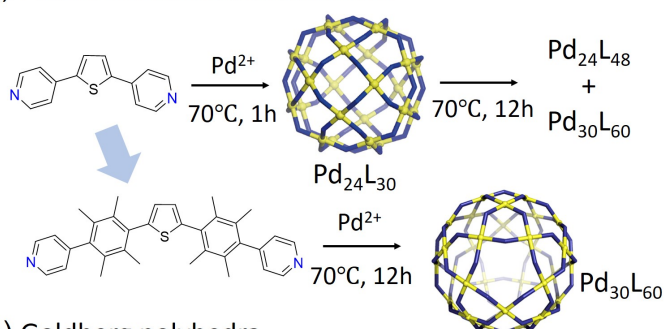
polyhedral spheres. So far, $M_{60}L_{120}$ has been predicted using graph theory, but it has still not been synthesized.

Most recently, the Platonic or Archimedean solid-based M_nL_{2n} polyhedra assemblies were revised by extending the description to unique Goldberg polyhedra.^[10a] In the revised design principle, the M_nL_{2n} polyhedra spheres that are possible include $n = 6, 12, 24, 30, 48, 54$ and 60 , two new tetravalent Goldberg polyhedra with the compositions of $M_{30}L_{60}$ and $M_{48}L_{96}$ were reported experimentally. Initially, this $M_{30}L_{60}$ framework was observed under conditions typical for targeting self-assembly of standard M_nL_{2n} complexes using a selenophene-cored bipyridyl-type ligand and $Pd(II)$, Figure 1.24. However, the self-assembled structure that formed was found to have a shape different from the previous $M_{30}L_{60}$ topology, consisting of a combination of 8 triangles and 24 squares. In addition to the simple 1H NMR spectrum, this new $M_{30}L_{60}$ structure was unambiguously characterized by X-ray crystallographic analysis and showed the three-dimensional tetravalent Goldberg polyhedra. As compared to the previous Platonic or Archimedean $M_{30}L_{60}$ structure, this new polyhedron does not have a mirror plane and features molecular chirality defined by its topology in the crystal structure.

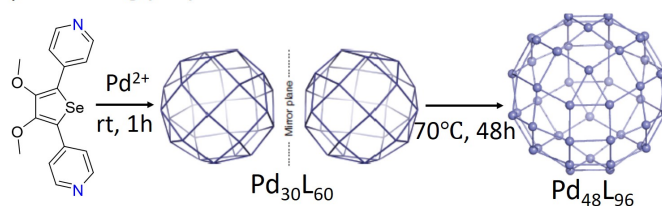
As shown in Figure 1.25, graph theory with classical and extended Goldberg polyhedral can be used to understand this novel structure. Based on the mathematical design, the possibility to self-assemble even larger M_nL_{2n} complexes, $M_{48}L_{96}$, $M_{54}L_{108}$ and $M_{60}L_{120}$, were predicted by this graph theory. A modeling study of the selenophene-cored bipyridyl-type ligand with a bend angle of 152° showed that it should favor a less distorted next-generation $M_{48}L_{96}$ complex rather than the observed $M_{30}L_{60}$ composition. Thus, this novel $M_{30}L_{60}$ structure should be a kinetically trapped metastable structure. This hypothesis was later supported by X-ray crystallographic evidence that $M_{30}L_{60}$ could be converted to $M_{48}L_{96}$ under suitable self-assembly conditions, such as changing the concentration, extending reaction time, using higher temperature, and so on. This opened up the possibility of achieving structures with an even larger number of components and verified the graph theory of Goldberg

polyhedral. While controlling the angular variation of ligands is useful to predict the products in the series of M_nL_{2n} ($n \geq 6$) spherical polyhedral, the few examples of the largest structure and the complexities in synthesizing and characterizing them mean that a complete understanding of how to form them is still lacking.

a) Platonic or Archimedean solids



b) Goldberg polyhedra



c) Crystal structure of $M_{30}L_{60}$

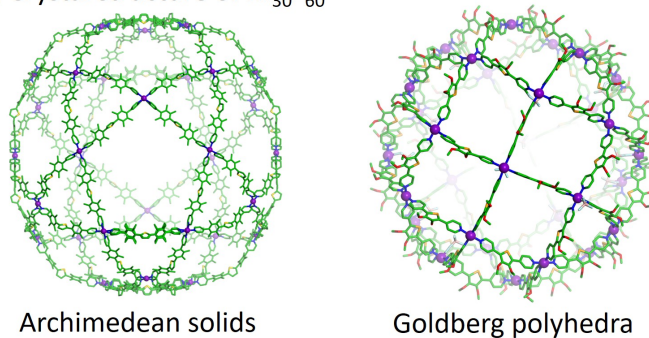


Figure 1.24 Self-assembly of a) $M_{24}L_{48}$ and $M_{30}L_{60}$ spheres based on platonic or archimedean solids, b) $M_{30}L_{60}$ and $M_{48}L_{96}$ spheres based on extending the description of Goldberg polyhedral, c) two different topologies of the three-dimensional coordination geometry of $M_{30}L_{60}$ complex.^[10a]

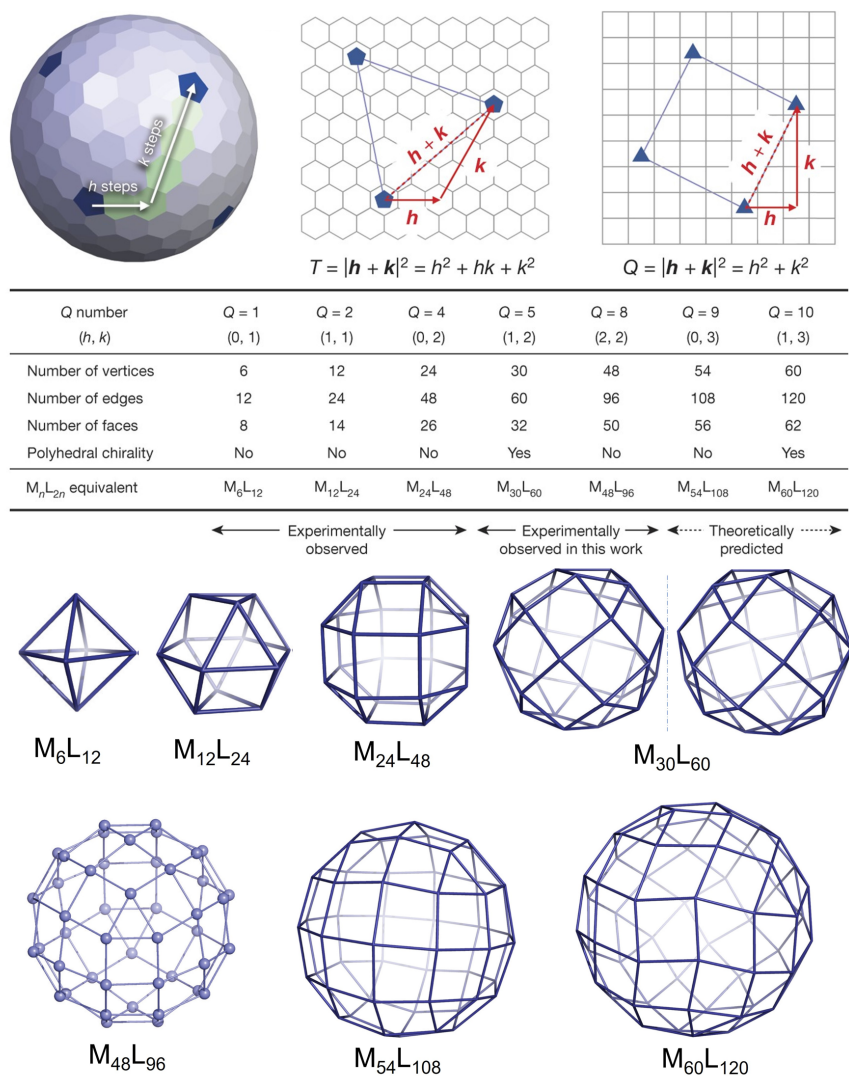


Figure 1.25 Schematic representation of the revised Goldberg polyhedral M_nL_{2n} -type spheres from Pd_6L_{12} up to $Pd_{60}L_{120}$.^[10a]

While graph theory has facilitated the prediction of the M_nL_{2n} type polyhedral spheres based on the bend angle of the ligands, this approach is still limited to theory, and the kinetic and thermodynamic stability of structures can lead to different results from what is predicted. A deep understanding of the mechanism underlying the self-assembly process is important for design

and function in such kinds of large polyhedra assemblies. Recently, experimental and computational studies have been used for better understanding the self-assembly process, Figure 1.26. Molecular dynamics simulations and NMR-based quantitative approaches can be used to consider the thermodynamic and kinetic stability of intermediates and structures formed through metal-ligand coordination interactions.^[48] One of the first examples studied using these techniques was an M_6L_8 octahedral complex with 6 Pd(II) ions and 8 pyridine-capped tridentate ligands. The simulations indicate the self-assembly process starts from random initial placement of the metals and ligands, followed by a more distinct process of assembly, evolution and fixation that is well-correlated with the experimental results. The difference of the lifetime (or the ligand exchange rate) between the smaller-sized incomplete clusters and the completed M_6L_8 complex was found to be crucially important in their self-assembly. Later, the self-assembly processes of three octahedron-shaped M_6L_{12} cages were investigated by an NMR-based quantitative approach.^[49] However, different from the M_6L_8 complex, the self-assembly of the M_6L_{12} cages, even with relatively rigid ditopic ligands, co-produced large-sized kinetic traps ($> M_6L_{12}$), which may because the energy landscape start to be more complicated after increase the number of components in the final assembly. It was found that when kinetically trapped species tend to be produced during the self-assembly, the use of a leaving ligand (3-chloropyridine) with slightly weaker coordination ability than that of the ditopic ligands is effective to direct the formation of the thermodynamically favored final self-assemblies. Based on this, molecular dynamics simulations were further used to simulate a higher nuclear $M_{12}L_{24}$ complex.^[50] In contrast to the M_6L_8 system, the larger $M_{12}L_{24}$ self-assembly process involves noticeable kinetic trapping at lower nuclearity complexes, e.g., M_6L_{12} , M_8L_{16} , and M_9L_{18} , Figure 1.26. They also found that the kinetic trapping behaviors sensitively depend on the bend angle of ligands and the metal-ligand binding strength. Kinetic effects have generally been neglected as an important factor in the self-assembled structure determination of larger complexes as $M_{12}L_{24}$. For the

same purpose experimentally, Fujita and coworkers reported geometrically and coordination restricted intermediate structures in self-assembly pathways.^[51] They followed up the self-assembly of a cuboctahedral $M_{12}L_{24}$ complex by time-dependent NMR and MS, and they characterized a short-lived M_8L_{16} and relatively long-lived M_9L_{18} as major intermediates. The geometrically restricted topology of the M_9L_{18} metastable intermediate structure was further confirmed by single-crystal x-ray crystallography using a smaller bend angle (112°) ditopic ligand to help kinetically trap the intermediate. Most recently, Reek and coworkers reported the contributions of steric bulk between the pyridyl residues on self-assembly of the $Pt_{12}L_{24}$ spheres by influencing kinetic trapping.^[52] A novel minority $M_{15}L_{30}$ topology was characterized experimentally with the prediction of the classical mechanics (CM) approach.

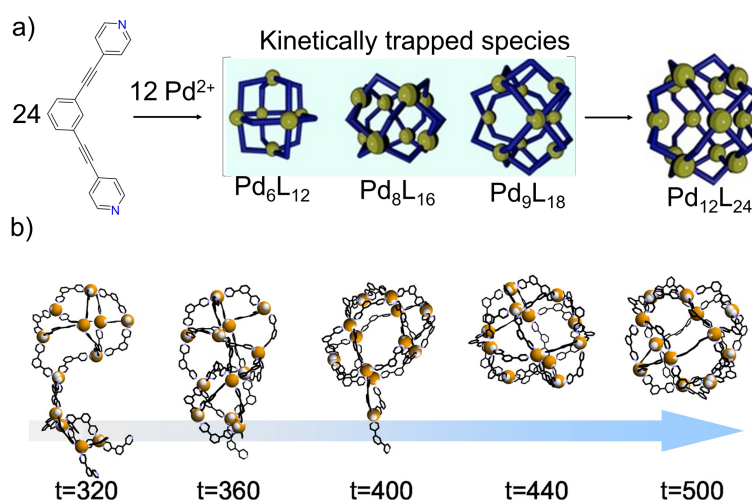


Figure 1.26 a) Several kinetic intermediates during the formation of the $M_{12}L_{24}$ sphere, b) Structural change during the evolution stage of 12 $Pd(II)$ and 24 ligand self-assembly of $M_{12}L_{24}$ sphere.^[48-52]

Coordination-driven self-assembly of M_nL_{2n} type of spherical cages is widely based on the geometric constraints of the complementary donors and acceptors present in the system. In addition to pyridyl moieties, the rotational flexibility of other coordination moieties often leads to difficulties in predicting

the expected architectures, especially in larger systems. However, although less explored, imidazole and benzimidazole-based ligands were reported for the self-assembly of M_nL_{2n} type of polyhedral spheres, Figure 1.27. For example, Mukherjee and coworkers have reported the synthesis of a set of M_6L_{12} spherical molecules by two-component self-assembly with imidazole appended bidentate ligands and Pd(II) centers.^[53] The solvothermal method has also been used for the construction of spherical molecules using carboxylate-based ligands.^[54]

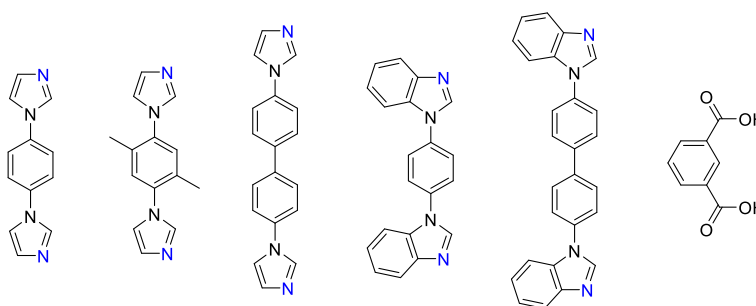


Figure 1.27 Chemical structures of ligands with imidazole, benzimidazole and other coordination moieties for self-assembly of spherical molecules.^[53-54]

2.3 M_nL_{2n} double-walled macrocycle

In addition to M_2L_4 capsule and M_nL_{2n} polyhedral spheres, M_nL_{2n} double-walled macrocycles are another important class of M_nL_{2n} assembly. Their geometry can be described as cyclic structures, where circularly arranged metal ions are doubly connected by bent ditopic ligands, Figure 1.28. In most cases, the ligands feature a bend angle smaller than 90° , and the outcomes are determined by the angle of bent ditopic ligand, counter anions, and solvents, under thermodynamic control. M_3L_6 triangles and M_4L_8 squares have been in many instances discovered as their structural motifs.

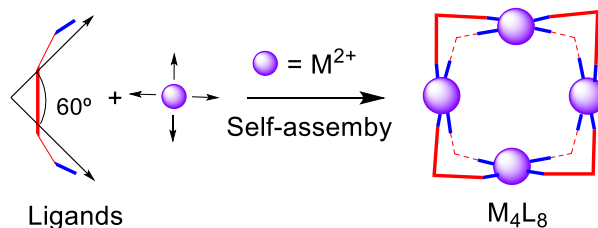


Figure 1.28 Schematic representation of coordination-driven self-assembly of bent ditopic ligands with bonding vector angle smaller than 90° with square-planar metal ions into M_nL_{2n} double-walled macrocycles, such as $\theta \sim 60^\circ$ favor the outcome of M_4L_8 double-walled square.

As shown in Figure 1.29, Chand, Fujita and coworkers initially reported this type of M_nL_{2n} double-walled macrocycles.^[28b] The ligand self-assembly was initially used to give a simple M_2L_2 framework by complexation with *cis*-protected Pd(II) ions. However, when they extended the complexation study from *cis*-protected Pd(II) ion to naked Pd(II) ion, a new single structure was formed and assigned to the M_4L_8 double-walled square structure based on NMR and CSI-MS analysis. Another similar ditopic ligand and *cis*-protected or naked Pd(II) ion were used for the self-assembly of the M_2L_2 framework and M_3L_6 double-walled triangle. In addition to commonly used NMR and MS characterization methods, their structures were unambiguously confirmed by single-crystal X-ray diffraction analysis.^[55] The overall structure of the M_3L_6 double-walled triangle contains three Pd(II) units located at the corner of an imaginary equilateral triangle, Figure 1.29. Any two metal centers are bridged by two strands of ligand, creating a macrocyclic fragment. As shown in the crystal structure, three macrocyclic fragments are created and arranged in circular/ring-like architecture. The coordination geometry around each Pd(II) center is approximately square planar, and the distance between two nonbonded palladium(II) units is 9.5 Å. Moreover, a cyclic tetrapeptide ligand has been reported to self-assemble into similar Pd_2L_2 and Pd_3L_6 structures.^[56]

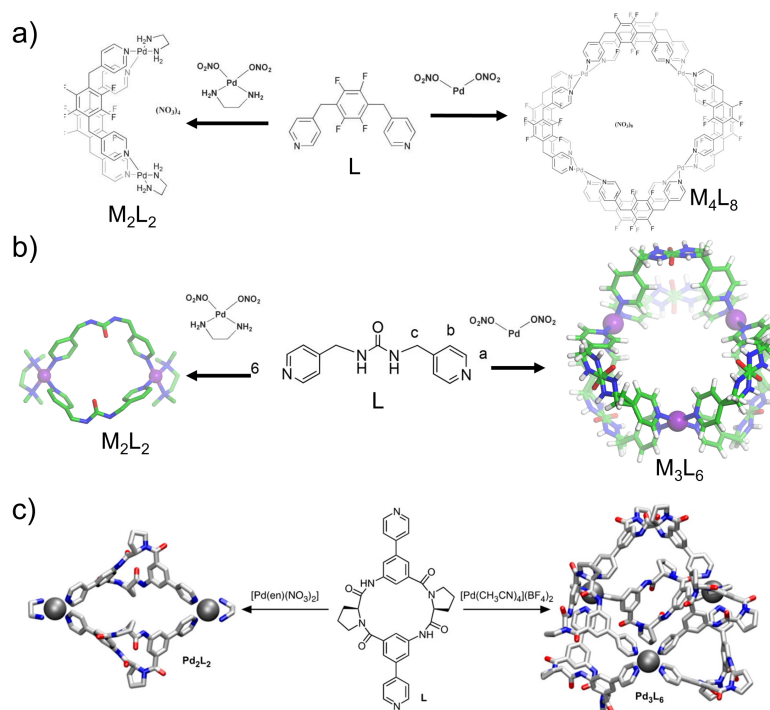


Figure 1.29 a) Structures of self-assembly of M_2L_2 framework and M_4L_8 double-walled square upon complexation with cis-protected $\text{Pd}(\text{II})$ ion and naked $\text{Pd}(\text{II})$ ion, respectively.^[28b] b) synthesis of the M_2L_2 -type binuclear complexes and the M_3L_6 -type trinuclear complex, their crystal structure is on the right.^[55] c) the cyclic tetrapeptide ligand and calculated structures of Pd_2L_2 (left) and Pd_3L_6 complex (right).^[56]

Different from large hollow M_nL_{2n} polyhedral spheres, these M_nL_{2n} double-walled macrocycles with a smaller cavity can better fit with counter anions and solvents, leading to significant template effects, Figure 1.30. A novel solvato-controlled self-assembly of a Pd_3L_6 double-walled triangle and a Pd_4L_8 double-walled square found that the distribution of the two macrocycles can be interconverted by adding or removing solvent or changing counter anion.^[57] When a mixture of the ligands with a 60° bent angle and $\text{Pd}(\text{NO}_3)_2$ in a ratio of 2:1 are reacted in DMSO, it leads to the quantitative formation of a single and highly symmetric Pd_4L_8 structure as confirmed by NMR and mass studies. The

geometric topology of the M_4L_8 double-walled square was found later, in its crystal structure, to possess a four-fold symmetry axis that passes through the center of the square vertically.

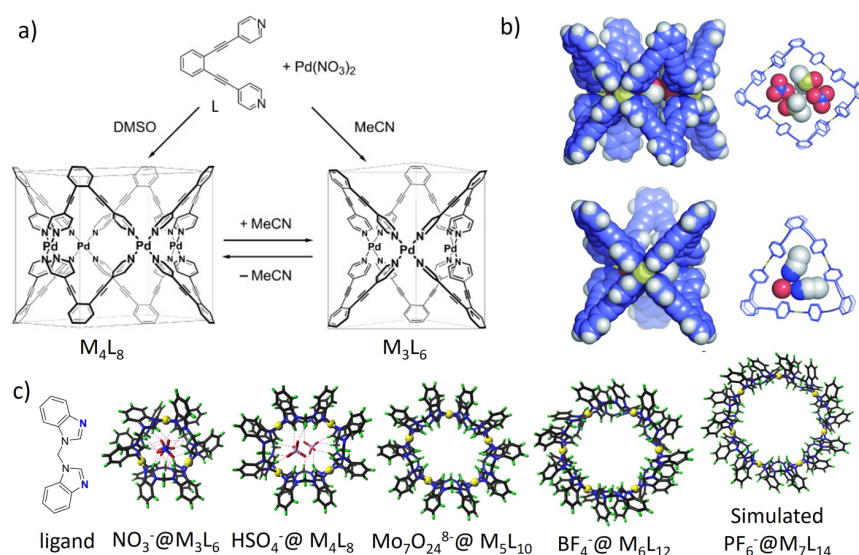


Figure 1.30 a) The solvato-controlled assembly of M_4L_8 and M_3L_6 structures and their interconversion, and b) their crystal structures of M_4L_8 double-walled square and M_3L_6 double-walled triangle.^[57] c) the structure of benzimidazole-based ligand, and its crystal structures of anion-binding metalorganic macrocycles Pd_nL_{2n} ($n = 3, 4, 5, 6, 7$).^[58]

Surprisingly, by simply changing the solvent from DMSO to CD_3CN , the same components assembled into another highly symmetrical complex, which was revealed by 1H NMR spectrum and CSI-MS measurements to be an M_3L_6 structure. Three Pd(II) ions are arranged in a regular triangle, in which the distance between the metal centers is 8.7 Å in its single-crystal structure. Interestingly, owing to the reversibility of Pd(II)-N bonds, the M_4L_8 and M_3L_6 assemblies are in equilibrium and a facile interconversion between them was observed by addition or removal of CD_3CN and DMSO. The smaller and flexible ligand has obtained other M_nL_{2n} double-walled macrocycles featuring template-induced self-assembly or structural transformation.^[58] For instance,

rotationally flexible benzimidazole-based ligands and square-planar Pd(II) ions show anion-adaptive self-assembly or induced-fit transformations leading to five M_nL_{2n} double-walled macrocycles ($n=3, 4, 5, 6, 7$), Figure 1.30.

Ligands featuring appropriate flexibility have been explored in the self-assembly of M_nL_{2n} double-walled macrocycles, leading towards novel structures and functions, Figure 1.31. Photoactive paracyclophane (pCp) scaffolds based on 4-pyridyl ligands and Pd(II) ions self-assemble to a fluorescent Pd_3L_6 double-walled triangle.^[59] An M_3L_6 double-walled triangle has also been synthesized using a ferrocene-containing rotationally flexible ligand to increase ligand flexibility and introduce redox-active functions.^[60] The structural analysis confirmed that double-walled triangle cage systems (with BF_4 and SbF_6 as counterions) were generated and showed host-guest interactions with the anionic guest, *p*-toluenesulfonate. However, the addition of the guest was not found to influence the redox potentials of the ferrocene. Chiral Pd_3L_6 double-walled triangles have also been achieved using an inherently chiral and flexible bipyridyl ligand derived from natural ursodeoxycholic acid (UDCA) and Pd(II) and shown to undergo reversible structure transformations in the presence of chloride ions.^[61]

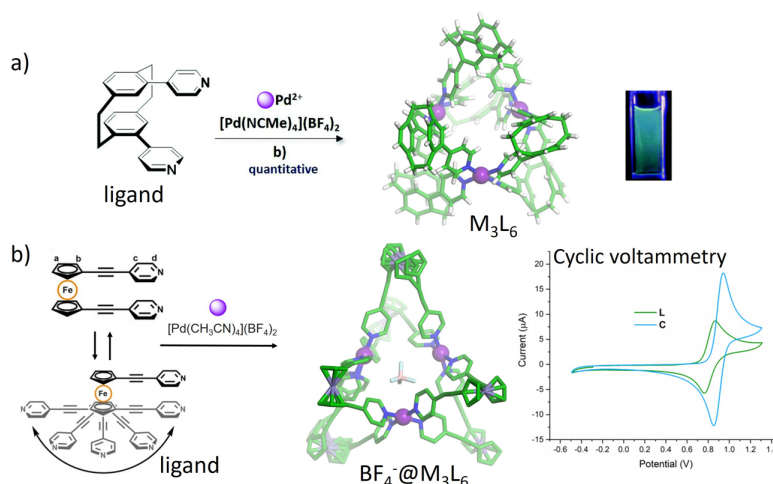


Figure 1.31 a) Photoactive paracyclophane scaffold based ligand and Pd(II) ions self-assembly of Pd_3L_6 double-walled triangle characteristic of an

intramolecular charge transfer state emission,^[59] b) structure of ferrocene-containing flexible ligand that can adopt a wide variety of bend angles and X-ray crystal structure of its triangular prismatic architecture displayed single reversible oxidation.^[60]

More functional M_nL_{2n} double-walled macrocycles were achieved by combining multiple functions into the building blocks, Figure 1.32. Zysman-Colman and coworkers designed a series of metalloligands and showed self-assembly of rare photoactive Pd(II) double-walled macrocycles. These were the first examples of emissive and homochiral $[Ir_8Pd_4]^{16+}$ double-walled macrocycles, which provide a suitably sized cavity to host large guest molecules and energy transfer was observed between the blue-emitting $NBu_4[Ir(dFppy)_2(CN)_2]$ guest and the red-emitting $\Delta_8-[Ir_8Pd_4]^{16+}$ macrocycle.^[62] A phosphorescent double-walled macrocycle of the form $[Ru_8Pd_4]^{24+}$ was later reported using Ru-based metalloligands.^[63] Most recently, a Ir(III) metalloligand was used to design functional double-walled macrocycles with one-photon and two-photon excited deep-red emission as well as large singlet oxygen quantum yields under visible light irradiation, therefore exhibiting great potentials in organelle-targeted cell imaging and photodynamic therapy.^[64] More complex self-assembly toward heterometallic double-walled macrocycles was also reported using platinum(II) metallo-ligands.^[65] As shown in Figure 1.33, the organic ligand has both monodentate and bidentate binding sites. With Pt(II) and/or Pd(II) ions, two examples of new nona-nuclear metallo-assemblies were accessed. The cages possess three clefts comprised of planar cationic panels. This structural feature enables the binding of planar aromatic guests such as anthracene. More interestingly, the heterometallic assembly was able to catalyze the light-induced [4+2] cycloaddition of anthracene with singlet oxygen.

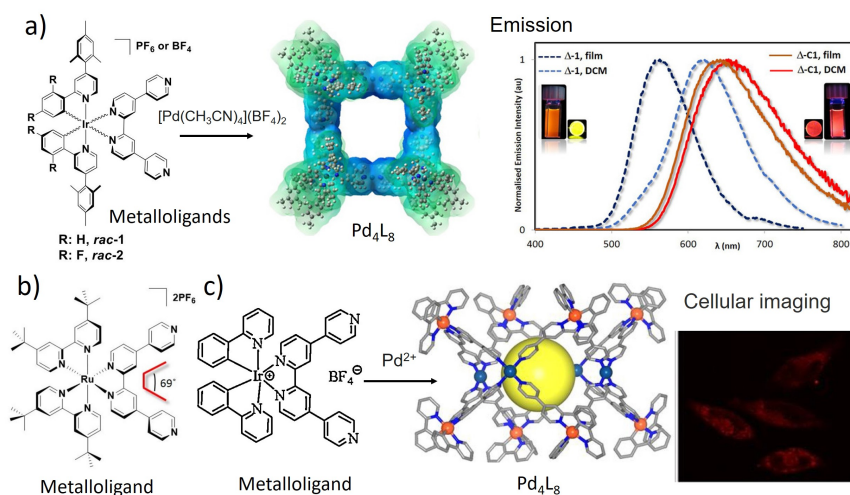


Figure 1.32 a) Two families of Ir(III) metalloligands self-assemble with Pd^{2+} ions yielding racemic, homochiral and red-emitting Pd_4L_8 double-walled square, b) a similar Ru(II) metalloligand, c) self-assembled Ir(III) metalloligand based Pd_4L_8 double-walled square used for cellular imaging.^[62-64]

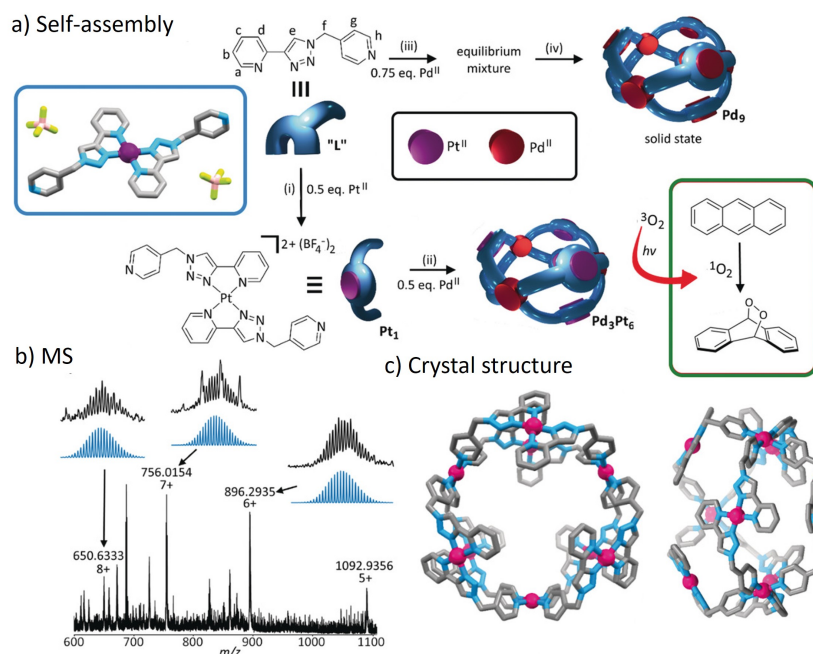


Figure 1.33 a) Self-assembly with platinum(II) and/or palladium(II) ions

yielding double-walled macrocycles of Pd_9L_{12} complex and heterometallic $\text{Pd}_3\text{Pt}_6\text{L}_{12}$ complex, b) Partial electrospray ionization mass spectrometry (ESI-MS) of heterometallic $\text{Pd}_3\text{Pt}_6\text{L}_{12}$ complex with isotopic distributions, c) X-ray crystal structure of Pd_9L_{12} from above and the side view.^[65]

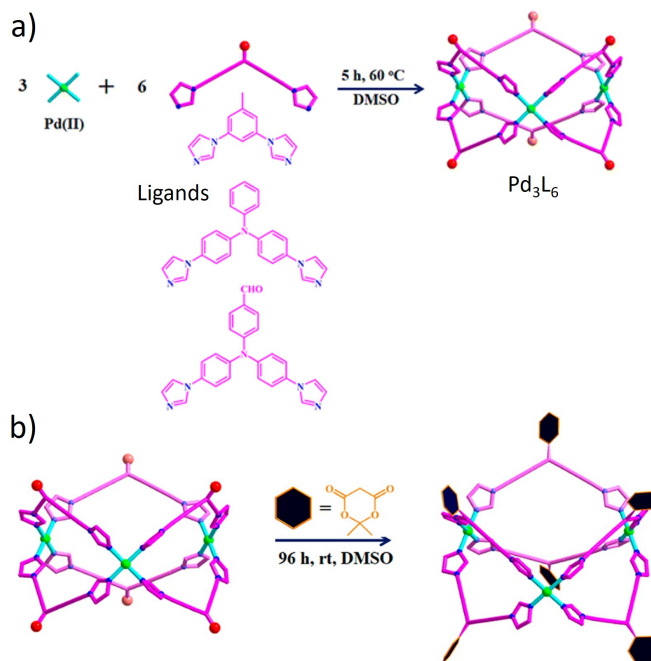


Figure 1.34 a) Structure of three diimidazole-based ligands and their self-assembly to a Pd_3L_6 double-walled triangle, b) Covalent post-modification of the aldehyde functionalized complex by Knoevenagel condensation with Meldrum's acid in DMSO.^[66]

The alternative approach to pre-functionalized building blocks is the covalent post-translational functionalization of metal-organic assemblies.^[66] As shown in Figure 1.34, Mukherjee and coworkers reported the design and synthesis of three new Pd_3L_6 double-walled triangles via two-component self-assembly of Pd(II) ions and ditopic imidazole-based ligands.^[67] X-ray crystal structure analysis confirmed the double-walled triangles and the crystal packing showed the presence of intermolecular channels/pockets filled with

NO_3^- counteranions. This enhanced hydrogen bonding with water molecules, giving adsorbed water affinity at room temperature up to $136.58 \text{ cm}^3 \text{ g}^{-1}$. They also showed that, for one of their ligands, an included aldehyde functionality in the bridging ligands of the double-walled triangle complex could be more reactive than in just the free ligand. This resulted in high yield Knoevenagel condensation with Meldrum's acid allowing postmodification and formation of a new double-walled triangle without disrupting the overall supramolecular structure.

As shown in Figure 1.35, towards understanding the self-assembly progress of double-walled macrocycles and their kinetic control, a novel experimental approach of NMR-based quantitative analysis of the self-assembly process (QASAP) was used in these systems.^[68] The M_3L_6 double-walled triangle as the smallest double-walled macrocycles was used as an example for the initial investigation with this technique.^[69] The same bent ditopic ligand and Pd(II) ions reported for the solvato-controlled assembly of M_4L_8 and M_3L_6 structures as discussed above were used.^[57] The ligands were self-assembled with $\text{PdPy}^*_4(\text{BF}_4)_2$ in which $\text{Py}^* = 3\text{-chloropyridine}$ for the QASAP investigation of self-assembly processes. The 3-chloropyridine as a leaving ligand increased the information gained on intermediates, substrates and products by NMR. By this approach, self-assembly pathways of the Pd_3L_6 double-walled triangle were found to occur through the fast formation of single-walled dinuclear chains with the formula $\text{Pd}_2\text{L}_4\text{Py}^*_3$ and then transformed into the single-walled trinuclear chain structures $\text{Pd}_3\text{L}_5\text{Py}^*_5$ and $\text{Pd}_3\text{L}_6\text{Py}^*_4$ as intermediate species. The macrocyclization and the formation of double walls in these structures to give the target Pd_3L_6 assembly then occurs through intramolecular ligand exchange in $\text{Pd}_3\text{L}_6\text{Py}^*$. In addition to this experimental approach, a theoretical numerical analysis of the self-assembly process (NASAP) of the Pd_3L_6 double-walled triangle revealed dominant self-assembly pathways and a balance between inter- and intramolecular reactions, which enabled prediction of the reaction outcomes depending on the initial stoichiometric ratio under kinetic control.^[70] Indeed, this mechanistic

investigation is important because these triangles, smaller than the final assembled structures, are often transiently produced during the self-assembly of Pd_4L_8 double-walled squares and tetrahedra.^[71] The formation of M_3L_6 double-walled triangles under kinetic control might be a general trend in the self-assembly of double-walled macrocycles and some other metal-organic architectures.

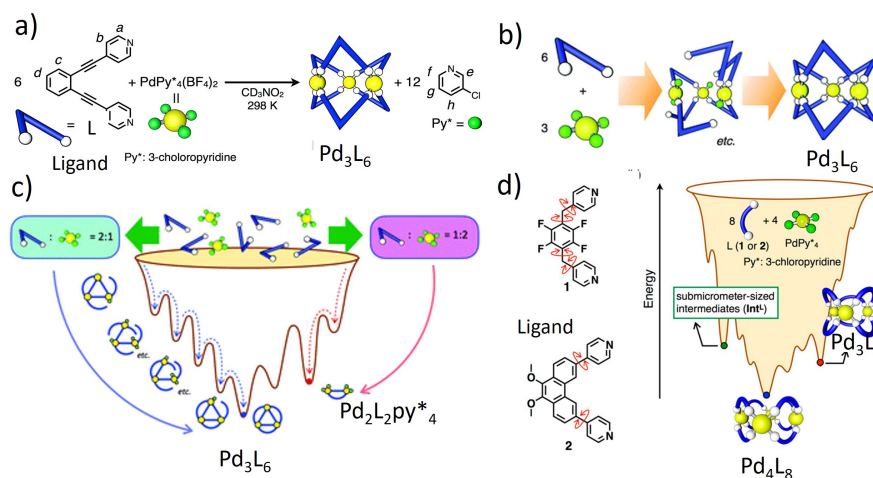


Figure 1.35 a) Self-assembly of the Pd_3L_6 double-walled triangle from $\text{PdPy}^*_4(\text{BF}_4)_2$ and bent ditopic ligand, b) self-assembly pathways of the Pd_3L_6 revealed by QASAP showing main intermediate trinuclear single-walled chains, c) prediction of the reaction outcomes depending on the initial stoichiometric ratio under kinetic control, d) chemical structures of flexible ditopic ligands to produce Pd_4L_8 double-walled square and the intermediates of M_3L_6 double-walled triangles.^[69-71]

3. Higher-order M_nL_{2n} assemblies

As an important biological process in nature, stimuli-induced structural changes are capable of achieving specific biological functions. With the aim to obtain an enhanced and integrated understanding of similar processes in artificial metal-organic architectures, the formation of M_nL_{2n} higher-order

assemblies will be discussed as three aspects: cage to cage transformations, cage-based extended structures, and hierarchical self-assembly into well-defined aggregates.

3.1 Cage to cage transformation

As discussed in the above sections, M_nL_{2n} assemblies include at least three different types of supramolecular structures from the simple M_2L_4 capsule to the more complex M_nL_{2n} hollow spheres and the novel M_nL_{2n} double-walled macrocycles. The outcomes of the self-assembly, i.e., the structure formed, are highly dependent on the shape and size of the ditopic ligands. However, we have also seen that the dynamic nature of the coordination bonds makes it possible to disrupt the equilibrium in self-assembly, pushing it from one form to another, resulting in new structures with specific properties. The M_nL_{2n} family of self-assembled architectures provides an ideal platform to study such supramolecular structural transformations and their effects on their properties. Indeed, this has been, in many cases, targeted by the use of external stimuli.^[72] Numerous studies aimed at promoting metal-organic structural transformations have been reported that make use of stimuli, such as change in solvent,^[57, 73] guests,^[17b, 74] concentration,^[75] post-modification,^[66, 76] light,^[41, 77] pH,^[78] metal-ligand ratio,^[79] etc.

As shown in Figure 1.36, an excellent light-switchable photochromic dithienylethene backbone was introduced by Clever and coworkers into a ligand design to achieve light-driven reversible structure transformations between a small Pd_3L_6 double-walled triangle and a giant $Pd_{24}L_{48}$ rhombicuboctahedral sphere up to 6.4 nm.^[80] Using photo-irradiation with different wavelengths, the dithienylethene-base gives photoswitchable control over the ligand structure. It can be stable in two forms that differ in length and angle, which is what decides the nature of outcomes when reacted with Pd(II) ions. Upon UV-light irradiation, the flexible open-ring form quantitatively transforms into the structurally rigid closed-ring form and it is reversible under the influence of 617 nm irradiation (or white light) both for the free ligands and

the self-assembled metal-organic assemblies. The interconversion rates between the two assemblies are drastically different in the two directions because of dissimilarities in the photoswitch conformations. Similarly, another light-switchable ligand reported by the same group enables reversible switching between two different forms of M_2L_4 cages allowing controlled guest binding.^[41-42] Moreover, using metal-organic cages as crosslinks, stimuli-responsive polymer networks were reported switching between two topological states, a Pd_3L_6 double-walled triangle and a $Pd_{24}L_{48}$ sphere, could tune the network properties.^[81]

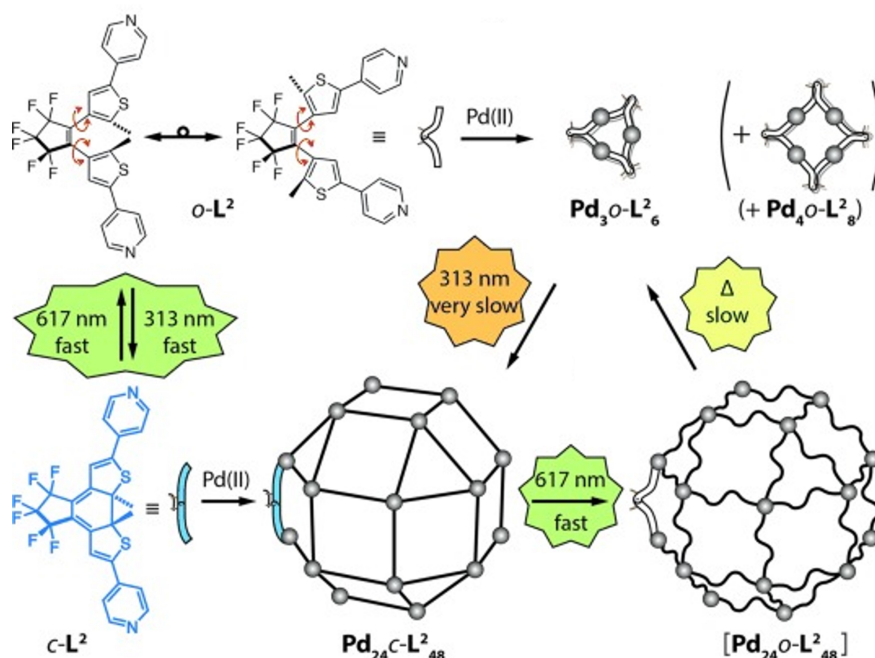


Figure 1.36 Dithienylethene-base photoswitchable ligand self-assembly and structural conversion of a) cages Pd_2L_4 cage and b-d) reversible structure transformations between Pd_3L_6 double-walled triangle and $Pd_{24}L_{48}$ sphere through photo-irradiation with different wavelength.^[80]

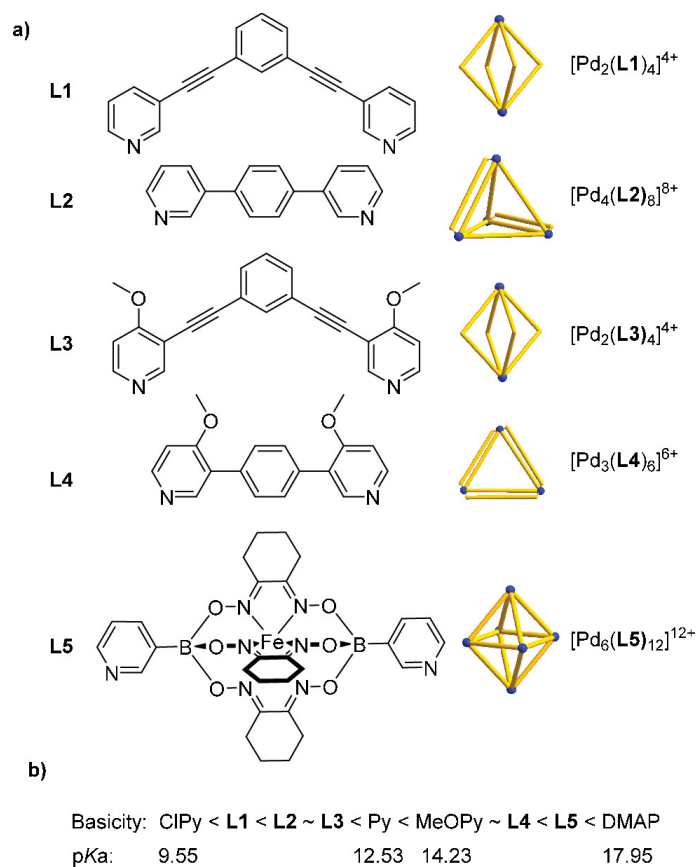


Figure 1.37 a) Structures of the N-donor ligands used in this study and the corresponding complexes with Pd(II) ions, b) relative basicity of the ligands.^[82]

Chemical stimuli can also be used. Most recently, the relation between the basicity of pyridine N-donor ligands and the stability of M_nL_{2n} assemblies has been investigated.^[82] As shown in Figure 1.37, the stability of five different assemblies from the M_2L_4 capsule up to the M_6L_{12} sphere was examined by the disassembly experiments with pyridine or trifluoroacetic acid. The Pd complexes containing N-donor ligands of low basicity was pronounced to disassembly by pyridine. However, these assemblies displayed high acid resistance. To this, the most acid-resistant complex $\text{Pd}_2(\text{L1})_4$ was disassembled to a large extent upon addition of pyridine (68%), whereas the most pyridine-resistant cage $\text{Pd}_6(\text{L5})_{12}$ was very sensitive to acid. Moreover,

the contrasting stability in the presence of acid or pyridine can be used for the pH-controlled switching between different supramolecular structures. Similarly, structural transformations from the M_2L_4 capsules to M_3L_6 double-walled triangles can be achieved by displacing the pyridyl ligands with more basic imidazolyl ligands.^[83] The highly basic N-donor ligand of 4-dimethylaminopyridine (DMAP) and *para*-toluenesulfonic acid has been reported to give reversible assembly and disassembly of M_2L_4 capsule and M_6L_{12} spheres.^[33, 84] The low ligand strength of pyrimidine allows pyrimidine-based ligands to be replaced entirely in a self-assembled structure with higher donating ability pyridine ligands leading to a cage-to-cage transformation of an $M_{12}L_{24}$ sphere.^[85]

3.2 Cage-based extended structures

As mentioned in section 1, metal-organic architectures can be used as building blocks in more complex hierarchical self-assembled systems or networks.^[22b] More complex cage-based extended structures or materials can be achieved based on these M_nL_{2n} type metal-organic assemblies, especially common with M_2L_4 capsules to form interpenetrated structures.^[86] For example, when using more extended size or semi-flexible ligands, interlocked M_4L_8 cages more often became the thermodynamically stable product while monomeric M_2L_4 cages are instead kinetic intermediates.^[31b, 87] This additional structural transformation opens up attractive multi-cavity metal-organic architectures with one to three cavities with decreased volume. It differs from the parent M_2L_4 cages in that the interlocked cage has three smaller cavities and the size of these cavities can be balanced or reorganized, Figure 1.38.

Indeed, the self-assembly of metal-organic cages with smaller cavities can be challenging. This spontaneous dimerization provides a strategy for smaller cavities, Figure 1.38. In 2008, Sekiya and Kuroda reported the first spontaneous dimerization of an M_2L_4 cage into an interlocked M_4L_8 cage, based on self-assembly with a conformationally flexible ditopic ligand and Pd(II) cations.^[88] A deeper understanding of these interpenetrated systems

with a series of investigations of interpenetrated architectures had provided some insight into their applications.^[89] For example, anions can be used to direct the formation and degradation of an interlocked M_4L_8 structure. When NO_3^- is used as the counterion, the interlocked structure forms with 3 NO_3^- anions caged between the 4 Pd(II) cation centers, Figure 1.38. By contrast, 2-naphthalenesulfonate introduced by anion exchange leads to the breaking of the interlocked structure and the formation of the single M_2L_4 cage structure. Interestingly, more examples of the interlocked cages were found to be strong acceptors for anions. The encapsulation of anions can be arranged in different preferences.^[90] All of the three cavities can have the same size or be different with mixed anions lead to a unique property of metal-organic cages systems. Moreover, the modification of the organic ligand backbones in these systems was also able to tune the size, shape, and chemical properties of their multiple cavities.^[91] This modification of the cavity has a pivotal role in anion selectivity and encapsulating preference and opens up promising approaches for the combined binding of anionic and neutral guest molecules, etc.

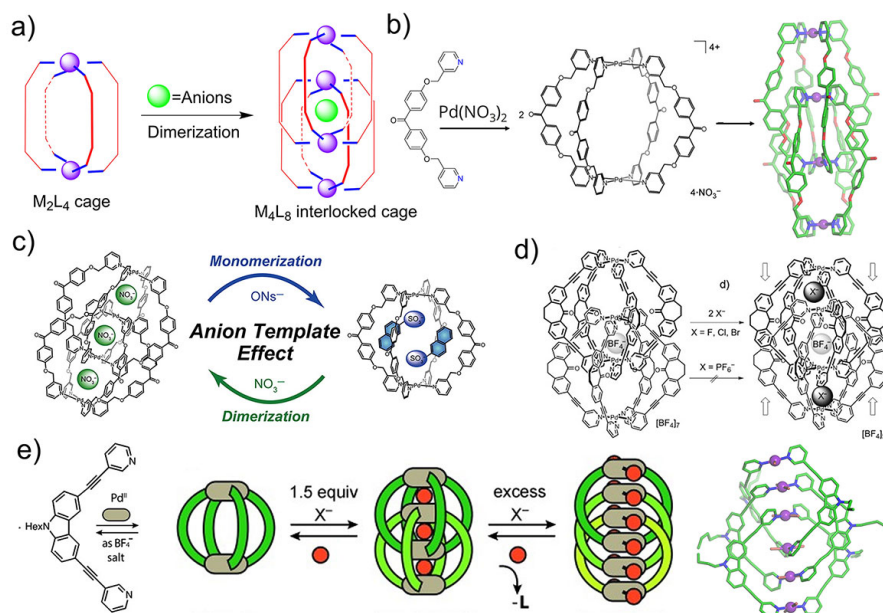


Figure 1.38 a) Schematic illustration of dimerization of M_2L_4 cages into an interlocked M_4L_8 cage, b) the first example of an interlocked M_4L_8 helicate, c)

anion-directed formation and degradation of an interlocked M_4L_8 cage, d) high affinity for the allosteric binding of halide ions between the interlocked cage, e) stepwise assembly of the monomeric M_2L_4 cage into the halide-templated interlocked double cage and triple catenane.^[88-91]

Construction of discrete metal-organic cages possessing multiple cavities can be a more complicated task but is also very promising for expanding the structures and functions of M_2L_4 capsules. Another approach for this uses a linear extension of the ligands with polytopic backbones for the design of M_2L_4 capsule-based multi-cavity cages.^[92] The ligands were designed with an overall “E-shape” containing three or more parallel monodentate coordination sites, Figure 1.39. This enables the creation of tunable cavities by keeping the donor units of the ligand intact and simply modifying the spacer moieties. The modification of the spacer units in the ligand backbones has been reported to give larger double-cavities. When using a similar tetrakis-monodentate ligand, the formation of three cavity cages can also be possible. Different from the single cavity in its parent M_2L_4 capsule and symmetrical double-cavities, the environments of the three cavities are more distinguishable, with the central cavity and terminal cavities having subtle differences due to the overall framework. However, there are few examples of this type of multi-cavity cage and with limited understanding and applications of multiple cavities. Still, there are some exciting novel properties described, such as accommodating multiple varieties of guests in a site-specific manner. Interestingly, although the structure is much more complicated, as shown in Figure 1.39-1.40, it can also be similar to M_2L_4 capsules, forming more complex interpenetrated cages.^[93]

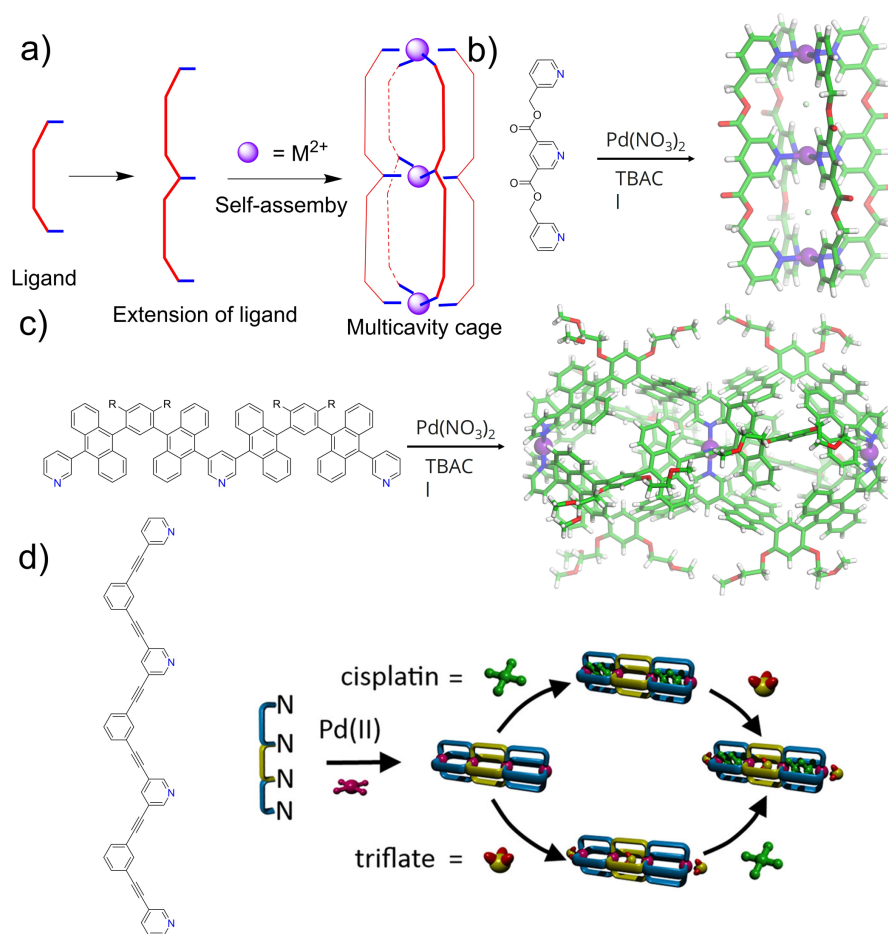


Figure 1.39 a) Schematic illustration of the approach by linear extension of the ligands with polytopic backbones for self-assembly of multi-cavity cages, b-c) representative examples of double cavity cages, d) synthesis of a novel triple cavity cage exhibiting selective binding of cisplatin in peripheral cavities (top) and triflate in the central cavity and exohedral faces (bottom).^[92]

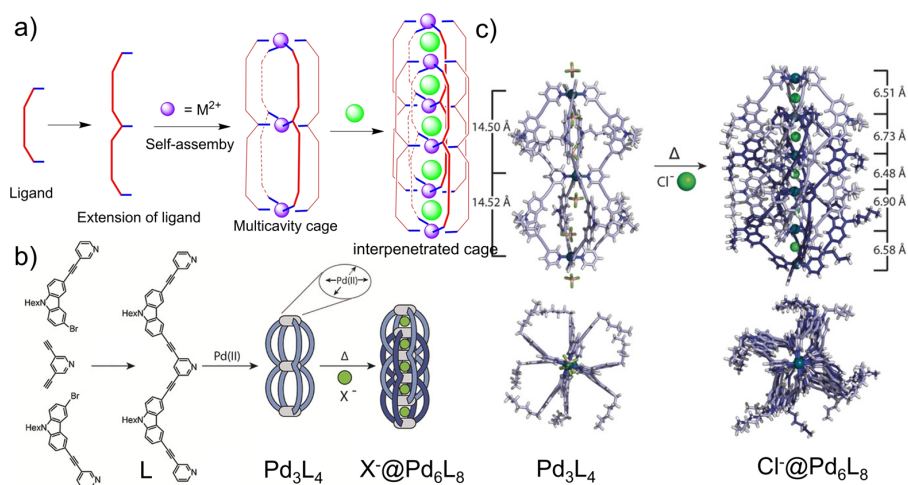


Figure 1.40 a) Schematic illustration of a double cavity cage with halide-templated interpenetration into the double cage, b-c) example of a tris-monodentate ligand with a polytopic backbone and Pd(II) ions self-assembling into a double cavity cage and its subsequent interpenetrated cage.^[93]

Towards the construction of multiple cavities, a promising strategy of conjoined cages with favorable integrative self-sorting of the participating components was reported recently.^[94] M_2L_4 capsule-based conjoined cages were achieved via peripheral decoration of a trinuclear Pd_3L_6 core with one or more Pd_2L_4 cage units, Figure 1.41. The formation of the tetranuclear and pentanuclear complexes is attributed to the favorable integrative self-sorting of the participating components. This is different from common superstructures in that the current set of cages are unique because of their structural features and associated binding properties. The concept of making conjoined cages effortlessly opens a plethora of possibilities through suitable ligand design that can help the construction of hitherto unknown architectures with unique structures.

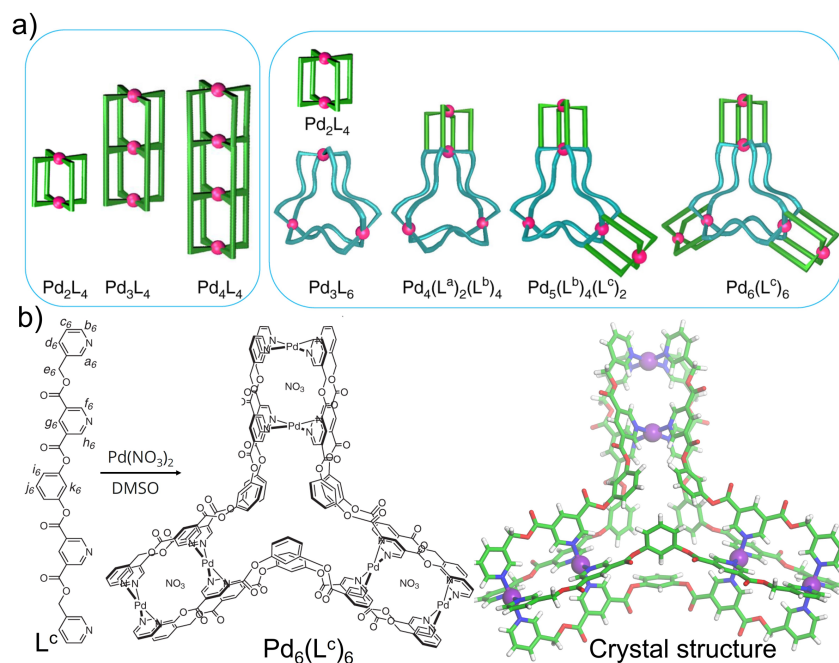


Figure 1.41 a) Cartoon representation of the design approaches for making self-assembled multi-cavity cages from linearly conjoined homoleptic cages linearly/laterally conjoined to target homo- and heteroleptic cages, b) self-assembly of cavity conjoined-cages of a trinuclear Pd_3L_6 core with three units of Pd_2L_4 cages.^[94]

In addition to more extended ligands or more complex structure connection, most recently, a complicated topology of new mechanically interlocked cage motif with a simple formula and low nuclearity M_2L_4 cage were reported by dimerization of two peptide-based lemniscates.^[95] The ligand was designed by Clever and coworkers using a chiral peptidic backbone with pyridyl coordination sites, Figure 1.42 The mononuclear complex was formed when ligand self-assembly with the square-planar coordinated $\text{Pd}(\text{II})$ cation was performed in DMSO. Interestingly, the use of CH_3CN as the solvent instead of DMSO yielded a new mechanically interlocked Pd_2L_4 cage. As a new structural variation, it is different from the well-known class of M_2L_4 cage with bridging ligands spanning neighboring metal centers directly, as the link

between the two halves of the cage is a result of mechanical bonds. The interlocked topology creates a cavity between the two palladium cations, able to encapsulate one anion such as BF_4^- or Cl^- . This nice example reveals that mechanical bonding has the potential to bestow metal-supramolecular assemblies with adaptive and stimuli-responsive behavior.

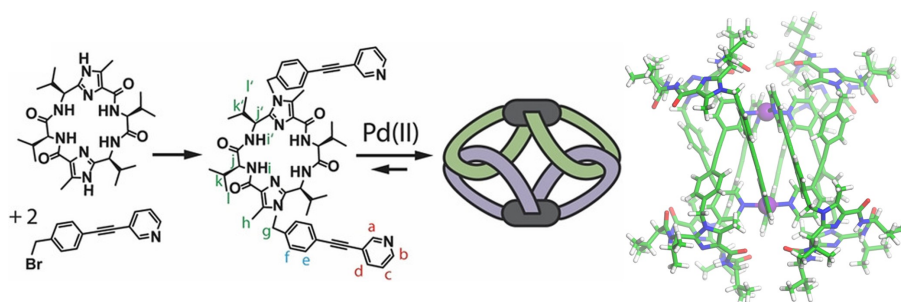


Figure 1.42 Synthesis of ligand and self-assembly with Pd(II) ions into an interlocked dimer of Figure-of-eights.^[95]

Similar to the well-known M_2L_4 capsule-based interpenetrated cages, self-assembly of 8 Pd(II) ions and 16 phenanthrene-derived bridging ligands with 60° bite angles was reported by Clever and coworkers to result in an undiscovered M_8L_{16} architecture composed of two interpenetrated M_4L_8 double-walled squares, which is the largest Pd_nL_{2n} catenane reported to date.^[96] Structural analysis shows that anions play a key role in stabilizing the large catenane, its channel-like cavities occupied by NO_3^- anions as catenation templates, Figure 1.43. Furthermore, higher-order supramolecular aggregation of this M_8L_{16} catenane into reversible vesicle-like aggregates was also achieved through alkyl functionalization of the ligand backbone into amphiphilic supramolecules. The following sections will look at this type of well-defined aggregates in more detail.

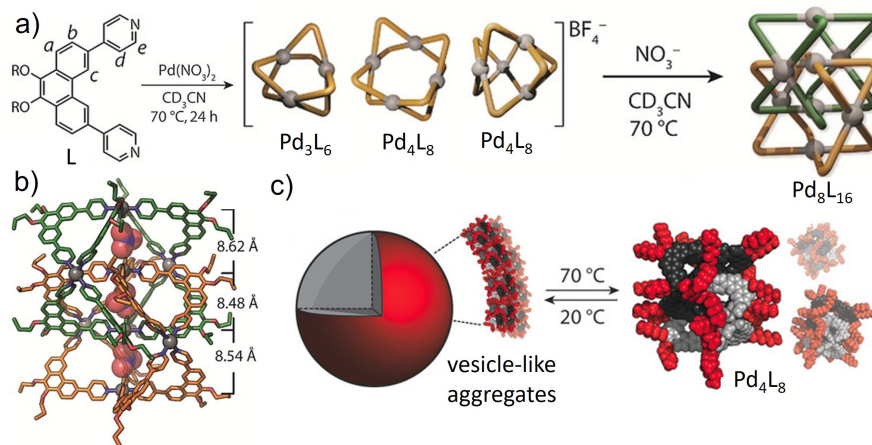


Figure 1.43 a) The ligand and Pd(II) ion self-assembly of a mixture of M_3L_6 and M_4L_8 assemblies, and their anion induced formation of interlocked M_8L_{16} molecule, b) X-ray structure of Pd_8L_{16} interlocked structure, c) temperature-dependent aggregation of M_8L_{16} molecule into vesicle-like aggregates in a reversible manner.^[96]

3.3 Well-defined aggregates

The unique and complex structures of metal-organic architectures make multiple types of intermolecular interactions that can more or less co-exist in solution, including electrostatic, hydrophobic, hydrogen bonding, van der Waals, π - π and host-guest interactions, etc. Although the cooperative or competitive interplay of these intermolecular interactions as a driving force leading to the aggregation of metal-organic assemblies is commonly overlooked, a number of examples in M_nL_{2n} type and the other metal-organic assemblies were reported describing such aggregates as micelles, fibers, nanosheets, nanocubes, nanorods, and blackberry structures.^[97] The self-assembly of octahedron Pd_6L_4 metal-organic cage into aggregates was first reported by Liu and coworkers in 2008.^[98] The well-studied octahedron Pd_6L_4 metal-organic cage was found to spontaneously self-assemble into giant hollow vesicle-like structures in polar water/acetone mixtures, Figure 1.44. Such highly soluble metal-organic cages have separated hydrophobic regions.

However, the linear relationship between the size of the assemblies and the inverse dielectric constant of the solvent indicates that the counterion-mediated attraction is the major driving force for the formation of the well-defined aggregates.

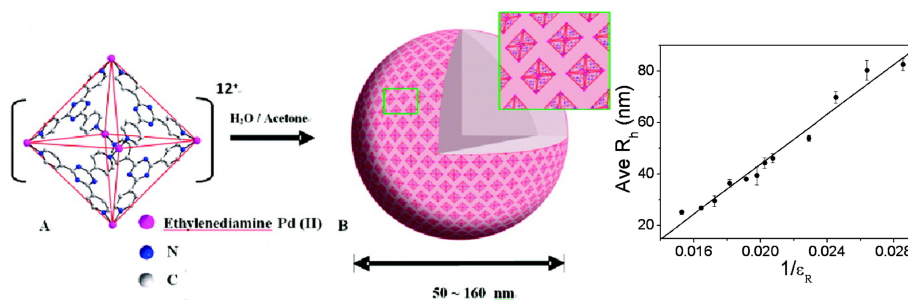


Figure 1.44 a) Schematic representation of the structure of the Pd_6L_4 metal-organic cage and its blackberry structure. b) R_h of vesicle-like structures assembled at different ratios of acetone/water versus inverse dielectric constant of the mixed solvent.^[98]

After that, the same group reported self-assembly of cuboctahedron $\text{M}_{12}\text{L}_{24}$ sphere into single-layered blackberry structures in DMSO by the addition of extra nitrates as counterions.^[99] In polar solvents, cationic $\text{M}_{12}\text{L}_{24}$ spheres are slowly assembled into hollow blackberry structures, which was further confirmed by SEM studies, Figure 1.45. Importantly, the size can be tuned by changing the counterion concentration or solvent polarity. They were increasing ionic strength of the solution results in different sized blackberry structures indicating the same counterion-mediated mechanism. This more complex structure introduces several types of intermolecular interactions that mimic biological processes showing similar kinetic and thermodynamic features to viral-capsid formation. Interestingly, a strategy using bulkier organic ligands successfully allowed controlled assembly/disassembly of the $\text{M}_{12}\text{L}_{24}$ sphere and aggregates.^[100] For this, PEG chains were introduced into the ligands to increase solubility, decreasing the non-specific interactions between $\text{M}_{12}\text{L}_{24}$ cages, and as a result, inhibiting them from coming close to

each other and self-assembling into blackberry structures.

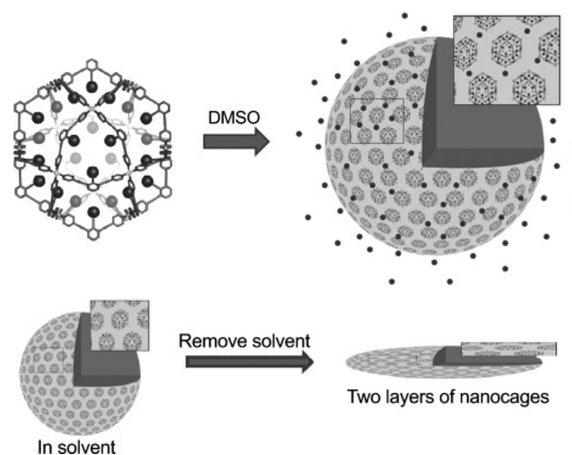


Figure 1.45 Schematic representation of a) $M_{12}L_{24}$ sphere into blackberry structures and distribution of nitrates (small dots), b) blackberry structures revealing that some of them are collapsed due to solvent evaporation.^[99]

Most recently, the partial aggregation of a chiral cationic $Pd_{12}L_{24}$ sphere was controlled by chiral counterions.^[101] The $Pd_{12}L_{24}$ metal-organic cages were functionalized with D- or L-alanine on their periphery leading to chiral cages, Figure 1.46. When small chiral molecules (e.g., Boc-alanine) were added, the D-cages and L-counterions interact more strongly than the D-cages and D-counterions, partially inhibiting the nitrate-cage binding and leading to a partial suppression of the self-assembly and smaller size of the blackberry aggregates. This study provided some additional evidence on the mechanism of the homochirality phenomenon, particularly for the evolution from macromolecular to supramolecular level via electrostatic interaction. Moreover, other intermolecular interactions, including hydrophobic effects, π - π stacking and host-guest interactions, have been described to stabilize aggregates of the M_2L_4 capsule and a lot of the other metal-organic assemblies, the similar spontaneously self-assembly into higher-order aggregates with various functions.^[97]

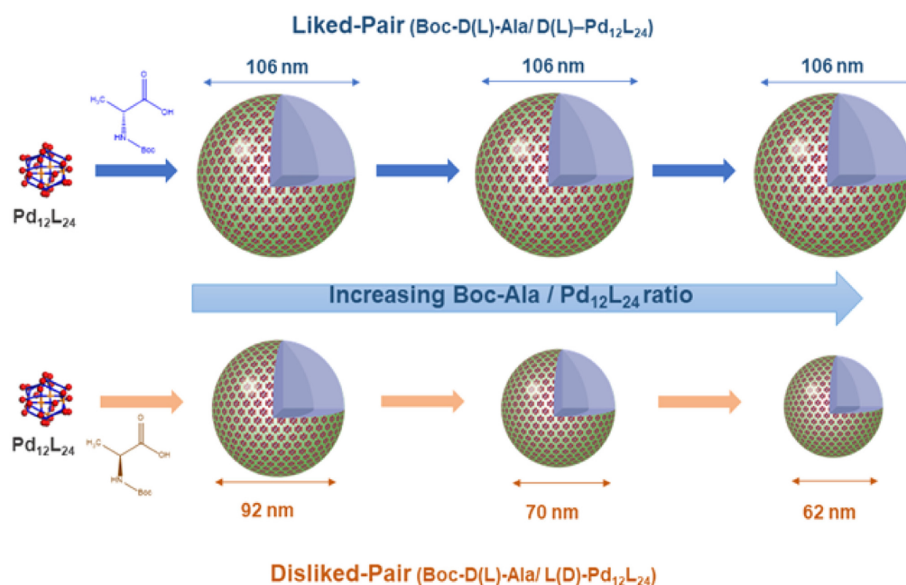


Figure 1.46 Schematic representation of the effect of Boc-Ala on the self-assembly behavior of Pd₁₂L₂₄ when liked-pairs are compared with disliked-pairs.^[101]

4. Self-sorting of metal-organic architectures

In these above sections, most of the examples of metal-organic architectures were formed through a combination of only two components: metal ions and one kind of organic ligand. The structure that forms is based on the ligand size and shape, and it is interesting to look at how multiple kinds of similar ligands behave when self-assembled as mixtures. Most commonly, when Pd(II) is used to self-assemble two different ligands (**LA** and **LB**) with similar shapes, it usually results in a statistical mixture of self-assembled products, for instance, a mixture of M₂L₄ capsules with a general formula of Pd₂(**LA**)_n(**LB**)_{4-n}, (n=0-4). However, depending on the structures of the ligands, more selective formation of specific assemblies can be possible. This is classified as self-sorting and has been demonstrated to be possible based on the design of the coordination moieties, added functional groups, and ligand size/shape compatibility.^[31c, 102] Generally, self-sorting is the high-fidelity recognition of self

from non-self within complex mixtures.^[103]

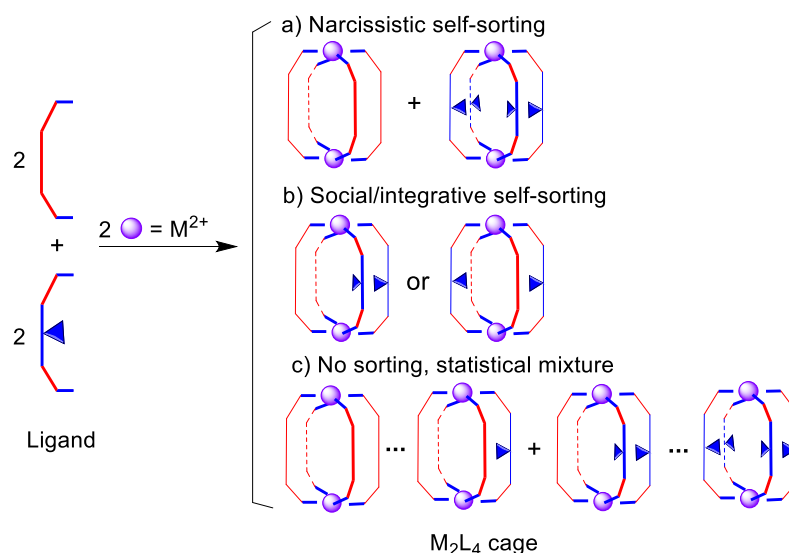


Figure 1.47 Different types of self-sorting behavior in coordination-driven self-assembly (eg. M_2L_4 capsule), a) narcissistic self-sorting, b) Social or integrative self-sorting, and c) non-sorted scrambled outcomes.

As shown in Figure 1.47, there are generally two types of self-sorting behavior in coordination-driven self-assembly of metal-organic architectures: narcissistic self-sorting and social self-sorting (or integrative self-sorting). In narcissistic self-sorting, the homo-selection of the different components leads to each component generating a homoleptic architecture with itself.^[104] However, in social self-sorting (or integrative self-sorting), pairs of different components self-discriminate from each other and assemble into heteroleptic products that precisely combine at least two different components.^[105]

4.1 Narcissistic self-sorting

Various methods can be used to promote narcissistic self-sorting, such as different ligand lengths, angles or symmetry, introducing weak interactions, or with guest templates, etc.^[104a, 106] One of the most common examples of self-sorting in self-assembly is based on chirality, where a mixture of two

enantiomers of a ligand only forms homochiral structures.^[44e, 107] As discussed in the formation of large M_nL_{2n} polyhedral spheres that is highly dependent on the size and the bend angle of the ditopic ligand. Interestingly, their narcissistic self-sorting can also be promoted depending on the angular variation of ligands between two coordinating sites.^[47b] This reliance can be strong enough to prevent the mixing of ligands in a single structure entirely. For instance, narcissistic self-sorting of large homoleptic spherical structures of $M_{12}L_{24}$ and $M_{24}L_{48}$ were observed when a 1:1 mixture of two ligands with bend angles of 127° and 149° were combined with Pd^{2+} , Figure 1.48. DOSY and TOF-MS analysis of a 1:1 mixture of individually prepared spheres confirmed that the formed products are distinct and distinguishable $M_{12}L_{24}/M_{24}L_{48}$ mixtures. Similar angle-dependent narcissistic self-sorting has also been shown in Ln -mediated assembly with smaller ligands.^[104b] Mixed organoplatinum-based ligands with different bend angles prefer narcissistic self-sorting into discrete 2D polygons.^[108] Prolonged heating of two or three organoplatinum reagents with 4,4'-dipyridyl in aqueous acetone results in the formation of a rectangle, triangle, and/or square.

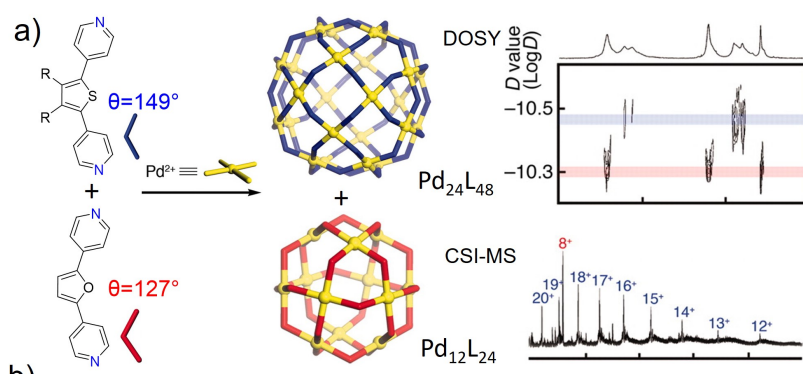


Figure 1.48 Different angles for narcissistic self-sorting of bent ditopic ligands into hollow M_nL_{2n} polyhedral spheres.^[47b]

4.2 Social or integrative self-sorting

Social self-sorting or integrative self-sorting has been much more studied than narcissistic self-sorting because it is more challenging but highly useful for

increasing structural and functional complexity.^[105b] The construction of heteroleptic metal-organic assemblies through this type of self-sorting with two or more different ligands has been reported for introducing unique functions to polygons, polyhedra, catenanes and knots, etc.^[31c, 102b, 105b, 109] Like narcissistic self-sorting, entropy should favor the formation of a statistical distribution of products. However, for integrative self-sorting, the entropic costs should be expected to be higher as only one product is formed. Thus, this type of self-sorting requires a more careful design and selection of building blocks to ensure the formation of heteroleptic outcomes. One of the earliest strategies used looked at varying the coordinating moieties in each ligand. In combination with *cis*-protected metal centers, the utilization of different donor combinations of bis-, tris- or tetrakis-monodentate bridging ligands has been a particularly effective approach in constructing multi-component heteroleptic assemblies with accessible cavities.^[110] As shown in Figure 1.49, a strategy utilizing *cis*-protected Pd(II) coordination, in addition to side group directed complementary of two pyridine-based ligands, leads to the highly selective assembly of two- and three-dimensional heteroleptic structures due to steric effects around the coordination sites.^[19a, 111]

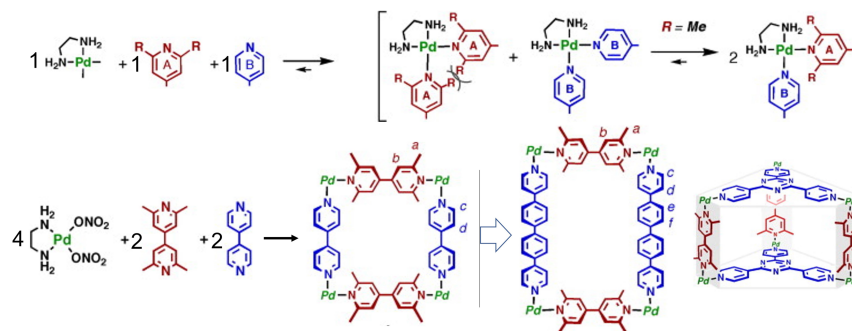


Figure 1.49 Coordination-dependent social or integrative self-sorting in the formation of heteroleptic metal-organic macrocycles and cages, side chain-directed complementary *cis*-coordination of *p*-substituted pyridine-based ligands.^[19a, 111]

In addition to straightforward selectivity from varying the coordinating

moieties in each ligand, the geometric principles based on size, angle and shape have also been established as another important approach, Figure 1.50. A very large heteroleptic cuboctahedron was achieved through the self-assembly of two different lengths bent ditopic pyridyl ligands with identical 120° bend angles.^[112] Normally, each of these ligands would be expected to form homoleptic $M_{12}L_{24}$ spheres. However, a 1:1 mixture of these two ligands with Pd(II) ions resulted in integrative self-sorting of heteroleptic $M_{12}(L1)_{12}(L2)_{12}$ sphere. A case study of this self-sorting behavior indicated that the ratio of the bridging lengths ($r > 2$) of the two different ligands was the key factor, in contrast to $r = 1$ -1.6, which resulted in a non-sorted statistical distribution of product mixtures.

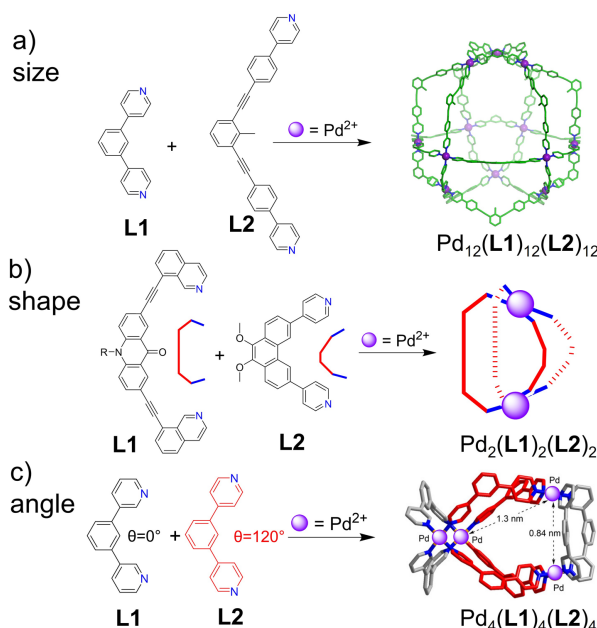


Figure 1.50 Geometric complementarity for social or integrative self-sorting of heteroleptic metal-organic cages, a) size complementarity,^[112] b) shape complementarity,^[113] and c) bend angle complementarity.^[115]

In another example, the geometric complementarity of two carefully designed ligands was shown to form a strained socially self-sorted

heteroleptic cage.^[113] The ligands were designed to be shape complementary with one another by combining a ligand with donor groups at a convergent 120° angle with another where the donor atoms were oriented at an outward angle of 60°, Figure 1.50. Because of their structure, their homoleptic cages have limited stability. Rather *cis*- heteroleptic cages were found to be energetically favored both through mixed ligand self-sorting studies and homoleptic cage-to-cage transformation. The ability to directly combine two different backbones in a controlled manner provides a powerful strategy for increasing complexity in the family of Pd₂L₄ cages and opens up possibilities of introducing multiple functionalities into a single self-assembled architecture. After this study, more additional heteroleptic cages based on mixed geometric complementarity ligands were reported.^[114] Most recently, the bend angle of ditopic ligands was reported to control the nuclearity of heteroleptic metal-organic cages with different sizes and geometries.^[115] The varying bend angle of the second ligand has been demonstrated to increase the nuclearity(n) of the assembly from 4 to 8, which represents an important advance in establishing the design rules for mixed-ligand assemblies.

As shown in Figure 1.51, another effective factor for controlling social or integrative self-sorting of heteroleptic metal-organic cages are steric effects, specifically the utilization of steric control around the metal center, steric substitution into the interior cavity and backbone steric bulk, etc. The self-assembly of multiple different ligands into heteroleptic supramolecular structures has been particularly successful through exploiting steric control around the metal center.^[116] For example, two 5- and 3-substituted acridone and phenothiazine picolyl ligands were designed and investigated for a donor-site engineering approach using steric control around the metal center.^[117] The formation of heteroleptic cage structures was reported through a favored *cis*-spatial configuration of the methyl groups, Figure 1.51. DFT calculations indicated that the *cis*-configuration in the heteroleptic cage was energetically favored to avoid considerable steric hindrance around the center Pd(II) ions.

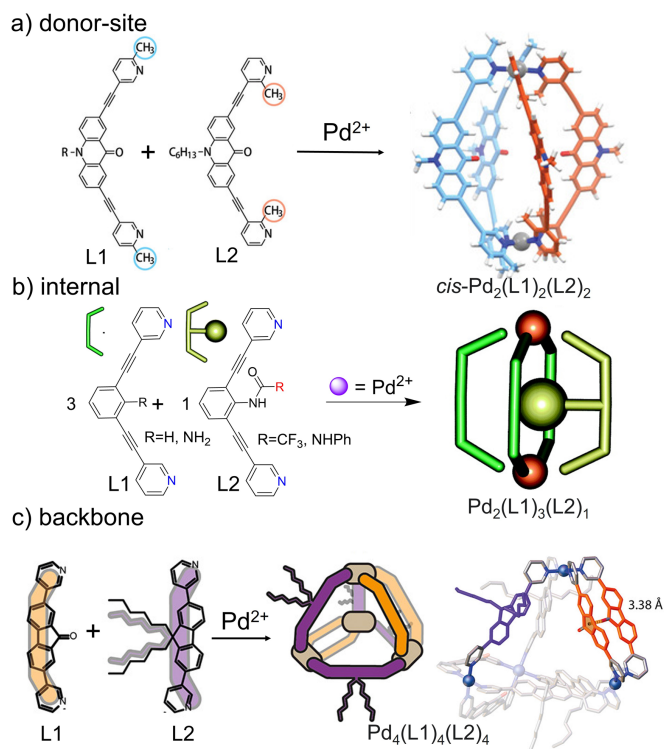


Figure 1.51 Steric effects control social or integrative self-sorting of heteroleptic metal-organic cages, a) coordination donor-site engineering approach,^[117] b) self-sorting controlled by substitution on the interior of M_2L_4 capsule,^[118] c) heteroleptic tetrahedra controlled by backbone steric bulk.^[105a]

More examples of steric effects controlling self-sorting have been reported by introducing steric substitution into the M_2L_4 cage interior cavity.^[118] Tuning the size of endohedral steric bulk of $\text{R} = \text{H}, \text{NH}_2, \text{CF}_3$ and NHPH into ditopic ligand backbones with identical bend angles and donor sites show the ability to self-discriminate, which allows self-sorting to form a heteroleptic cage by non-covalent and space-filling interactions, Figure 1.51. Most recently, an unprecedented heteroleptic tetrahedral cage was reported through backbone steric bulk controlled integrative assembly.^[105a] The bent fluorenone-based ligand and ligands with backbone steric bulk were used in integrative self-sorting based on the structural peculiarity of the Pd_4L_8 tetrahedral topology

where the four narrow ligands occupy two doubly bridged edges and the bulky ligands span the four remaining singly bridged edges. The formation of the smaller heteroleptic $\text{Pd}_4(\text{L1})_4(\text{L2})_4$ tetrahedra versus homoleptic $\text{Pd}_6(\text{L2})_{12}$ was attributed to a combination of entropic favorability due to the fewer components required and better spatial arrangement of the two bulky ligands on the same edge of the $\text{Pd}_3(\text{L1})_6$ double-walled triangle.

Social self-sorting or integrative self-sorting for the exclusive formation of heteroleptic metal-organic structures has also been explored based on non-covalent interactions, Figure 1.52. The amino-functionalized ligand has been reported to increase the donor properties of the ligands and provide steric protection of the metal and inter-ligand hydrogen-bonding interactions giving robust heteroleptic *cis*- $\text{Pd}_2(\text{L1})_2(\text{L2})_2$ cages.^[119] Non-covalent interactions in certain cases have been demonstrated to provide additional benefits associated with social self-sorting or integrative self-sorting outcomes. Some other examples were reported for this purpose, such as through specific host-guest interactions,^[110c, 120] to promote diversity by covalent bridges between ligands,^[121] a novel approach of charge separation^[122] and kinetic capture,^[102a, 123] etc. Indeed, the controlled social self-sorting or integrative self-sorting opens up rational approaches to novel heteroleptic supermolecular architectures that allow for incorporating multiple functionalities into these assemblies.

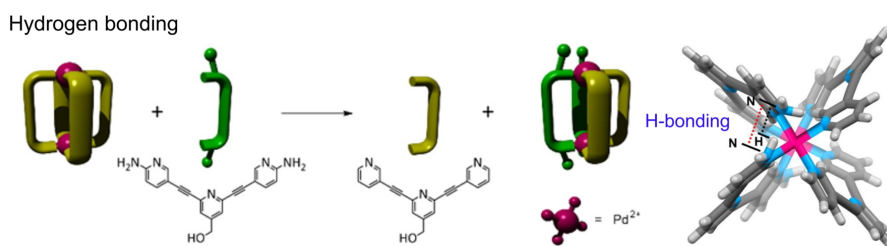


Figure 1.52 Non-covalent interactions control social or integrative self-sorting of heteroleptic metal-organic cages, hydrogen-bonding interaction between the 2-amino groups of ligands stabilized the *cis*- heteroleptic cage ($-27.2 \text{ kJ mol}^{-1}$) vs *trans* isomer.^[119]

5. Low symmetry metal-organic architectures

Most of the metal-organic architectures reported in the literature are highly symmetrical and often shaped similar to Platonic or Archimedean solids and obtained by coordination-driven self-assembly of highly symmetrical building blocks. This high symmetry promotes predictability and controllability for ultimate assemblies by avoiding the formation of multiple species with similar thermodynamic stability and physical properties in the multi-component self-assembly.^[9b] Nevertheless, the construction of metal-organic architectures with low symmetry is interesting for mimicking the dissymmetrical and widespread natural receptors and enzyme pockets in living systems.^[124] However, creating metal-organic architectures with low symmetry is challenging and currently very limited to small sizes and simple structures because of hindering factors related to the isolation and characterization of larger complicated structures. In this regard, the multi-component self-assembly of metal-organic architectures with low symmetry by several different approaches allows heterometallic or heteroleptic assemblies to form. It also leads to increased complexity and novel geometries and directional asymmetry in their structures, Figure 1.53. Straightforwardly, low-symmetry metal-organic assemblies can be made by self-assembly with low-symmetry building blocks through controlled self-sorting into single assemblies out of a potential mixture. Also, low symmetry structures can be achieved by a mix of two or more organic building blocks or metal ions through integrative self-sorting into heteroleptic or heterobimetallic assemblies. Entropically driven formation of statistical mixtures is the major challenge to be overcome here by sophisticated thermodynamically or kinetically controlled reaction sequences. Besides, less symmetric defective porous assemblies with missing linkers or metals were reported recently. However, the efforts will pay off since low-symmetry cages offer greater possibilities of implementing multiple functions, which, compared to highly symmetrical cages, make them promising candidates for numerous applications.

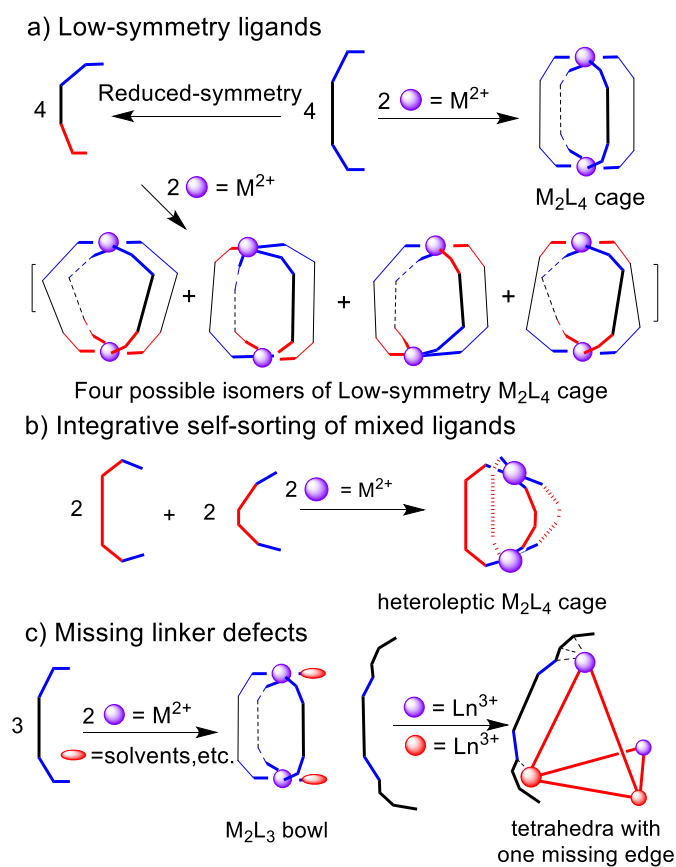


Figure 1.53 Schematic representation of the main approaches towards low-symmetry metal-organic cages, a) self-assembly with reduced-symmetry ligands, b) integrative self-sorting of mixed ligands, c) missing linker defects lead to symmetry breaking in assemblies.

5.1 Low-symmetry ligands

The challenge in the construction of metal-organic architectures with low symmetrical or unsymmetrical ligands is the difficulty of controlling the outcome from the initial building blocks. This symmetry breaking in initial building blocks might lead to the formation of isomers of a given molecular formula by the random relative arrangement of the ligand moieties around the metal centers. The incorporation of geometric or steric constraints into low-symmetry ligands with different coordination moieties enables an alternative

model for controlling the self-assembly process to avoid the formation of isomeric mixtures.^[125] Due to the lack of bilateral symmetry in these bent ditopic ligands with pyridine/isoquinoline donors, four possible Pd₂L₄ cage isomers could arise, Figure 1.54. However, the ligands were shown to assemble into a single cage isomer with minimal distortion in solution and solid-state. In this manner, it is possible giving access to Pd₂L₄ cage architectures of reduced symmetry, demonstrating that the direct effects of the combination of geometric complementarity and steric repulsion are effective to control assembly with low-symmetry ligands. Moreover, this type of ditopic ligands incorporates functional moieties by Cu(I)-catalyzed azide-alkyne cycloaddition have been accessed to give multi-functional and low symmetry structures.^[126] Another strategy extended the symmetry breaking of cages by building up the structure in a step-wise fashion to give cages that were asymmetric both concerning the organic building blocks and the incorporation of different metal ions.^[127] This heterometallic cage has been synthesized relying on differing labilities of an inert Pt(II) tetrapyridylaldehyde complex serving as a building block for a subcomponent self-assembly method, Figure 1.54. The organic groups on this structure were then extended into ditopic ligands by a condensation reaction with a suitably substituted pyridylamine to produce an additional binding site that could coordinate Pd(II) ions. Although self-assembly of metal-organic architectures with low-symmetry ligands is scantily explored, several different approaches have been used to control self-assembly with low-symmetry ligands, including the use of mixed-denticity ligands, charge separation strategies, and the use of repulsive or attractive non-covalent interactions between ligands.^[124, 128]

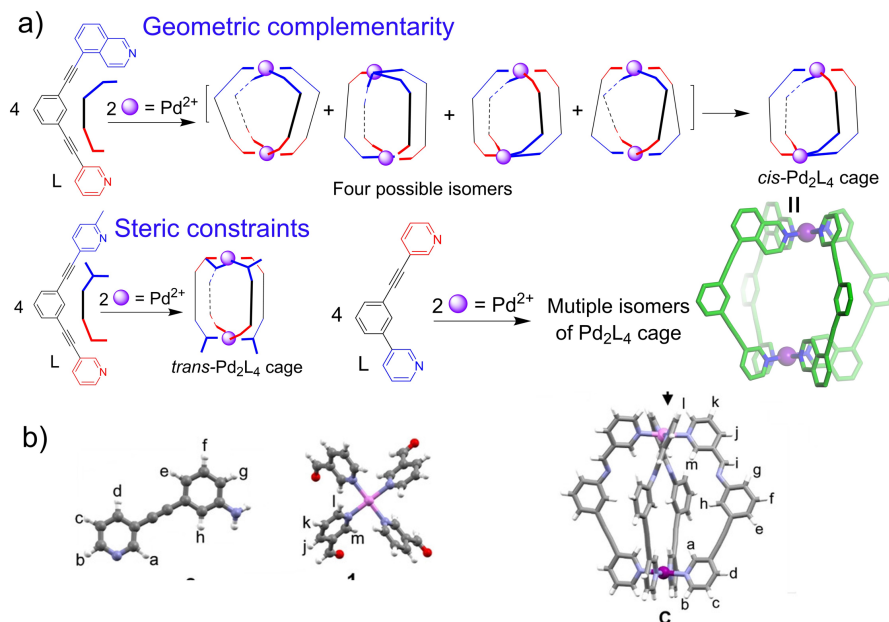


Figure 1.54 Self-assembly with low-symmetry ligands: a) unsymmetrical ligands with geometric complementarity and steric constraints to ensure selectivity of isomers^[125] and b) heterobimetallic coordination environments and imine bond formation.^[127]

5.2 Mixing different types of symmetrical ligands

Different from the straightforward use of low symmetrical building blocks, the low symmetrical heteroleptic structures can be achieved by social or integrative self-sorting of mixtures of different types of symmetrical ligands. Different approaches based on the rational design and control of complementary geometry, intermolecular interactions, steric effects, and guest templates have been developed to control multiple building blocks through integrative self-sorting into the single heteroleptic assembly. However, most of these heteroleptic assemblies still feature high symmetry.^[31c, 102b, 105b, 109] Accessing heteroleptic metal-organic architectures with low symmetry requires further increasing the difference between the two or more types of ligands used. Still, the representative approaches to balance self-sorting and

symmetry have been developed for the heterogeneous distribution of ligands to induce directional low-symmetry in the cage architecture, Figure 1.55. A good number of low-symmetry metal-organic architectures with different ligand geometries, backbones and endohedral or exohedral functional groups have been reported through integrative self-sorting of heteroleptic assemblies.^[129]

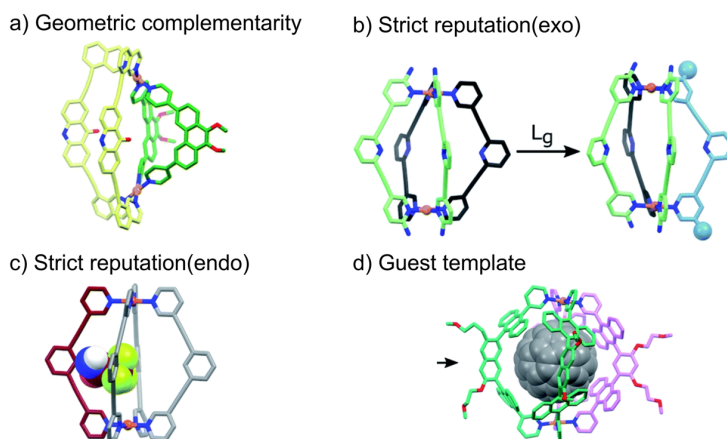


Figure 1.55 Integrative self-sorting of different mixed types of ligands into low-symmetry cages through a combination of different constraints, e.g. M_2L_4 capsule.^[129]

5.3 Defects in assemblies

Typically for self-assembly, the most stable structures that form are ones where all coordination sites are occupied (maximal site occupancy).^[8] However, some examples of defects containing metal-organic assemblies or materials with missing linkers or metals have been reported and shown novel applications versus their parent assemblies.^[130]

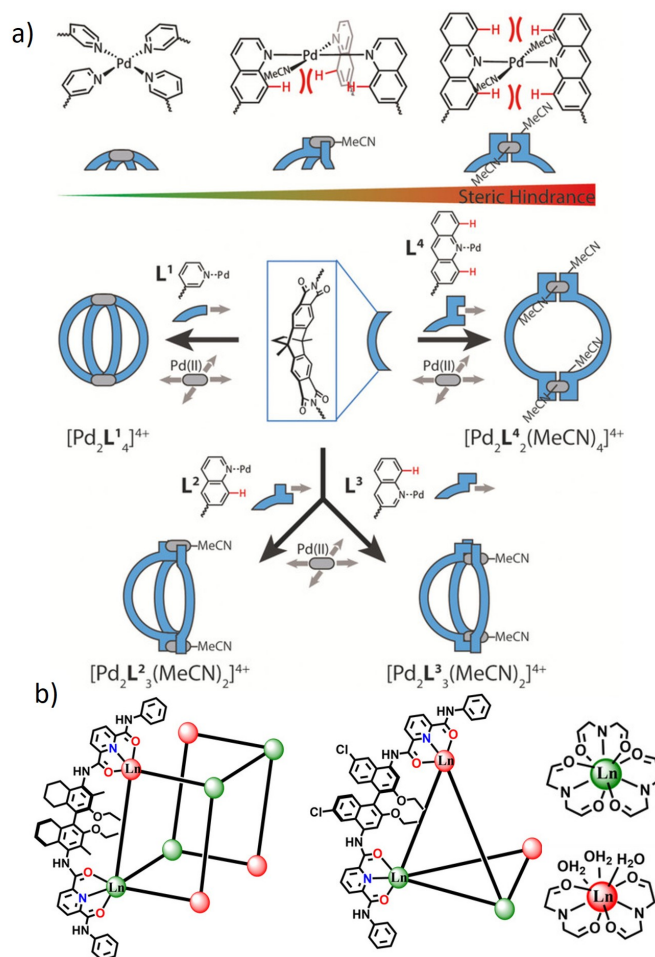


Figure 1.56 Metal-organic cages with missing linker defects, a) Increasing steric demand determines the number of nitrogen heterocycles in the coordination sphere of the Pd(II) dinuclear assemblies,^[131] b) tetrahedron and hexahedron Ln(III)-organic cages with missing edges.^[132]

Clever and co-workers employed a coordination sphere engineering (CSE) approach to design defective Pd(II) assemblies that rely on a bulky design of coordination moieties surrounding the metal center.^[131] As shown in Figure 1.56, when moving from pyridine to sterically more demanding coordination moieties like quinoline and larger acridine, it can change the number of nitrogen heterocycles that can be incorporated into the square

planar geometry around the Pd(II) ions, the combination of these sterically demanding bent ditopic ligands allows controlling the size and shape of the assembled product, from Pd₂L₄ cages to Pd₂L₃ bowl-shaped structures or even Pd₂L₂ rings. Interestingly, low symmetrical Pd₂L₃ bowl-shaped structures are visually different from their parent Pd₂L₄ cages as they are missing one bridged bent ditopic ligand. This open structure has been used for the binding of fullerenes and as protecting group to control their functionalization. Similar steric bulk controlled self-assembly was reported for the construction of defective lanthanide-organic cages, including both a tetrahedron and hexahedron with missing edges.^[132]

6. Endohedral functionalization of metal-organic cages

The cavities in cages offer well-defined microenvironments that open up important perspectives in various applications such as sensing, catalysis, drug delivery, gas separation, storage, and biological activity, etc.^[14b, 133] Part of the goal of the research and strategies described in section 5 is to be able to generate cavities with more diverse functionalization, similar to active sites in enzymes. Over the past several decades, the defined microenvironments in metal-organic cages have been investigated for various applications, Figure 1.57. For example, they are tuning the shape, cavity size, metal, and ligand properties of metal-organic cages to increase the specificity and strength of host-guest encapsulation of one or more anions, neutral molecules and cations.^[134] Related to this, supramolecular catalysis inside the cavity of metal-organic cages can enable remarkable rate enhancements and product selectivity as a result of specific host-guest interactions and increased effective concentration of substrates into the cavity.^[135] To this end, the unique confined space within the cage can be used to control the nature of incorporated substrates and products through steric constraints, stabilization of intermediate species or transition states by secondary interactions, and solvent exclusion. Consequently, unusual reaction pathways have

occasionally been observed for metal-organic hosts where reactivity differs from the classical organic reaction.^[136] This has led to significant work towards tuning the interior cavity environment. Notably, the addition of endohedral functional groups in a precise arrangement has attracted significant interest for the potential to perform more complex tasks inside the cavity, such as promoting tandem multi-step reactions.

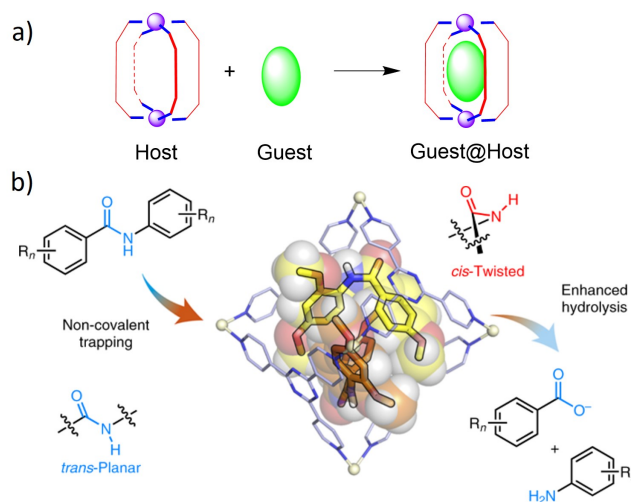


Figure 1.57 Representative applications of metal-organic cages, a) host-guest chemistry, and b) supramolecular catalysis and enhanced reactivity of twisted amides inside a metal-organic cage.^[136]

Of note, most of the metal-organic cages that have been reported were designed and synthesized with ligands where the faces of flat aromatic panels are oriented toward the cavity. This increases the size of the cavity and can potentially strengthen the host-guest encapsulation due to solvophobic effects or π -stacking interactions. However, this orientation limits possibilities for the internal functionalization of these cages.^[8] Even in M_nL_{2n} structures where the edge of the aromatic is often oriented towards the interior of the cavity, space limitations or competition of added functional groups for dynamic coordination bonds makes endohedral functionalization challenging. As such, there are relatively few examples of endohedrally functionalized metal-organic cages reported in the literature currently.^[137] Several types of metal-organic cages

were often used for endohedral functionalization, including giant hollow $M_{12}L_{24}$ spheres or simple M_2L_4 capsules through edge modification of aromatic groups on the ligands and M_4L_6 tetrahedra by using slightly bent ligands or doubly edge functionalized linear ligands, Figure 1.58.

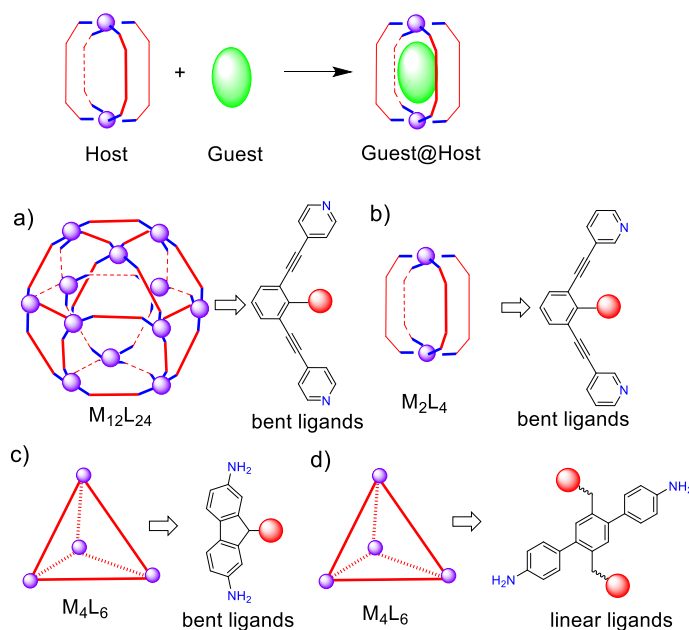


Figure 1.58 Representative strategies for incorporating endohedral functions in metal-organic cages.^[137]

Due to the large size and well-defined shape of hollow self-assembled $M_{12}L_{24}$ spheres, these structures have been one of the most diversely functionalized, Figure 1.59. A variety of functional groups ranging from simple alkyl chains to even proteins have been attached on the interior edge of ligands and the resulting building blocks are shown to self-assemble.^[18f, 23b] In contrast, the smaller cavity of the M_2L_4 capsule requires a careful selection of small endohedral groups to confer novel properties to the self-assembled cages.^[33, 138] Notably, the relatively small cavities in these structures can benefit from the design of heteroleptic cages to allow including only one or two endohedral groups.^[118] For M_4L_6 structures, functionalization is also

challenging as bent ligands can lead to the formation of M_2L_3 helicate structures with minimal or no cavity.^[10c, 139] Free rotation of double edge functionalized linear ligands can limit functional groups present in the cavity.

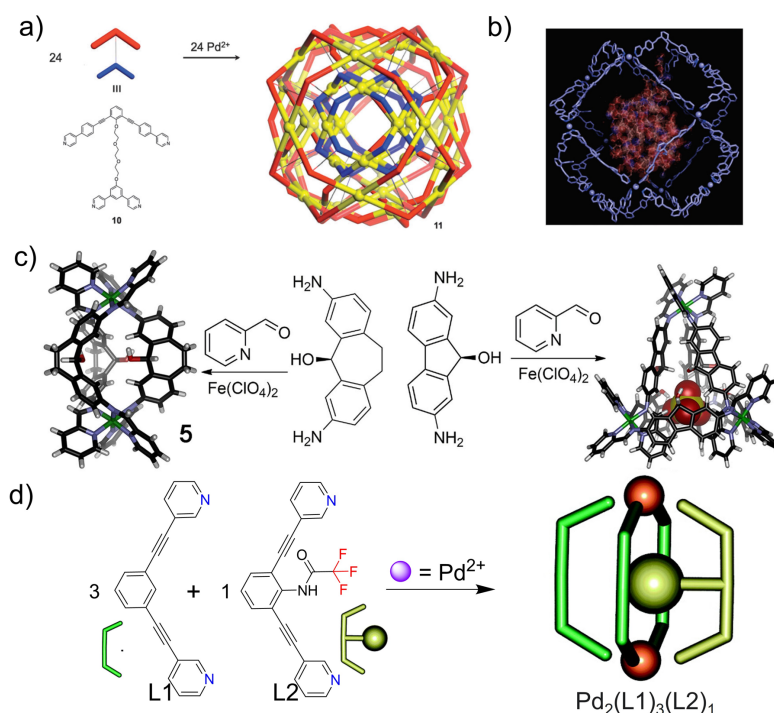


Figure 1.59 Unprecedented endohedral functionalization of a) cage in a cage,^[18f] and b) protein encapsulation,^[23b] c) slightly bent ligands depend on the formation of M_4L_6 tetrahedra and M_2L_3 helicates,^[10c, 139] d) self-sorting with endohedral functions into the heteroleptic cage.^[118]

Among all the applications for endohedral functionalization of metal-organic cages, biomimetic catalysis by mimicking certain key features of enzymatic systems is one of the most enticing.^[140] Metal-organic cages with well-organized endohedral reactive functional sites in the cage cavity can enable cooperative effects between the added groups and the cavity of the cage, allowing the activation of substrates to be combined with site isolation effects and enhanced local concentration from the cavity. For example, the

large internal spaces and robust nature of the $M_{12}L_{24}$ spheres have allowed the internalization of metal-coordinating groups such as phosphines that can be used to bind additional metals for performing catalytic reactions in the internal cavity.^[133e, 141] These cationic hosts were shown to be able to encapsulate multiple gold catalysts, increasing their local concentration beyond their solubility in bulk solution and additionally pre-organize the acetylenic acid substrates, leading to selective cyclization, Figure 1.60.

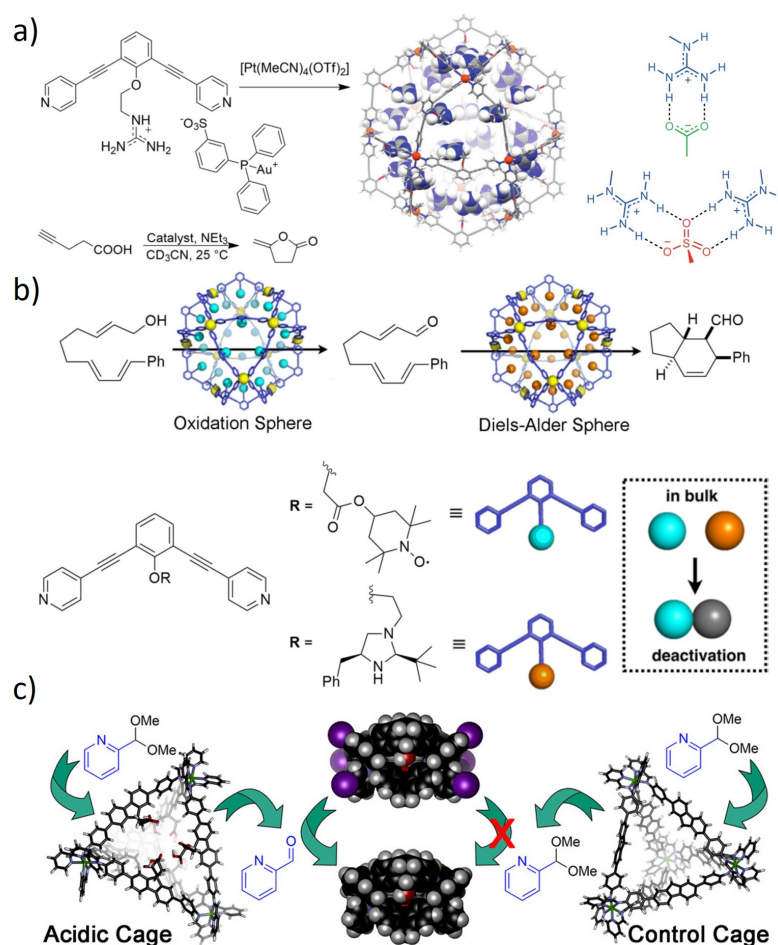


Figure 1.60 Representative examples of the enticing application of endohedral functionalization in self-assembled metal-organic cages as biomimetic catalysts.^[133e, 141-143]

Moreover, multiple functional groups can be organized inside the cavities of different self-assembled structures to isolate catalytic sites from each other. Fujita and co-workers demonstrated this with two different self-assembled $M_{12}L_{24}$ spheres for a stereocontrolled cascade reaction.^[142] The two different catalysts employed in the synthesis are TEMPO for an oxidation reaction and MacMillan's catalyst for a Diels-Alder (DA) reaction, Figure 1.60. These two catalysts are normally incompatible with each other. Without isolation, the DA catalyst is promptly oxidized by TEMPO. By encapsulating each of them separately within the cavity of different $M_{12}L_{24}$ -type capsules, the cascade oxidation/DA could be performed in a one-pot reaction without loss of stereoselectivity. In another example, the sensitivity of the coordinating motifs to added carboxylic acid functional groups was investigated.^[143] Self-assembly of a carboxylic acid-containing ligand into a Fe_4L_6 aminopyridine cage allows endohedral positioning of the acid groups while maintaining a robust cage structure, Figure 1.60. The cage is an effective supramolecular catalyst, providing up to 1000-fold rate enhancement for acetal solvolysis. This enhanced reactivity allows a tandem deprotection/cage-to-cage interconversion that cannot be achieved with other acid catalysts. The combination of rate enhancements and sequestration of the reactive function confers both activity and selectivity on the process, mimicking enzymatic behavior.

7. Conformational control and folding

In the previous sections, self-assembly was shown to be a powerful tool for the formation of complex metal-organic architectures that rely on bringing together many molecular components through defined local interactions between them. These same interactions can also generate complex architectures in an intramolecular fashion by directing conformational control of oligomeric systems into discrete stable three-dimensional structures.^[144] The best example is how non-covalent interactions between units in a peptide

chain lead to specific controlled conformations that result in functional secondary or tertiary structures, Figure 1.61. This process, termed folding, is essential for many biological functions. As shown at the start of this introduction, it is one of the key steps for forming many of the complex building blocks used in biological self-assembly. A major advantage of folding is that it allows different combinations of the same building blocks to produce a wide range of different structures. Moreover, because the interactions that control the folded structure are weak, reorganization of them can lead to novel structures with equally novel functions. Mimicking the folding process can thus be an interesting approach to achieve these same advantageous aspects or functions in synthetic molecules. This idea has led to substantial work towards developing synthetic molecules that adopt stable higher-ordered structures in solution through the same interactions that control biological folding. This family of molecules is called foldamers.

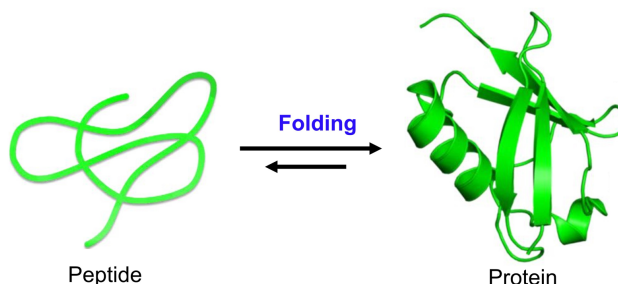


Figure 1.61 Conformational control of a peptide chain through non-covalent interactions leads to folding into higher-order secondary or tertiary structures of protein.

7.1 Foldamers

While the term foldamers were initially coined by Gellman to describe “any polymer with a strong tendency to adopt a specific compact conformation”, different definitions have been proposed.^[145] More stated that foldamers are any oligomer that folds into a conformationally ordered state in solution, the structures of which are stabilized by a collection of noncovalent interactions

between nonadjacent monomer units. The emphasis of this definition was placed on the fact that the ordered states should be secondary structures such as helices or sheets and that the molecules should have multiple possible conformational states that are differentiated through non-covalent interactions. This excluded polymeric systems or proteomimetics (tertiary structures) and molecules like helicenenes where covalent bonds directed their structures. However, in recent years this definition has again expanded to include any artificial folded molecular architecture. Still, by any of these definitions, a large number of different oligomeric systems can be considered foldamers and numerous classes of this family of the molecule have been described. These include biologically similar aliphatic β -peptides, oligo(m-phenylene ethynylenes), oligo(pyridine-pyrimidines), aromatic oligoamides and many others which have been the subject of multiple reviews.^[146] Of the different classes, aromatic oligoamide has shown particular promise for the formation of highly stable and predictable complex structures, making them interesting tools for combining with self-assembly.

7.2 Aromatic oligoamide foldamers

Aromatic oligoamide foldamers are oligomers of heterocyclic or heteroatom functionalized aromatic units connected by amide bonds.^[147] Their structures are the result of two important effects. First, conjugation between the aromatic units and the amides gives a planar or close to the planar system. Based on this, intramolecular hydrogen bonding and electrostatic interactions between the amide groups and the heteroatoms on the aromatic rings lead to strong conformational preferences between either the syn or anti forms, as depicted in Figure 1.62. When this same structural motif is repeated in the sequence, the resulting structure should be the sum of these local conformational preferences. In the case of curved structures, elongation of the oligomer will eventually lead to the one end of the strand stacking onto the other and additional stabilization through π -stacking or solvent effects. Based on this design, a variety of different secondary structural motifs, including helices, sheets, linear strands, zig-zag structures and others, have been reported.^[148]

Importantly, because of the modularity of these foldamers, monomers with different sizes, connectivities, and functionalization can be readily substituted to change the shape or properties of the folded structure. This has been used by Huc and co-workers for the generation of folded aromatic capsules.^[147a] Through careful choice in the curvature and length of monomers used in a sequence, they were able to gradually increase the diameter of a helical structure, resulting in hollow cavities that could be tuned for specific guest binding properties, Figure 1.62.

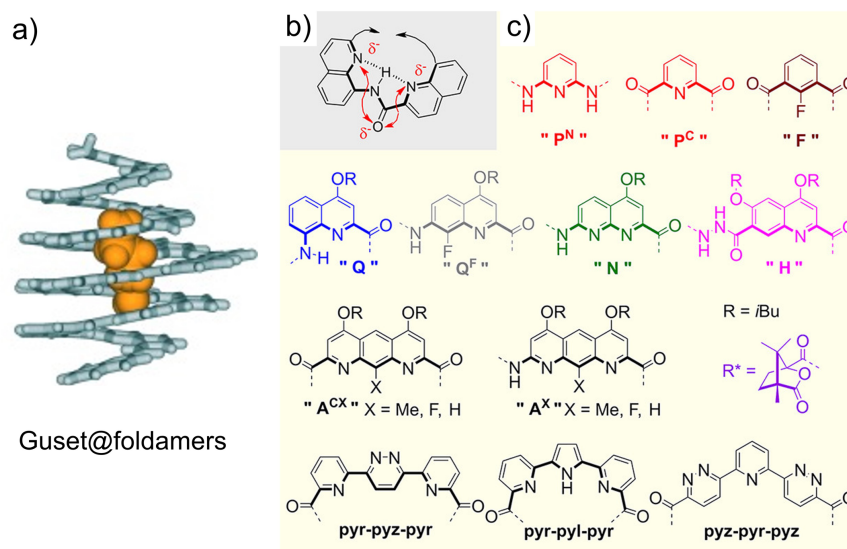


Figure 1.62 a) aromatic oligoamide foldamers as versatile capsules for host-guest encapsulation, b) local interactions that govern aromatic oligoamide folding of foldamers, c) formula of main chain units derived from diamine, diacid and amino acid monomers that constitute helical capsules.^[147a]

Another interesting property of aromatic oligoamide foldamers is that some helical strands have been found to undergo spontaneous hybridization into multi-helical structures in solution with self-association constants in some cases greater than 10^8 M^{-1} .^[149] The mechanism described for this process involves a spring-like extension of the different strands followed by intercalation and sliding of the two oligomers along with each other, Figure

1.63. The multi-helical assemblies have been reported to be largely stabilized by inter-strand π - π interactions, with longer chain lengths or monomer sizes generally leading to the greater formation of the multiple helix structure.^[150] Notably, for a double helical structure, the helical pitch of a single strand must increase to 7 Å to allow the second strand to intercalate. In this respect, longer oligomers also decrease the energy required for the spring-like extension by minimizing the distortion needed in the torsion angles around the amides. Indeed, replacing pyridine units with units such as anthracenes or quinolines can allow even greater extension and the formation of triple or even quadruple helices.^[149a, 149d] For instance, stable parallel and antiparallel triple helices can form from 1,8-naphthyridine oligoamides, Figure 1.63.

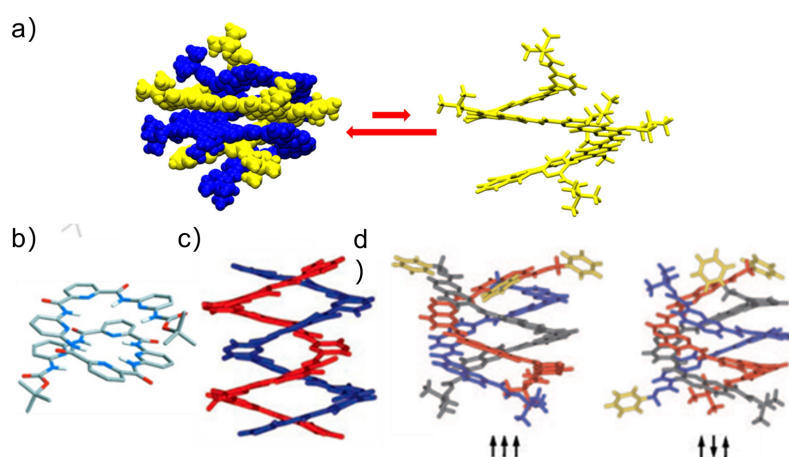


Figure 1.63 a) the formation of double helix dimer through a spring-like extension of the different single-stranded helix, b) single-stranded helix, c) double-stranded helix, d) parallel and antiparallel triple-stranded helix.^[149-150]

7.3 Aromatic amides and self-assembly

As reviewed in the previous section, the outcome of coordination-driven self-assembly is primarily controlled by geometrical aspects originating from the organic building blocks as well as the metal precursor. To this, the facile rotation of aromatic amides-based ligands offers structural flexibility and the

ability to adjust to their geometrical requirements for the construction of metal-organic architectures. Conformational control of such aromatic amides-based structural flexibility has been reported to allow the possibility of several geometrical isomers and thus provides another architectural parameter. As shown in Figure 1.64, Puddephatt and coworkers designed ligands with aromatic amides that can adopt the conformation as a consequence of intramolecular hydrogen bond or dipole-dipole attraction.^[151] Interestingly, the self-assembly behavior of ligands with or without the above intramolecular interactions is remarkably different. Ligands with approximately right-angled coordination geometry determined by intramolecular hydrogen bonding form only the cyclic dimers by self-assembly, however, the ligands without the above intramolecular interactions are more flexible, leading to the formation of zigzag polymers in the solid state. To this end, architectural shapes including rectangles, squares, triangles, cages, and prisms are shown to be constructed by self-assembly employing designed conformational control of aromatic amide-based ligands.^[39b, 43a, 152] Different from the cavities of common metal-organic assemblies, the presence of hydrogen bonding synthons in these assemblies opens up the binding and/or sensing possibilities via amide C=O and N-H groups.^[39b, 152c] However, the few reported examples and very limited studies on small systems with simple and symmetric ligands indicate that the development of conformationally controlled amide-based metal-organic assemblies is still in its infancy. Still, the novel yet predictable self-assembled architectures and their tailor-made applications are anticipated to remain a productive discipline for greater exploration and creativity.

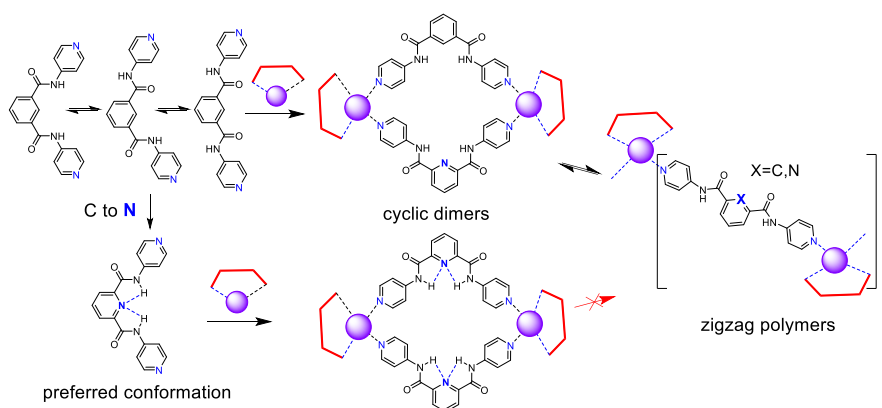


Figure 1.64 Example of aromatic amides used in coordination-driven self-assembly, equilibria between conformers of the free ligand, and preferred conformation of the ligand with hydrogen bond or dipole-dipole attraction for conformational control of outcomes.^[151]

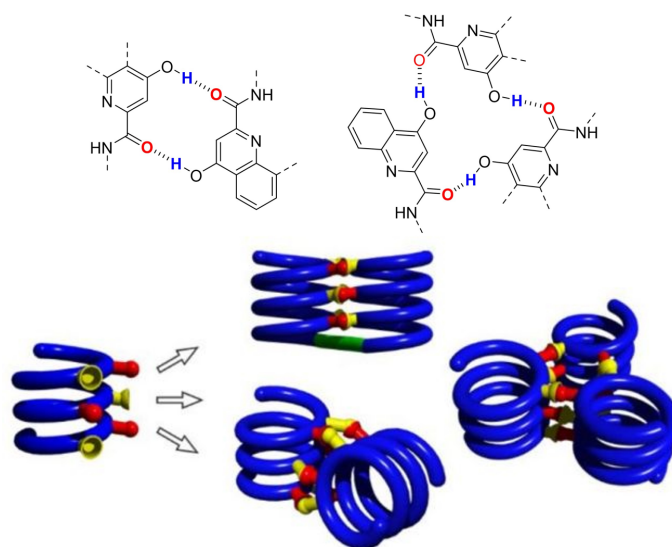


Figure 1.65 Examples of hydrogen-bonding patterns between aromatic oligoamide foldamers used for directing self-assembly of abiotic tertiary structures.^[153]

Relative to the great variety of secondary structures that were achieved through the folding of aromatic oligoamide foldamers, the design of abiotic

tertiary and quaternary structures is a considerable challenge because these higher-order structures need the overall 3D arrangement of their secondary structures as subcomponents for self-assembly. However, the tertiary structure of a protein is the level at which sophisticated functions emerge. In nature, the tertiary structures of proteins are generally stabilized by outside polar hydrophilic hydrogen and ionic bond interactions and internal hydrophobic interactions between nonpolar amino acid side chains. Interestingly, a similar self-assembly process can be expected for aromatic oligoamide foldamers by introducing hydrogen-bonding functionalities at defined locations on the aromatic amide backbones.^[153] As shown in Figure 1.65, the abiotic tertiary fold was rationally designed interactional patterns to guide the folding and self-assembly. The hydrogen-bond-directed aggregation of helices is not linked by a turn unit self-assembly of several thermodynamically and kinetically stable homochiral dimeric and trimeric bundles. Relative helix orientation within the bundles may be changed from parallel to tilted based on subtle solvent variations. Altogether, these results highlight the richness and uniqueness of abiotic tertiary structure behavior. Still, the rational design of abiotic tertiary folded structures as large, complex, and functionally efficient as proteins represents an exciting yet formidable challenge for chemistry. Recently, more examples of aromatic amides-based abiotic tertiary and quaternary structures were achieved by combined strategies of computational design, solution-phase synthesis and structural characterization.^[154] Importantly, self-assembled tertiary folding stabilizes otherwise flexible secondary structures and the disruption of tertiary folds upon adding polar solvents follows different mechanisms depending on whether secondary structures are inherently stable or not. These findings constitute a solid basis for further increasing the size and complexity of abiotic folded structures and eventually orchestrating folding dynamics and responsiveness.

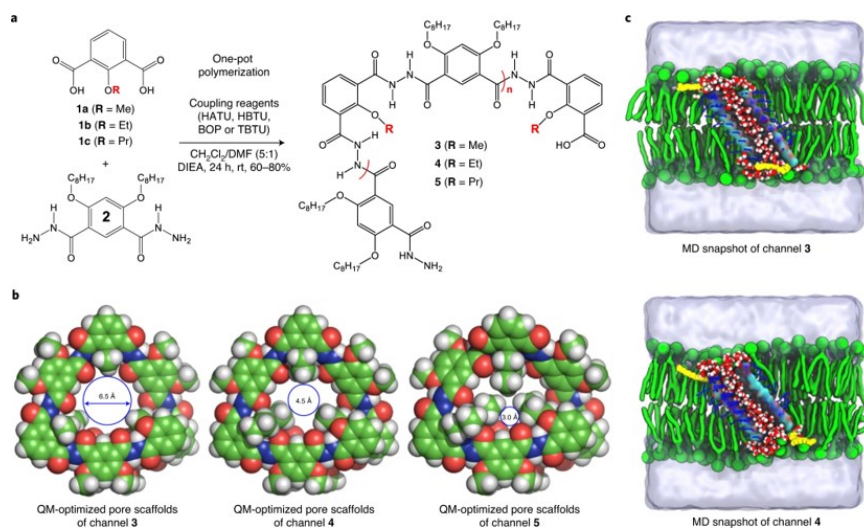


Figure 1.66 Molecular design for one-step synthesis of foldamer-derived polymer-based synthetic water channels.^[155]

For aromatic oligoamide foldamers, their more complex or higher-order structures often need the multi-step synthesis of long oligomers with low yields of the coupling reactions as a result of increased intramolecular stacking. In contrast, polymeric analogs are more attractive because they enable the formation of aromatic polymer-based helices with high stability and can be synthesized from one-pot reactions of readily available monomers. Indeed, extending aromatic amides for self-assembly and folding from the molecular level to material science has been vigorously studied because of their high structural predictability and modifiability. For instance, as shown in Figure 1.66, a class of biomimetic, helically folded pore-forming polymeric foldamers was achieved by one-step coupling reactions that can serve as long-sought-after highly selective ultrafast water-conducting channels while concurrently rejecting salts (NaCl and KCl) and even protons.^[155] Other similar aromatic amides-based polymeric helices have also been described, showing various structures and material functions such as macromolecular receptors for various guests or transmembrane channels for transporting various ions.^[156]

While the use of aromatic oligoamides for self-assembly is still limited, the

Chapter I

above examples show the promise of this class of molecule for designing advanced molecular architectures. Extending on the self-assembly properties of aromatic oligoamides, both through metal-coordination driven self-assembly and their ability to form multiple helices, can open new doors for achieving new structural and functional complexity levels from synthetic self-assembled systems, ultimately allowing chemists to design novel structures that rival those found in biology.

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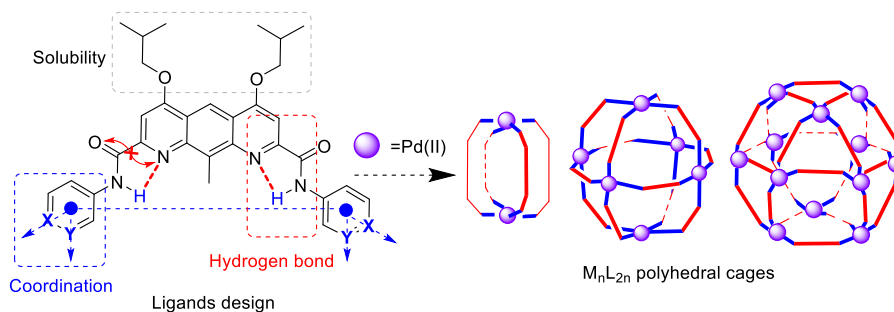
Chapter II

Objectives

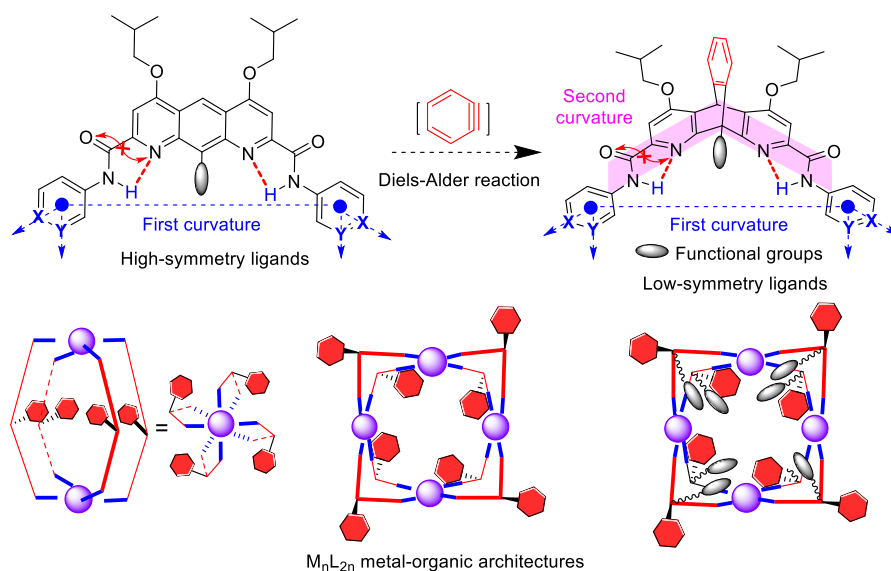
Non-covalent interactions play an essential role in the folding and self-assembly of large supramolecular biological assemblies in nature. These interactions are not only a driving force for the formation of large structures but also control conformation and complementary shapes of subcomponents that diversify the complexity and functionality of outcomes. 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. Indeed, current artificial self-assembly systems, especially coordination-driven self-assembly, highly rely on symmetrical and rigid building blocks to promote the predictability of the final structure and avoid the formation of mixtures. Aromatic amide-based ligands could avoid these limitations through the use of non-covalent interactions to control ligand structure and thus coordination-driven self-assembly. This can allow the use of conformationally flexible amide bonds to attach different ligand building blocks, allowing for a highly modular system. However, reports of amide-based ligands for metal-based self-assembly are limited and have mainly been used for small self-assembled systems. Examples with larger assemblies or more complex structures are rare due to the challenges of introducing additional complementary shapes and functional groups for diverse structures and applications. Thus, developing an approach for designing these types of ligands and mimicking certain features of natural systems to advance knowledge in control self-assembly with non-covalent interactions and complementary shapes will be important.

My doctoral research looks at how aromatic amides or oligoamides can be used for designing self-assembled supramolecular structures and the applications of these systems for host-guest chemistry and catalysis. This focuses on two different but complementary topics: 1) Using endohedral non-covalent interactions in symmetric or low symmetry aromatic amide ligands for assisting or directing self-assembly of well-defined metal-organic architectures. 2) the use of aromatic oligoamide secondary structures for driving the self-assembly of complex supramolecular architectures via the formation of double (or higher-order) helices. These works are divided into the specific aims shown below:

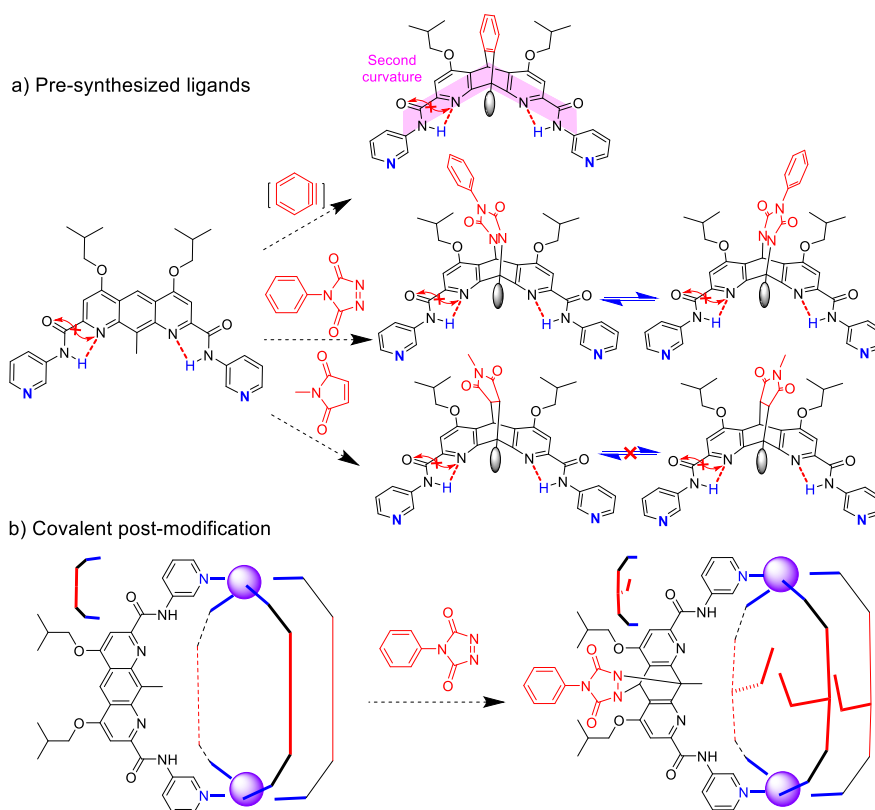
a) The design and synthesis of heteroaromatic amide-based ligands with endohedral non-covalent interactions for coordination-driven self-assembly of M_nL_{2n} polyhedral cages. Two ligands with endohedral non-covalent interactions, differentiated by the approximate bend angle(θ) between the donating lone pairs of pyridine, and one ligand lacking the above-mentioned interactions, will be designed and used in this study. These ligands can be used to look at the role of endohedral non-covalent interactions on rigidity and conformational stability of the ligands for coordination-driven self-assembly of different metal-organic cages. Moreover, as the interactions in the ligands should result in self-assembled cages with endohedral hydrogen bond donors and acceptors, the interior cavities of the assemblies should differ from common metal-organic cages and potentially lead to higher affinity host-guest binding.



b) Controlled coordination-driven self-assembly with low symmetry and flexible building blocks could potentially allow more complex structures closer to those found in nature to be obtained. However, the main challenges in these systems are the limitations on control over the self-assembly process that frequently results in complex mixtures of products. Thus, a strategy that advances knowledge on controlling self-assembly and that can open the door to converge these complex mixtures into single species is highly important in this field. We hypothesized that a strategy for this purpose could combine the endohedral non-covalent interactions in aromatic amide ligands with the design idea of additional shape complementarity between ligands. In order to prove this hypothesis, the Diels-Alder reaction can be used to break the symmetry of the diazaanthracene units in aromatic amide ligands that allow the formation of dual curvature ligands. These low-symmetry ligands with defined size, shape, and bend angle are ideal for examining the non-covalent interactions and complementary aspects of steric and conformational constraints for control over the self-assembly process. We will thus study their self-assembly with Pd^{2+} and explore possible applications for the resulting structures.



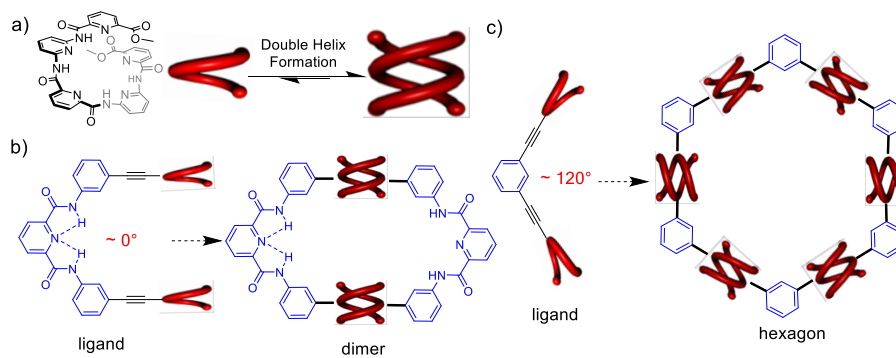
c) Next, we aimed to study the possibility of achieving the same types of structures using the Diels-Alder reactions for covalent post-modification. This is interesting because it could potentially allow stimuli-responsive host-guest behavior in the cages. In most metal-organic supramolecular structures, covalent reactions are exclusively used to synthesize and modify ligands before self-assembly. Thus, the outcomes have only functional groups already present in the initial building blocks, and adding or removing any functional groups to the assemblies must be designed and synthesized from the beginning. Covalent post-modification could be a shorter alternative pathway to achieve similar complex structural and functional diversity and provide unique access to novel supramolecular structures and functions that are unable to be realized through self-assembly. To this end, two dienophiles, 4-Phenyl-1,2,4-triazoline-3,5-dione and 1-Methyl-1H-pyrrole-2,5-dione, with different reactivity and conditions for the Diels-Alder reaction, will be used for ligand design and their self-assembly behavior studied in order to try to optimize conditions for covalent post-modification. The dynamic structural properties of the Diels-Alder adducts with these two dienophiles are significantly different and can also give a chance to understand how the ligands adapt to self-assembly outcomes in a complex system.



d) Based on the knowledge and experience of coordination-driven self-assembly, we then wanted to study a new concept that uses multiple helix formation of aromatic oligoamide foldamers in the absence of metals to form discrete supramolecular assemblies and potentially more complex foldamer-based higher-ordered architectures. Relative to coordination-driven self-assembly, the multiple helix formation would function like the formation of metal-ligand bonds and open up new exciting possibilities for self-assembly. By incorporating two double helix forming sequences into a larger molecular structure that could be used to control their orientation, we expect that the bend angle between the helices could be used in a similar fashion as for coordination-driven self-assembly to predict the final structure. Importantly, this would represent a highly novel approach as no examples of using this multi-helix formation to generate discrete cage-like supramolecular structures with a well-defined cavity between their secondary subunits have been

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reported. Thus, we have set out to develop a proof of concept for studying this idea.



Chapter III

Balancing ligand flexibility versus rigidity

Non-covalent interactions are important for directing protein folding across multiple intermediates and can even provide access to multiple stable structures with different properties and functions. In this chapter, we describe an approach for mimicking this behavior in the self-assembly of metal-organic cages. Two ligands (**L1** and **L2**) whose bend angles are controlled by non-covalent interactions and one ligand(**L3**) lacking the above-mentioned interactions were synthesized and used for self-assembly with Pd^{2+} . As these weak interactions are easily broken, the bend angles have controlled flexibility giving access to $\text{M}_2(\text{L1})_4$, $\text{M}_6(\text{L2})_{12}$, and $\text{M}_{12}(\text{L2})_{24}$ cages. By controlling the self-assembly conditions, this process can be directed in a step-wise fashion. Additionally, the multiple endohedral hydrogen bonding sites on the ligand were found to play a role in the binding and discrimination of neutral guests. Part of the work of this chapter was published in Liu et al. *Chem. Eur. J.* **2020**, 26, 11960-11965.

1. Introduction

The last decades have seen significant advances in the development of molecular systems capable of self-assembling into discrete complex structures.^[1] Of the reported approaches, metal-ligand coordination-based self-assembly has become one of the most widely used.^[2] Numerous nano-sized molecular objects have been reported and found to have interesting applications for sensing, catalysis, drug delivery, storage, and molecular

recognition, etc.^[3] One of the central tenets in the design of these systems is that the size and shape of the final self-assembled structures can to an extent be predicted based on the shape of the ligands and the coordination preferences of the metal.^[4] As an example, the most studied metals for self-assembly, Pd^{2+} and Pt^{2+} , form square planar complexes.^[5] When combined with rigid, bent, ditopic ligands, this leads to metal-organic polyhedra of M_nL_{2n} stoichiometry, where values for n for the thermodynamically most stable species are generally dependent on the bend angle (angle between donor sites) of the ligand and limited to certain values as a result of geometric constraints.^[6] By this strategy, numerous self-assembled M_nL_{2n} cages with $n=2, 4, 6, 8, 9, 12, 24, 30, 48$ have been described.^[2d, 7]

As the number of components involved is generally large, the self-assembly process for even small cages is complex. Multiple factors (examples: counter ion, solvent, etc.) can influence the topology and nuclearity of the self-assembled structures^[8]. In the case of $\text{M}_{12}\text{L}_{24}$ assemblies, studies by the groups of Yoneya,^[9] Fujita^[9-10] and Hiraoka^[11] have highlighted the diversity of the different possible self-assembly pathways on the potential energy landscape leading to the final most stable structure. Several metastable species, notably M_6L_{12} , M_8L_{16} , and M_9L_{18} , have been identified as kinetic intermediates. However, these species typically exist as mixtures and clean formation of single intermediates in the assembly of larger structures is rare,^[12] their stability being limited in part due to tension imparted by the rigid ligands being forced to adapt to narrower bend angles. Though less predictable, flexible ditopic ligands, containing for example aliphatic segments, can lead to the formation of multiple structures, with templates being generally required to shift the equilibrium between them.^[13] As such, these provide systems that can evolve, both in terms of structure and function, in response to stimuli.^[14] Nevertheless, flexible ditopic ligands generally give smaller self-assembled structures and their use for the formation of larger metal-organic cages is limited.^[15]

2. Design and synthesis of ligands

Interestingly, ditopic ligands that have properties in between flexible and rigid have been less explored^[16] but could allow multiple large cages to be selectively obtained from a single combination of metal and ligand. Heteroaromatic amide-based ligands, such as in Figure 3.01, can be an interesting candidate for this purpose. These ligands are flexible in the torsion angles around the amides. However, conjugation across the amide leads to a preferred planar structure and dipole-dipole/hydrogen bonding interactions give strong conformational preferences for the curved structures shown. This motif has been widely used for the development of aromatic oligoamide foldamers with highly predictable and stable structures^[17]. For coordination-driven self-assembly, ligands of this type have been used for the formation of small Pd₂L₄ cages but have never been shown to be applicable for larger structures.^[16b-d] As the above interactions should limit the flexibility of the bend angle, we reasoned that large cages could be accessible. Moreover, as minor deviations in the torsion angles can lead to an increase in the ligand bend angle, transformation to larger cage structures can potentially be facilitated just by heating; the energetic cost of the less favored conformation being compensated by the additional M-L bonds.

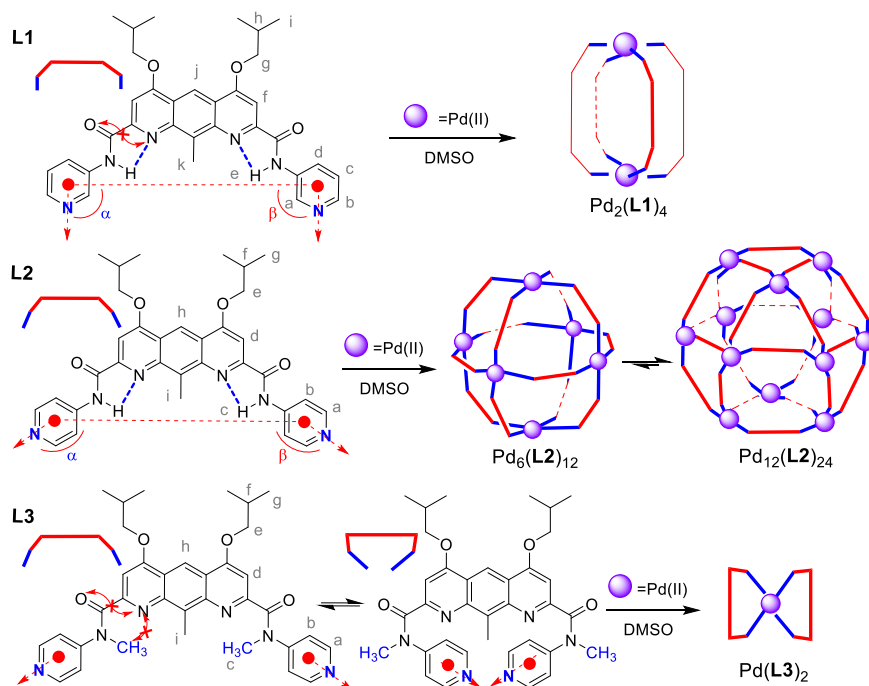


Figure 3.01 Design of ligands **L1-L3**, showing the important non-covalent interactions and the bend angle. Cartoon representations of the products of their self-assembly with Pd²⁺ are shown at the right. The angle between donor atoms on the ligands are calculated as: Bend angle = $(\alpha - 90^\circ) + (\beta - 90^\circ)$.

Based on this idea and to study how conformational preferences for the ligand can be used to control self-assembly, we developed ligands **L1-L3**, Figure 3.01. **L1** and **L2** favor the concave structures because of electrostatic/hydrogen bonding interactions, while **L3** lacks the above-mentioned N-H-N interactions and is expected to be more flexible. The X-ray structures of **L1** and **L2** indeed show the expected curved flat structures, Figure 3.02. To look at the restriction of the torsion angles around the amides and the flexibility of the ligand, molecular dynamics simulations were used to compare the properties of **L2** to the analogous structure lacking endocyclic nitrogens, **L4**, Figure 3.03. These indeed show that while the latter is wildly flexible, the two pyridyl moieties in **L2** prefer the conformation observed in the X-ray structure. Still, a range of bend angles is possible, potentially giving

access to multiple stable species. This variability can also be seen in the self-assembly of **L1**.

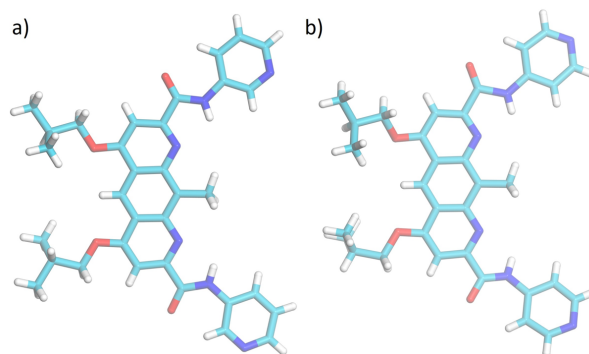


Figure 3.02. Crystal structure of a) ligand **L1** and b) ligand **L2**.

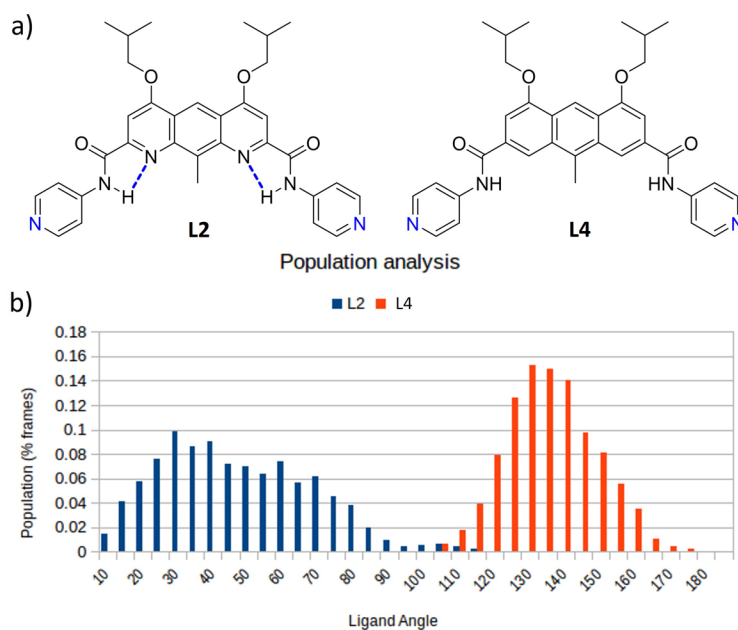
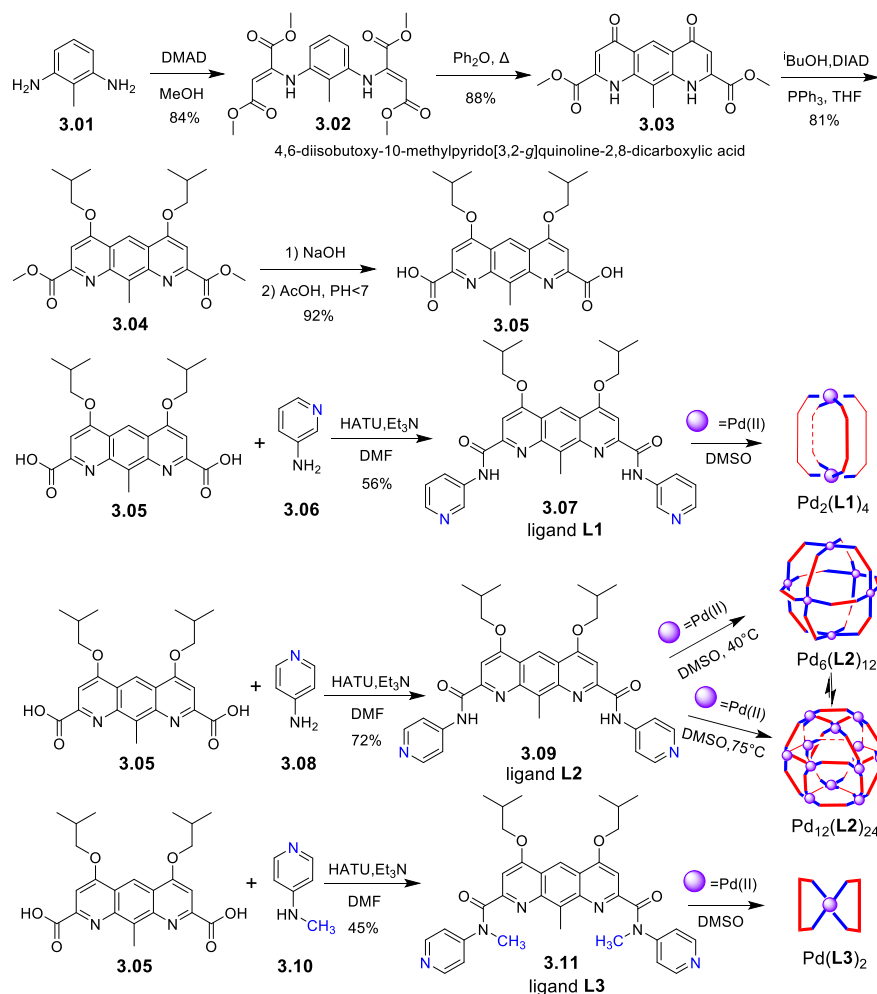


Figure 3.03 a) The structure of the ligands **L2** and **L4**, endohedral hydrogen bonding sites are shown for ligand **L2** with; b) population analysis of bend angle of ligands **L2** and **L4** using tight-binding molecular dynamics.



Scheme 3.01 Synthetic routes for ligands **L1-L3**, and their self-assembly with Pd²⁺ into metal-organic cages.

Ligands **L1-L3** were efficiently synthesized by an amide coupling of dicarboxylic acid 1,8-diazaanthracenes with the corresponding aminopyridine and used in this study as shown in scheme 3.01. All of the ligands are fully characterized by NMR and HR-MS and also by single-crystal X-ray diffraction for **L1** and **L2**. The monomer acid precursor of 1,8-diazaanthracene **3.05** was derived in four steps starting from 2,6-diaminotoluene **3.01** following described procedures. First, a Michael addition of dimethyl acetylenedicarboxylate (DMAD) with the appropriate 2,6-diaminotoluene **3.02** was performed,

followed by thermal cyclization in refluxing diphenyl ether at 260 °C to form 4,5-dihydroxy-9-methyl-1,8-diazaanthracenes **3.03**. Alkylation of this intermediate under Mitsunobu conditions gives product **3.04**. Subsequent saponification yields the 1,8-diazaanthracene diacid **3.05**, which was used for the amide couplings to give the ligands.

3. Self-assembly of metal-organic cages

3.1 Self-assembly of M_2L_4 capsule

Complexation of **L1** with Pd^{2+} (NO_3^- , BF_4^- , $CF_3SO_3^-$ or PF_6^- salt) in d^6 -DMSO, results in significant shifts of the proton resonances as depicted in the 1H NMR, Figure 3.04. The formation of a single species was supported by diffusion-ordered 1H NMR (DOSY), which shows all new signals having the same diffusion coefficient of $D = 7.49 \times 10^{-11} m^2/s$. The diffusion coefficient in hand, a radius of 13.4 Å can be estimated for the formed system using the Stokes-Einstein-Equation. HR-MS analysis suggests a complex with the formula $Pd_2(L1)_4(BF_4)_4$ being formed, based on a series of the isotopic pattern corresponding to the loss of two, three, and four BF_4^- counterions. The composition was further supported by its solid-state structure. Each of the palladium ions is found in a square planar N_4 coordination environment comprised of four pyridine units. The N-Pd-N bond angles are all between $\sim 89-91^\circ$ and the tetrahedral twist is less than 4° , indicating minimal distortion around the metal. The two Pd(II) ions are bridged by four ligands with a metal-metal distance of 13.3 Å. However, the curved structure of the ligands and the *iso*-butoxy side chains result in a larger diameter for the cage. Distances between terminal carbons on the side chains ranged between 22.9 - 26.7 Å, consistent with the value obtained by 1H DOSY.

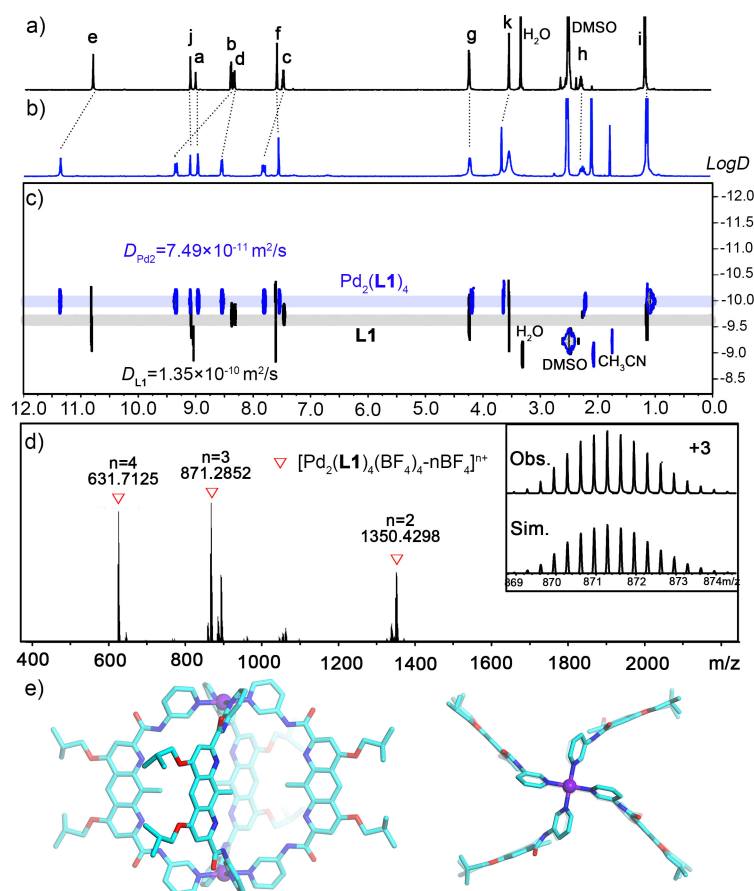


Figure 3.04 ^1H NMR spectra of a) **L1** and b) its self-assembly product $\text{Pd}_2(\text{L1})_4$. c) an overlay of the DOSY spectra of **L1** and $\text{Pd}_2(\text{L1})_4$. All signal assignments correspond to those shown in Figure 3.01. d) HR-MS for $\text{Pd}_2(\text{L1})_4$ as its BF_4^- salt. Inset shows the comparison of the observed isotopic pattern with the simulated spectrum. e) X-ray crystal structure of $\text{Pd}_2(\text{L1})_4$ with views perpendicular (left) and along (right) the Pd-Pd axis. Protons, solvent molecules and counterions are omitted for clarity.

3.2 Self-assembly of M_6L_{12} and $\text{M}_{12}\text{L}_{24}$ spheres

Importantly, compared to the crystal of free **L1**, where the bend angle is $\sim -36^\circ$, the average bend angle has increased to $\sim 0^\circ$ in the $\text{Pd}_2(\text{L1})_4$ complex. This difference can be partially attributed to distortions of the C-C-N (113° to

116° in complex) and C-N-C (128° to 124° in complex) angles of the amides. However, the pyridine amides are also twisted away from coplanarity with the central diaazanthracene by ~37-60°, further increasing the bend angle. Similar twisting was observed by Gan and co-workers for an analogous complex containing 9-fluorodiazaanthracene units.^[16b] These changes show that the bend angle of these ligands can adapt to form well-defined self-assembled structures at the expense of weakening the non-covalent interactions. The balance between flexibility and the rigidity imparted by these interactions should have important directing effects for the self-assembly of ligands with larger bend angles, such as **L2**.

To study this, the self-assembly of **L2** with Pd²⁺ (NO₃⁻, BF₄⁻, CF₃SO₃⁻ or PF₆⁻ salt) was followed by ¹H NMR. Within ten minutes of mixing **L2** with Pd²⁺ at 75°C in DMSO, the ligand is converted into a single high symmetry species, Figure 3.05. Once formed, this species can be kept in solution at room temperature with no discernable change observed over the course of at least several days. ¹H DOSY experiments on this complex indicate a discrete species with $D = 4.21 \times 10^{-11} \text{ m}^2/\text{s}$, corresponding to a radius of 23.8 Å. This size fits within the calculated dimensions of a Pd₆(**L2**)₁₂ cage structure ($18.8 < r_{\text{calcd}} < 29.2$ Å), *vide infra*, and is comparable to sizes for M₆L₁₂ structures with similar distances between the N-donor atoms.^[7e] Further evidence for the Pd₆(**L2**)₁₂ was obtained by cold-spray ionization mass spectrometry (CSI-MS) on the BF₄⁻ salt of the compound, Figure 3E. A series of isotopic patterns corresponding to [Pd₆(**L2**)₁₂(BF₄)_{12-n}BF₄]ⁿ⁺ (n=4-9) were observed, which match well with the simulated isotopic spectra.

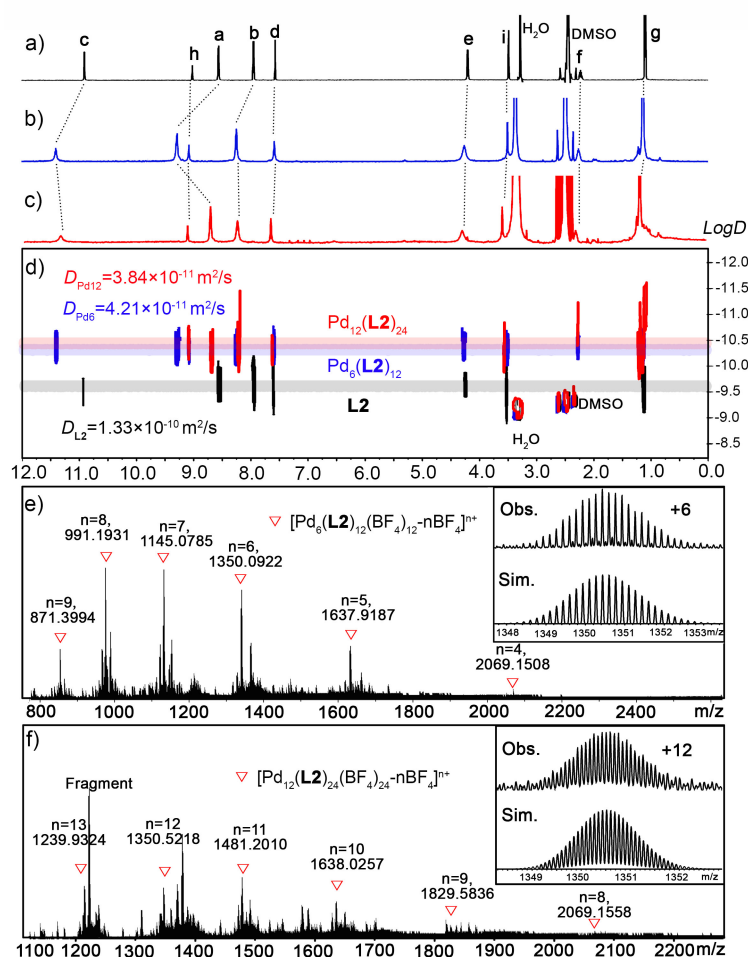


Figure 3.05 ^1H NMR spectra of a) **L2**, b) $\text{Pd}_6(\text{L2})_{12}$, and c) $\text{Pd}_{12}(\text{L2})_{24}$. d) An overlay of the DOSY spectra of **L2**, $\text{Pd}_6(\text{L2})_{12}$ and $\text{Pd}_{12}(\text{L2})_{24}$. Corresponding average diffusion coefficients are shown. e) Portion of the UHR CSI-MS for $\text{Pd}_6(\text{L2})_{12}$, and f) $\text{Pd}_{12}(\text{L2})_{24}$ as their BF_4^- salts. Insets show the comparison of the observed isotopic bundles with the simulated spectra.

After continued heating for one hour, $\text{Pd}_6(\text{L2})_{12}$ remains the major species in solution by ^1H NMR, however, a new set of signals starts to appear. These become the major species over the course of four hours giving spectra with a single set of signals, suggesting the formation of a large symmetric structure, Figure 3.05-3.06. When this change is followed by CSI-MS, the signals for

$\text{Pd}_6(\text{L}2)_{12}$ disappear and are replaced by a series of isotopic patterns corresponding to $[\text{Pd}_{12}(\text{L}2)_{24}(\text{BF}_4)_{24-n}\text{BF}_4]^{n+}$ ($n=8-13$), Figure 3.07. Consistent with this, a single diffusion band ($D = 3.84 \times 10^{-11} \text{ m}^2/\text{s}$) is seen in the ^1H DOSY spectrum indicating an object with a larger radius (26.4 Å) than the M_6L_{12} species, which based on the CSI-MS results is assigned to $\text{Pd}_{12}(\text{L}2)_{24}$.

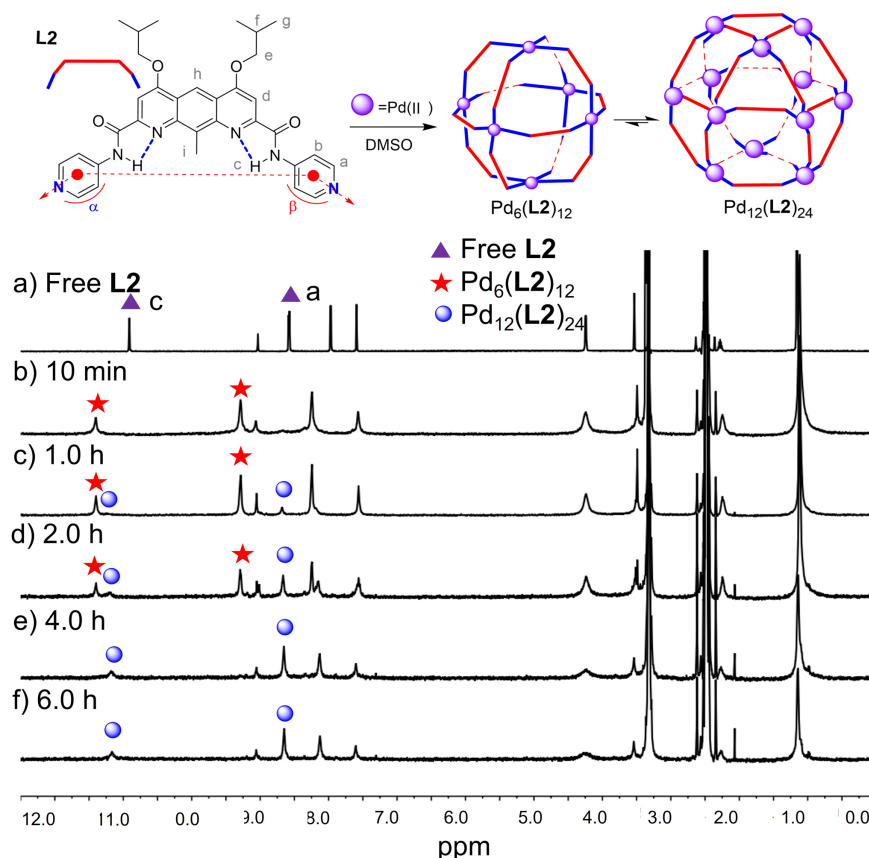


Figure 3.06 ^1H NMR (500 MHz, $\text{DMSO}-d_6$, 298 K) spectra of time-dependent self-assembly of ligand **L2** with 0.5 equivalent $\text{Pd}(\text{NO}_3)_2$ at 75°C .

Chapter III

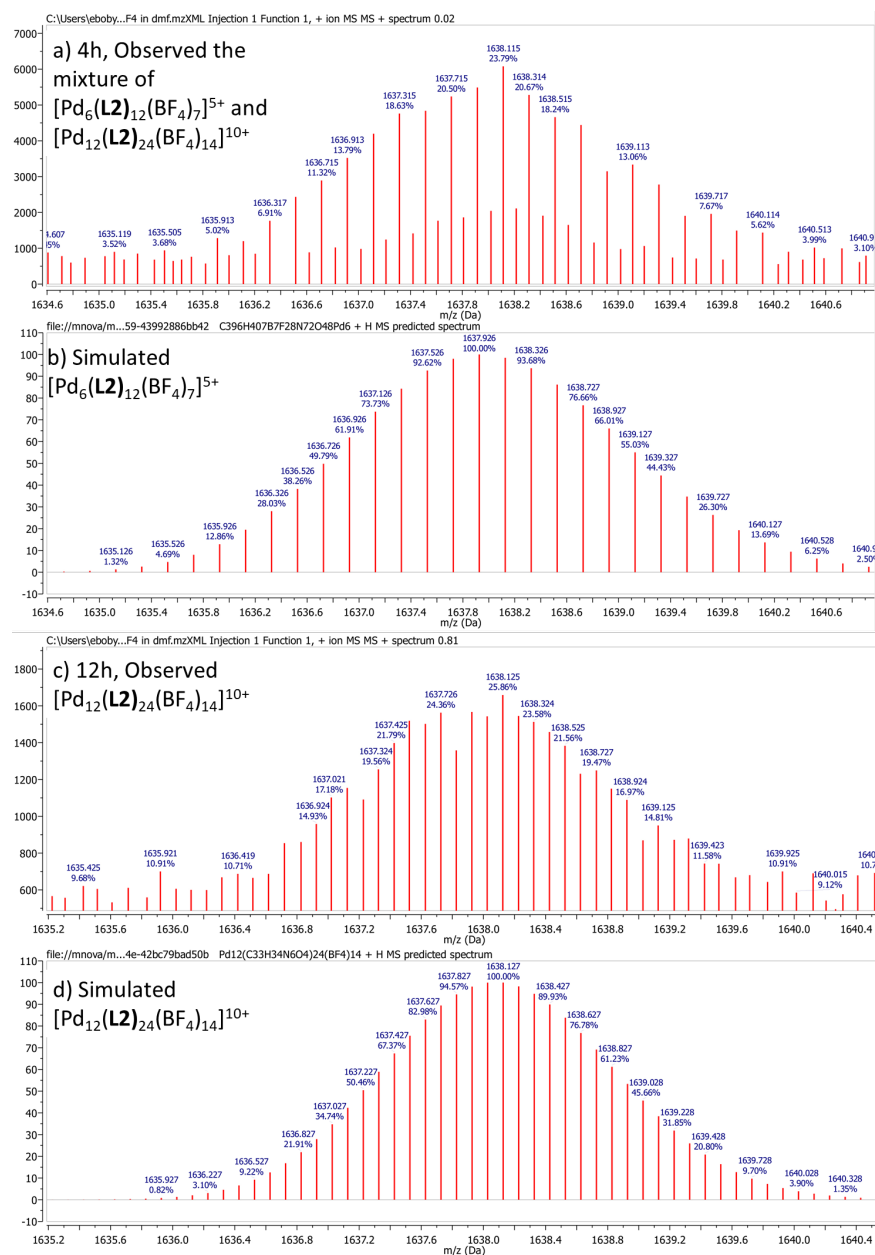


Figure 3.07 CSI-TOF mass expanded spectrum for time-dependent self-assembly of ligand **L2** with 0.5 equivalent $\text{Pd}(\text{CH}_3\text{CN})_4(\text{BF}_4)_2$ at 75°C , the intermediate M_6L_{12} charged species $[\text{Pd}_6(\text{L2})_{12}(\text{BF}_4)_7]^{5+}$ convert to the $\text{M}_{12}\text{L}_{24}$ charged species $[\text{Pd}_{12}(\text{L2})_{24}(\text{BF}_4)_{14}]^{10+}$ upon heating.

3.3 Control experiment

As the components of the solution are not changed and the self-assembly occurs with a range of counterions, the step-wise process may be rationalized based on the conformational control of the ligand. The *para* relationship in the amino-pyridine groups in **L2** results in an average free ligand bend angle of $\sim 82^\circ$, based on the X-ray structure. This value should favor the formation of the observed M_6L_{12} cage.^[7e] However, a 30° increase, as observed with **L1**, can permit the formation of the $M_{12}L_{24}$ cage.^[7f] While the latter should ultimately be thermodynamically favored,^[10b] a significant distortion from the preferred conformation of the ligand is needed. By contrast, the narrower angle needed for the former should be more easily accessible and the formed M_6L_{12} structure should further benefit from stronger intraligand non-covalent interactions.

For both cages, the control of the ligand conformation by the non-covalent interactions is important. This control has been well studied in aromatic oligoamide foldamers and numerous structures were reported to adoptable stable folded states both in solution and in solid-state.^[17] For the ligands, molecular dynamics simulations of **L2** to an analogous structure lacking endocyclic nitrogens **L4** indicate that non-covalent interactions in ligand were able to reduce the flexibility of the structure. However, the ligand **L4** being difficult to access by synthesis, we synthesized the tertiary amide ligand **L3** where the amide proton is replaced by a methyl group, which cannot participate in hydrogen bonding. This was used as a control ligand to look at the effects of the non-covalent interactions. In ligand **L3**, the increased flexibility does not permit the formation of the larger structures. The self-assembly of **L3** with $Pd^{2+}(NO_3^-, BF_4^-, CF_3SO_3^- \text{ or } PF_6^- \text{ salt})$ in all conditions was found to form the smallest mononuclear $Pd(L3)_2$ species due to its flexibility, Figure 3.08. The formation of a single mononuclear species was supported by 1H NMR and diffusion-ordered 1H NMR (DOSY), which shows one set of signals, which have the same diffusion coefficient of $D = 7.58 \times 10^{-11} m^2/s$. Thus, a complex with a radius of $13.2 \text{ \AA}$ can be estimated using the

Stokes-Einstein-Equation. HR-MS analysis also suggests a complex with the formula $\text{Pd}(\text{L3})_2(\text{BF}_4)_2$ was formed, based on a series of the isotopic pattern corresponding to the loss BF_4^- counterions. These experimental results indicate that the self-assembly behaviors of ligand **L3** were extremely different from its analog ligand **L2**, whose bend angles are controlled by non-covalent interactions. This further supports that the non-covalent interactions are essential for the self-assembly of the larger cages.

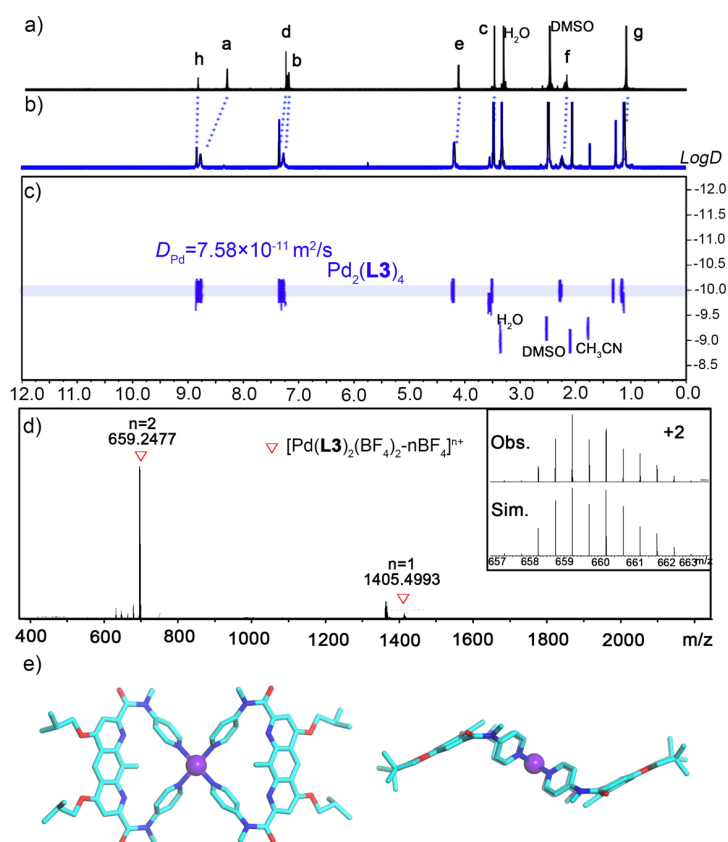


Figure 3.08 ^1H NMR (500 MHz, $\text{DMSO}-d_6$, 298 K) spectra of a) **L3** and b) its self-assembly product $\text{Pd}(\text{L3})_2$. c) DOSY spectra of $\text{Pd}(\text{L3})_2$. d) HR-MS for $\text{Pd}(\text{L1})_2$ as its BF_4^- salt. The inset shows the comparison of the observed isotopic pattern with the simulated spectrum. e). Computationally (PM6)

optimized structures of $\text{Pd}(\text{L3})_2$. Protons are omitted for clarity.

3.4 PM6 model of M_6L_{12} and $\text{M}_{12}\text{L}_{24}$ spheres

To look at changes in the ligands in the M_6L_{12} and $\text{M}_{12}\text{L}_{24}$ complexes, theoretical calculations at the semi-empirical PM6 level using Gaussian 09 were employed.^[18] The computed structures obtained for **L1**, **L2**, and $\text{Pd}_2(\text{L1})_4$ agree well with the structures determined by X-ray diffraction. The geometry-optimized structures proposed for $\text{Pd}_6(\text{L2})_{12}$ and $\text{Pd}_{12}(\text{L2})_{24}$, Figure 3.09, show highly symmetric assemblies with radii of 22 and 29 Å respectively, within range of the values determined from the ^1H DOSY studies. Relative to the calculated structure of free **L2**, noticeable distortions are present in both cages. First, the average bend angles have increased to 97° and 120° for $\text{Pd}_6(\text{L2})_{12}$ and $\text{Pd}_{12}(\text{L2})_{24}$ respectively. Unlike $\text{Pd}_2(\text{L1})_4$, the calculated C-C-N and C-N-C angles show only modest changes between the M_6L_{12} and $\text{M}_{12}\text{L}_{24}$ cages (114.8° vs 115.2° for C-C-N and 125.5° vs 124.7° for C-N-C). The difference in bend angle appears to result primarily from the twisting of the pyridine amides. Average torsion angles between the amides and the central aromatic units for the $\text{Pd}_6(\text{L2})_{12}$ and $\text{Pd}_{12}(\text{L2})_{24}$ structures are 36° and 55° respectively, versus an angle of nearly 0° in **L2**. For the free ligand, the observed coplanar conformation results from a combination of conjugation and dipole-dipole interactions. Deviation from this conformation to reach the larger bend angles should thus entail a weakening of these interactions. This can be seen in the intraligand hydrogen bonding, where the longer NH...N distance and smaller NH...N angle calculated for $\text{Pd}_{12}(\text{L2})_{24}$ (2.67 Å) versus $\text{Pd}_6(\text{L2})_{12}$ (2.48 Å) would be consistent with a weaker interaction. Conversely, the narrower ligand bend angle in $\text{Pd}_6(\text{L2})_{12}$ allows stronger intraligand interactions, which should help stabilize this intermediate during self-assembly.

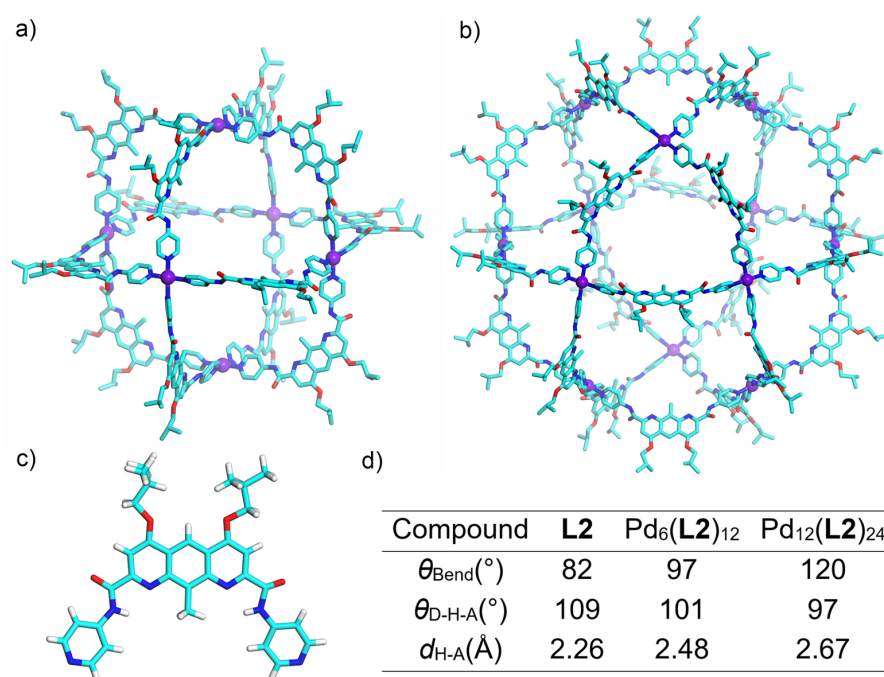


Figure 3.09 Computationally (PM6) optimized structures for a) $\text{Pd}_6(\text{L2})_{12}$, b) $\text{Pd}_{12}(\text{L2})_{24}$ and c) the crystal structure of **L2**. Protons in cages are omitted for clarity. d) Comparison of the bend angle and relevant intraligand hydrogen bonding geometric parameters for the structure of free **L2** versus in the ligands of the calculated structures of the M_6L_{12} and $\text{M}_{12}\text{L}_{24}$ cages.

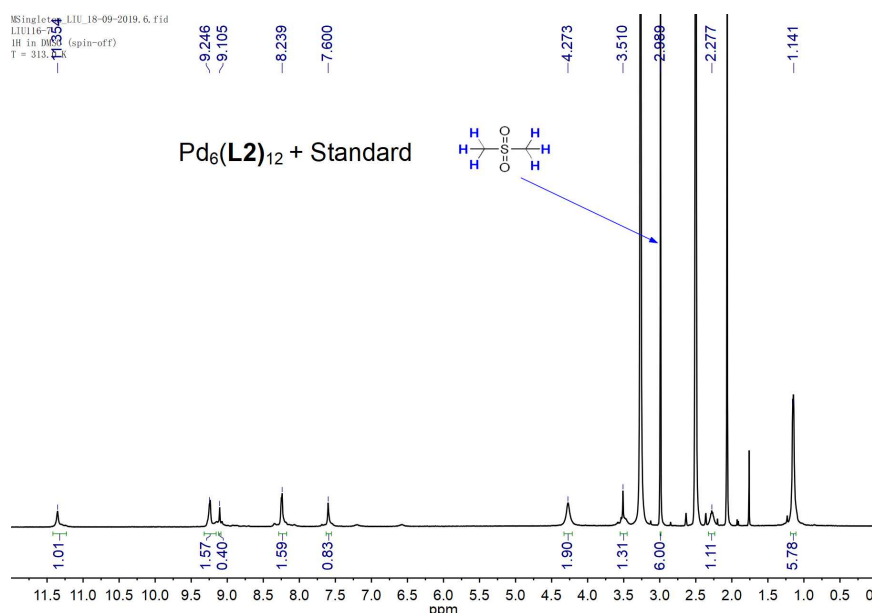
4. Higher-order supramolecular aggregation

Of note, during the self-assembly with **L2**, a decrease in signal intensity was observed in the NMR upon going from M_6L_{12} to $\text{M}_{12}\text{L}_{24}$. As shown in Table 3.01 and Figure 3.10, using methylsulfone as an internal standard showed that, while for $\text{Pd}_2(\text{L1})_4$ the ^1H NMR signals represent >90% of the initial ligand concentration, for $\text{Pd}_6(\text{L2})_{12}$ and $\text{Pd}_{12}(\text{L2})_{24}$ the signals correspond to 51% and 13% respectively. As no precipitation was observed, this was postulated to be due to aggregation of the complexes, a phenomenon previously observed with some metal-organic cages.^[19] Indeed, dynamic light scattering (DLS)

measurements on solutions of $\text{Pd}_2(\text{L1})_4$, $\text{Pd}_6(\text{L2})_{12}$ and $\text{Pd}_{12}(\text{L2})_{24}$ indicated the presence of well-defined particles with hydrodynamic radii of 63-85 nm, Figure 3.11-3.12. For $\text{Pd}_{12}(\text{L2})_{24}$, this was further confirmed by SEM analysis which found spherical particles with sizes consistent with radii determined by DLS. For the other two complexes, no particles were observed by SEM. This could be due to the lower concentration of the aggregates as indicated in the NMR. Additionally, the lower value of scattered light intensity (I/I_0) in the DLS studies of $\text{Pd}_6(\text{L2})_{12}$ suggests that the aggregates are present in small quantities in this sample.

Table 3.01 Summary of variable temperature studies for the self-assembled M_nL_{2n} complexes determined by ^1H NMR with internal standard (Ligand: methyl sulfone = 1:1).

Complexes	Yield(25 °C)	Yield(40 °C)	Yield(60 °C)	Yield(80 °C)
$\text{Pd}_2(\text{L1})_4$	96.7%	/	/	/
$\text{Pd}_6(\text{L2})_{12}$	50.8%	45.1%	40.4%	/
$\text{Pd}_{12}(\text{L2})_{24}$	12.7%	13.9%	17.7%	21.3%



Compound	NMR signal	Calcd H	Found H	Yield (%)
Standard	2.98 ppm	6	6.00	100
Pd ₆ (L2) ₁₂ complex	1.14 ppm	12	5.78	48.1
	2.27 ppm	2	1.11	55.5
	3.51 ppm	3	1.31	43.6
	4.27 ppm	4	1.90	47.5
	7.60 ppm	2	0.83	41.5
	8.24 ppm	4	1.59	39.7
	9.10 ppm	1	0.40	40.0
	9.24 ppm	4	1.57	39.2
	11.35 ppm	2	1.01	50.5
	Average			45.1

Figure 3.10 Example of using methylsulfone as an internal standard for determining self-assembly yield, ¹H NMR (500 MHz, DMSO-*d*₆, 313 K) spectra of self-assembled Pd₆(L2)₁₂ from ligand L1 with methylsulfone as an internal standard (L2: methylsulfone = 1:1), the average yield of Pd₆(L2)₁₂ determined to 45.1%.

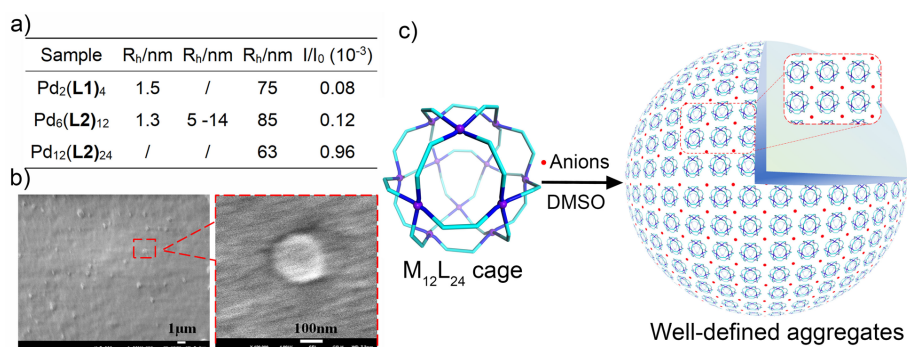


Figure 3.11 a) CONTIN size distribution obtained by DLS data for the three complexes; b) SEM of Pd₁₂(L2)₂₄; c) Schematic illustration of self-assembly of M_nL_{2n} cages into well-defined aggregates determined by NMR, DLS and SEM.

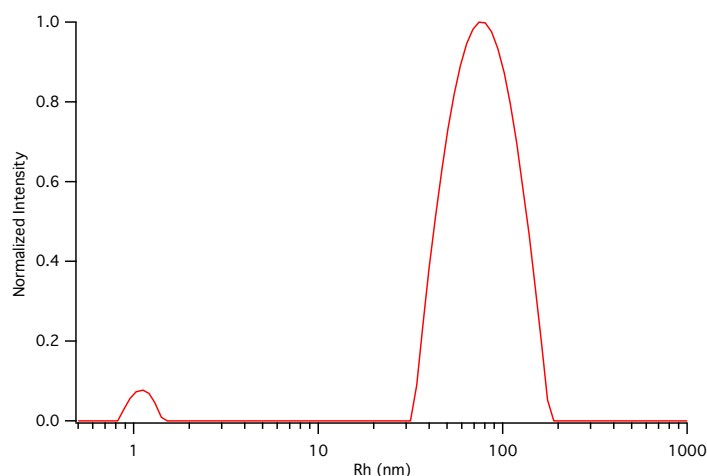


Figure 3.12 Example of using dynamic light scattering (DLS) to monitor the aggregation of the self-assembled complexes, CONTIN size distribution of $\text{Pd}_6(\text{L2})_{12}$ in DMSO ($c = 1\text{mg/mL}$).

As shown in Table 3.01, variable temperature NMR studies suggest that the aggregates are quite stable. Heating a DMSO sample of $\text{Pd}_{12}(\text{L2})_{24}$ gives a minor increase in intensity for the signals corresponding to the cage at 80°C . Nevertheless, this still only accounts for around 21% of the total ligand concentration, indicating only slight disaggregation. Similar results were obtained by variable temperature DLS studies. As reviewed in chapter 1 during the discussion of higher-order aggregates in metal-organic cages, the cooperative or competitive interplay of multiple attractive forces that lead to their formation includes electrostatic interactions, hydrophobic interactions, host-guest interactions, π - π stacking, Van der Waals interactions and hydrogen bonding. These were all reported as the driving force for the formation of various higher-order aggregates.^[19] Similar to the reported examples, our cages have large π -surface anthracenes as the central units in ligands with multiple aromatic amide hydrogen bonding donors and acceptors that could promote these different types of intermolecular interactions. However, although iso-butyl has been introduced in the design of ligands to increase the solubility of self-assembled cages in solution, the ligands still

have a quite low solubility in DMSO and DMF. Thus, solubility may be an important aspect for aggregates in our systems that may affect the process of self-assembly and the outcomes.

To understand the potential different mechanisms for the aggregate formation, we synthesized a new ligand **L5** with high solubility in DMSO, which was used for self-assembly and further study of aggregation, Figure 3.13. The solubility of ligand **L5** was increased by replacing the iso-butoxy side-chains with triethylene glycol monomethyl ether, following the same synthesis method for ligand **L2**. The self-assembly of **L5** with Pd^{2+} (NO_3^- , BF_4^- , CF_3SO_3^- or PF_6^- salt) was followed by ^1H NMR showing the same self-assembly behavior as its analog **L2**. However, even if the self-assembly conditions are carefully selected for the smaller M_6L_{12} cage rather than the $\text{M}_{12}\text{L}_{24}$ cage to reduce the possibility of aggregation, the dynamic light scattering (DLS) measurements on solutions of $\text{Pd}_6(\text{L5})_{12}$ still indicated the presence of well-defined particles with hydrodynamic radii of 65 nm. The aggregates in solutions of $\text{Pd}_6(\text{L5})_{12}$ are comparable with its analog $\text{Pd}_6(\text{L2})_{12}$, which indicates that the polyethylene glycol (PEG) functionalized ligand has a limited effect on the aggregation. Based on these results, it seems unlikely that aggregation in our system is caused only by the low solubility of ligands. Thus, a similar reported mechanism of aggregation through intermolecular interactions is proposed for our systems. These intermolecular interactions should include π - π stacking of intermolecular anthracenes and counterion-mediated attraction as the major driving forces for the self-assembly of higher-order aggregates. This was also supported by the observation that these intermolecular interactions, particularly π - π stacking, appear to be important in the crystal packing of $\text{Pd}_2(\text{L1})_4$ into well-organized frameworks.

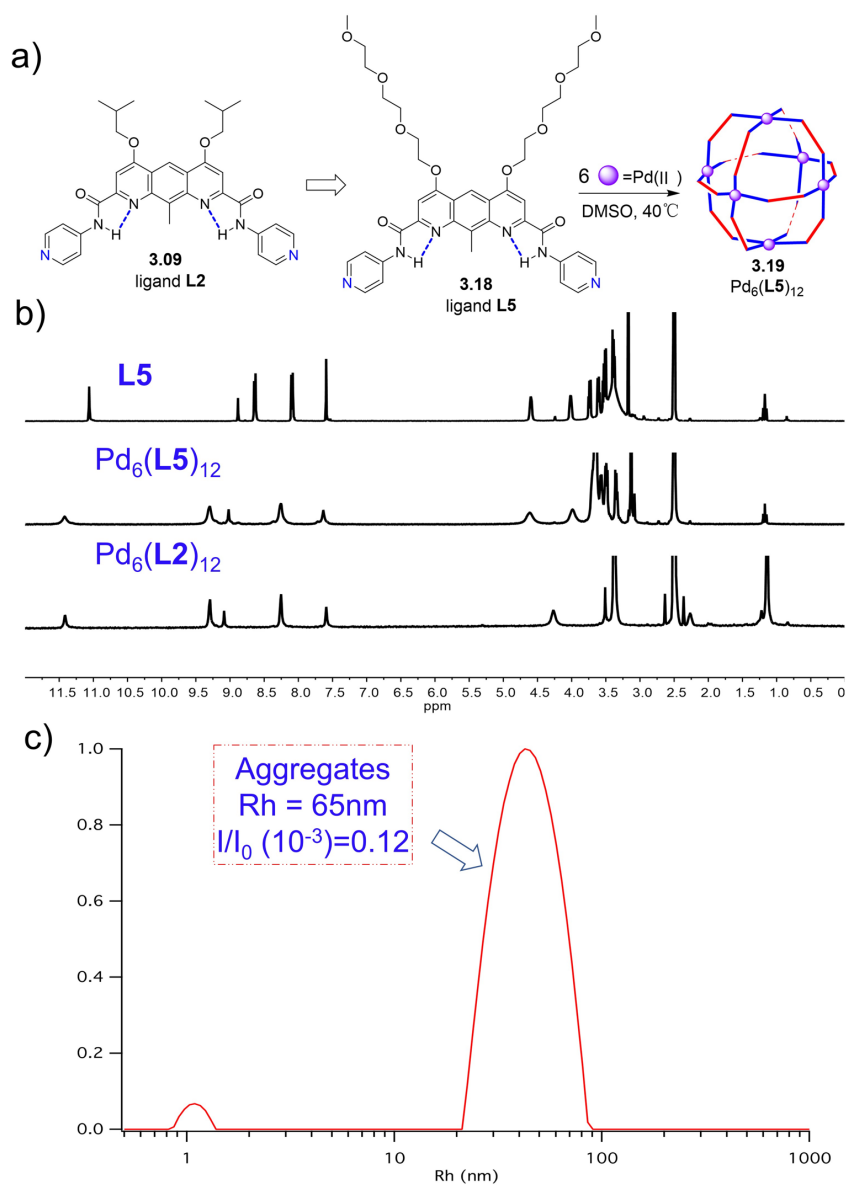


Figure 3.13 a) Optimized design of ligand **L5** with increased solubility in DMSO, b) ^1H NMR (500 MHz, $\text{DMSO-}d_6$, 298 K) spectra of **L5**, $\text{Pd}_6(\text{L5})_{12}$ and $\text{Pd}_6(\text{L2})_{12}$, c) CONTIN size distribution of $\text{Pd}_6(\text{L5})_{12}$ in DMSO ($c = 1 \text{ mg/mL}$).

5. Host-guest encapsulation

In addition to their structural role, the endohedral functionalization by the groups on the ligands can potentially assist in the binding and discrimination of guests. Indeed, the amides appear to interact with the included solvent molecules in the crystal structure of $\text{Pd}_2(\text{L1})_4$. While metal-organic cages have been widely exploited for host-guest chemistry, binding neutral guests in polar solvents is still challenging due to competition with counterions and favorable solvation of the guests.^[20] To look at the guest binding ability of the aromatic amides cages, we performed preliminary studies on the interaction of neutral guests pyromellitic diimide (**G1**) and pyromellitic dianhydride (**G2**) with the $\text{Pd}_2(\text{L1})_4$ cage, Figure 3.14-3.15. Both guests are highly soluble in DMSO. The addition of **G1** to a solution of $\text{Pd}_2(\text{L1})_4$ cage in d_6 -DMSO, resulted in obvious shifts in the proton resonances of the cage, including a noticeable upfield shift for the amide N-H and methyl resonances. NMR titrations for the host-guest binding suggest an affinity of $\sim 11 \text{ M}^{-1}$ in DMSO, Figure 3.16-3.17. Similar association constants in DMSO were reported for other Pd_2L_4 cages with polar nitrile-containing guests.^[20d] For the interaction between **G1** and the cage, aromatic stacking interactions likely play a role given the shielding observed for the majority of the ligand resonances in the presence of the guest. Still, the different binding between **G1** and **G2** indicates that hydrogen bonding interactions between the guest and the host C-H or N-H groups may also be important. The small downfield shift for the signal at 8.9 ppm suggests an interaction between the guest carbonyls and the 2-position C-H of the pyridines as has been previously observed in other cages.²⁰

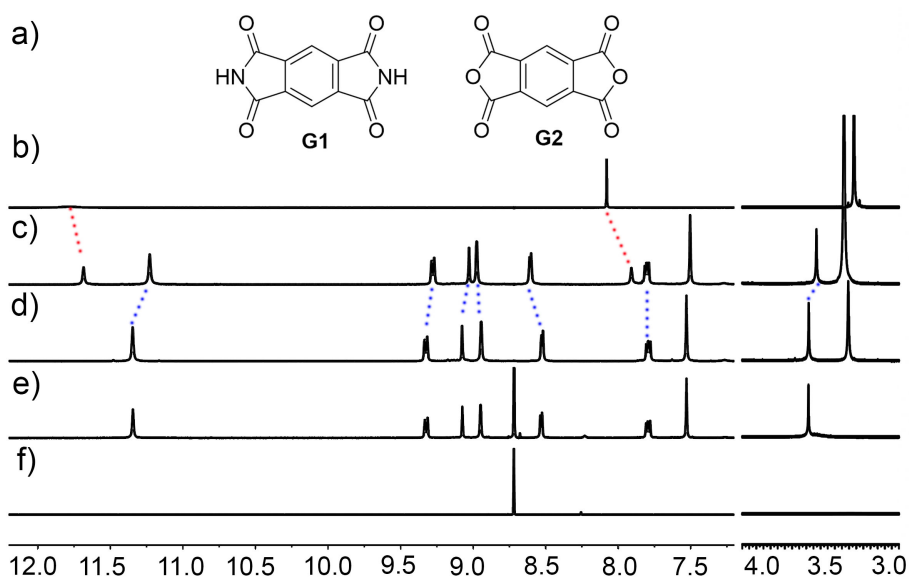


Figure 3.14 a) Chemical structures of neutral guests **G1** and **G2**, Partial ^1H NMR spectra of b) **G1**, c) $\text{Pd}_2(\text{L1})_4 + 2.0$ equivalent of **G1**, d) $\text{Pd}_2(\text{L1})_4$, e) $\text{Pd}_2(\text{L1})_4 + 4.0$ equivalent of **G2** and f) **G2**.

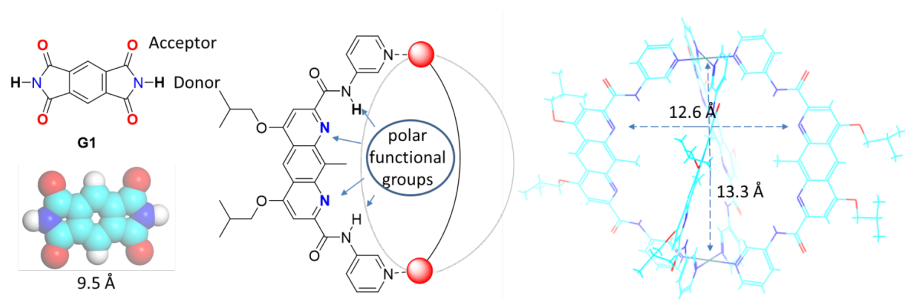


Figure 3.15 The amide and endocyclic nitrogens of the ligand offer additional sites for interaction with neutral guest molecules.

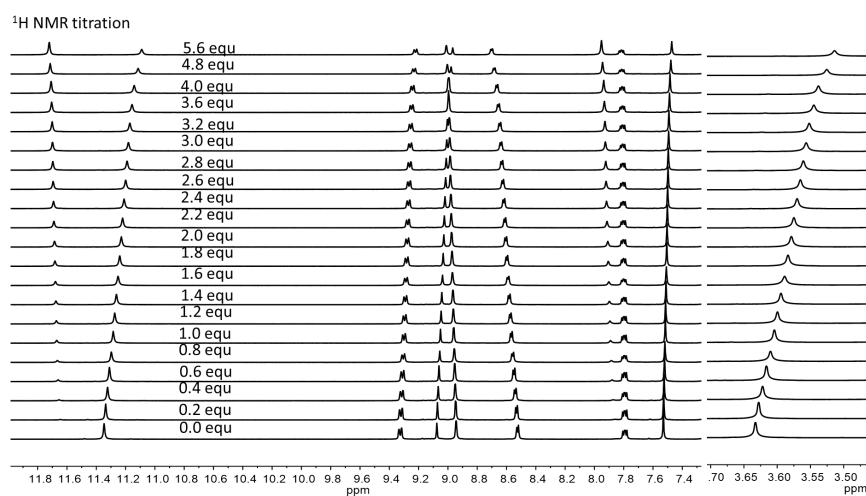


Figure 3.16 The ^1H NMR (500 MHz, $\text{DMSO}-d_6$) titration of $\text{Pd}_2(\text{L1})_4$ with pyromellitic diimide (**G1**) ($c=5\times 10^{-4}$ M).

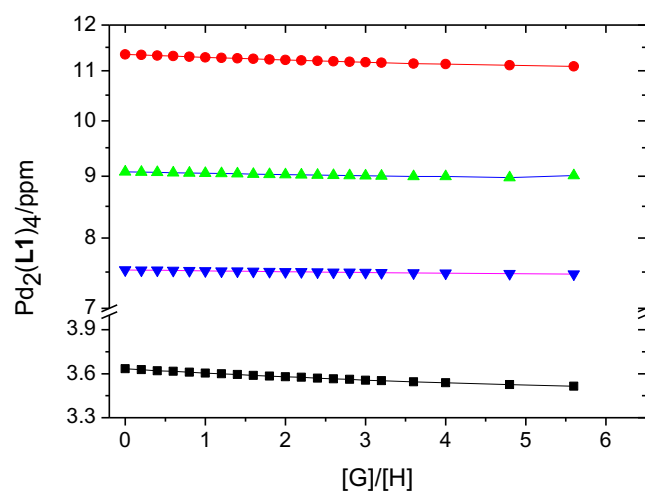


Figure 3.17 Fitted curves for change in the peak position of $\text{Pd}_2(\text{L1})_4$ host with different equivalents of pyromellitic diimide (**G1**) with an affinity of $\sim 11 \text{ M}^{-1}$ in DMSO .

6. Conclusion

In summary, we have shown that aromatic amide-based ligands are capable of self-assembling with Pd^{2+} to give access to multiple M_nL_{2n} ($n=2, 6$ and 12) metal-organic cages. The shape of these ligands is stabilized by non-covalent interactions. This bestows a rigidity that allows access to the larger structures, while at the same time permitting a moderate degree of flexibility so that the bend angle can adapt to both the M_6L_{12} and $\text{M}_{12}\text{L}_{24}$ cages. While the self-assembly of ligand **L2** eventually gives an $\text{M}_{12}\text{L}_{24}$ cage ($\sim 120^\circ$), the narrower bend angle ($\sim 97^\circ$) in the M_6L_{12} structure can allow for stronger intraligand non-covalent interactions. This can potentially stabilize it as a kinetic intermediate and allow for the unique step-wise self-assembly observed. Preliminary studies with $\text{Pd}_2(\text{L1})_4$ showed the potential for interaction and discrimination of charge-neutral guests in highly polar solvents. This can be potentially interesting for applications in catalysis.

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Chapter IV

Dual curvature ligands

Based on the promising results with endohedral non-covalent interactions for control self-assembly of large M_nL_{2n} polyhedral cages, this chapter develops a strategy for controlling more complex self-assembly with lower symmetry and flexible building blocks that combine the endohedral non-covalent interactions in dual curvature ligands with additional shape complementarity. A Diels-Alder reaction was used to break the symmetry of the diazaanthracene units in the previous series of ligands to give a series of dual curvature ligands with different shapes and endohedral groups (**L6-L18**). 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. Part of the work related to the organic synthesis and Diels-Alder reactions used for the ligands designed in this chapter was reported in F. Kerff, C-L Liu, et al. *ChemPlusChem* **2021**, 86, 1162-1166. The main work of this chapter has been finalized into a manuscript that will be published soon.

1. 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.^[1] Over the past decades, the possibility of generating synthetic molecules with similar complexity and functions has inspired significant progress in designing self-assembled cavitands.^[2] 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.^[3] Notably, the combination of Pd²⁺ or Pt²⁺ with ditopic ligands for the formation of M_nL_{2n} structures has attracted substantial attention and led to some of the largest well-defined systems.^[4] A wide range of applications related to the cavities of these structures has been reported, including sensing, catalysis, drug delivery, storage, and molecular recognition.^[5] Nevertheless, there remains a large disparity between these structures and those found in nature despite these advances.

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.^[6] 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.^[7] For example, with M_nL_{2n} assemblies, the ligands are most commonly flat curved organic molecules where N-heterocyclic donor groups are connected by aromatic or alkyne spacers, the rigidity of which allows the angle between coordination sites, the bend angle to be well-defined.^[4b,8] 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 design strategies and more complex structures.^[9] 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.^[10] The latter using additional functional groups included near the coordination sites on the ligands to provide complementarity interligand steric or electrostatic

interactions.^[11]

In the previous chapter, we succeed in using heteroaromatic amide-based ligands for the self-assembly of multiple Pd_nL_{2n} ($n=2, 6, \text{ or } 12$) 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.^[12] Nevertheless, these ligands are still best seen as flat and, based on our previous results, 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_nL_{2n} assemblies.^[4] 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 shown that the large diazaanthracene units used for our ligands are amenable to modification via Diels-Alder reaction leading to diazaptycene or triptycene units in the preliminary work of the chapter.^[13] 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 ligands, would add an additional curvature to their structure perpendicular to the curvature that defines the bend angle. In this chapter, we demonstrate that this dual curvature, combined with the electrostatic interactions that dictate the bend angle, can direct self-assembly towards a single M_2L_4 cage or M_4L_8 double-walled metallomacrocycle out of hundreds of possible isomers, Figure 4.01. 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.

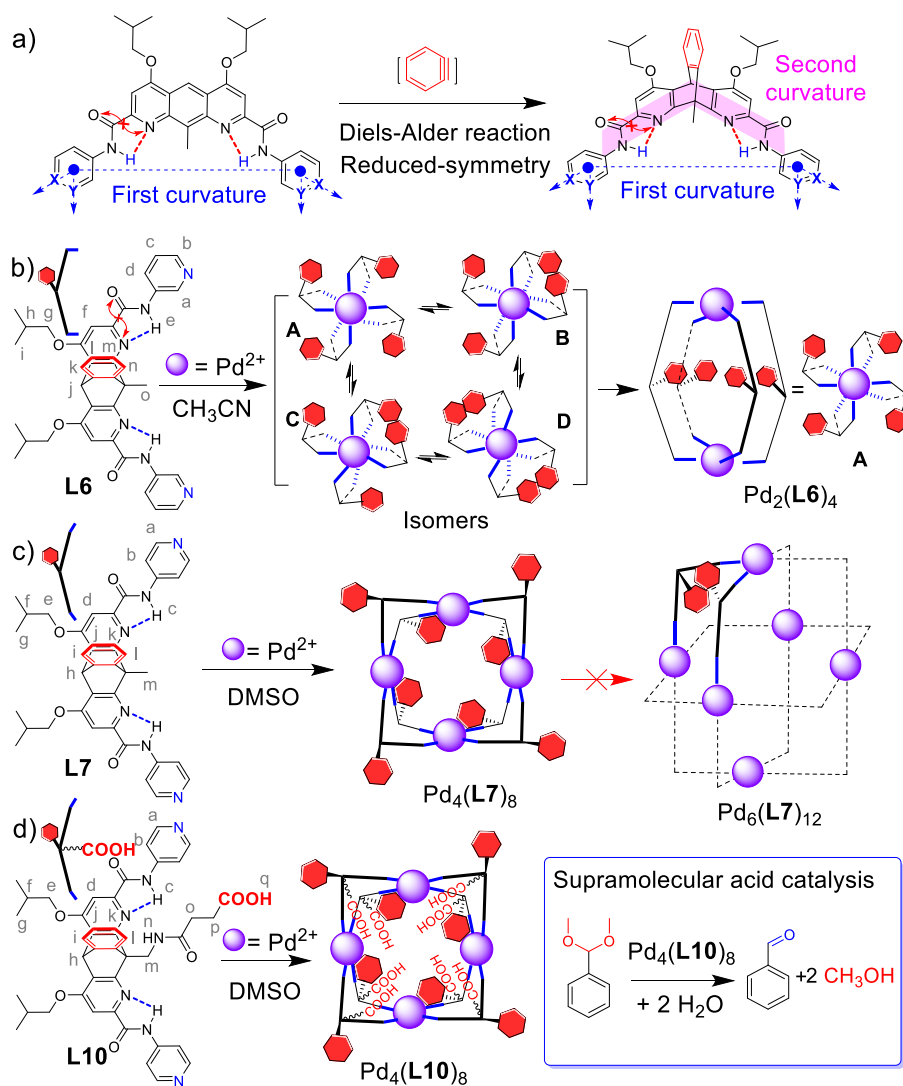
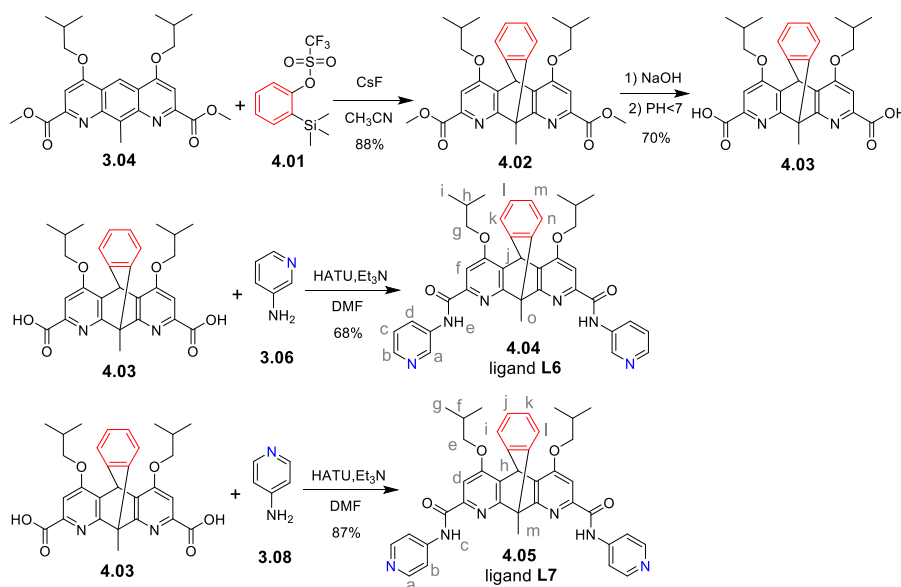


Figure 4.01 a) Reduced-symmetry of the formed triptycene structures by cycloaddition of benzyne into 1,8-diazaanthracenes; b-d) the structure of ligands **L6**, **L7**, **L10** and their self-assembled products.

2. Initial ligand design and synthesis

Diazatriptycene ligands **L6** and **L7** were synthesized in three steps, Scheme 4.01, starting with a [4+2] cycloaddition between in situ generated benzyne

4.01 and a functionalized 1,8-diazaanthracene-2,7-dicarboxylate ester **3.04**. Subsequent saponification and amide coupling with either 3-aminopyridine or 4-aminopyridine gave compound **4.04** (ligands **L6**) and compound **4.04** (ligand **L7**), 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 4.01. 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 to help control the self-assembly.



Scheme 4.01 Synthetic procedures for compound **4.04** (ligands **L6**) and compound **4.05** (ligand **L7**).

3. Self-assembly with **L6** and **L7**

Complexation of **L6** with Pd²⁺ (NO₃⁻, BF₄⁻, CF₃SO₃⁻, or PF₆⁻ salt) in a 2:1 molar ratio in CD₃CN or D₇-DMF at 40 °C results in a clear yellow solution. The ¹H NMR spectrum shows a single sharp set of signals with the same number of resonances as the starting ligand after two hours, Figure 4.02. However, relative to **L6**, significant shifts to several resonances are observed. Notably,

the 2- and 6-position protons of the pyridine groups appear further downfield, implying the formation of coordinative pyridine-Pd(II) bonds. Together, these observations suggest forming a single symmetric species derived from the interaction of **L6** 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. Electrospray ionization time-of-flight mass spectrometry (ESI-TOF-MS) further supported this assignment; a series of isotopic patterns corresponding to [Pd₂(**L6**)₄(BF₄)_{4-n}BF₄]ⁿ⁺ (n=2-4) were observed, Figure 4.02.

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 4.04-4.05. These nevertheless appear to converge to a single stable species, and time-dependent NMR studies of the self-assembly of **L6**, even at room temperature, did not show any clear signs of other isomers forming as intermediates, Figure 4.03. Within ten minutes of mixing the ligand with Pd²⁺ ions, a clear solution was obtained. While the ¹H NMR of the solution exhibited relatively broad signals with low intensity, ESI-TOF-MS analysis of the solution mainly found Pd₂(**L6**)₄(BF₄)₄ suggesting the composition of this mixture was mainly 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. Relative to the possibility for different conformations, the conjugation and electrostatic interactions around the amides give high control over the ligand conformation, limiting the likelihood that isomers derived from different configurations of the amides should form, even with this new backbone in **L6**.

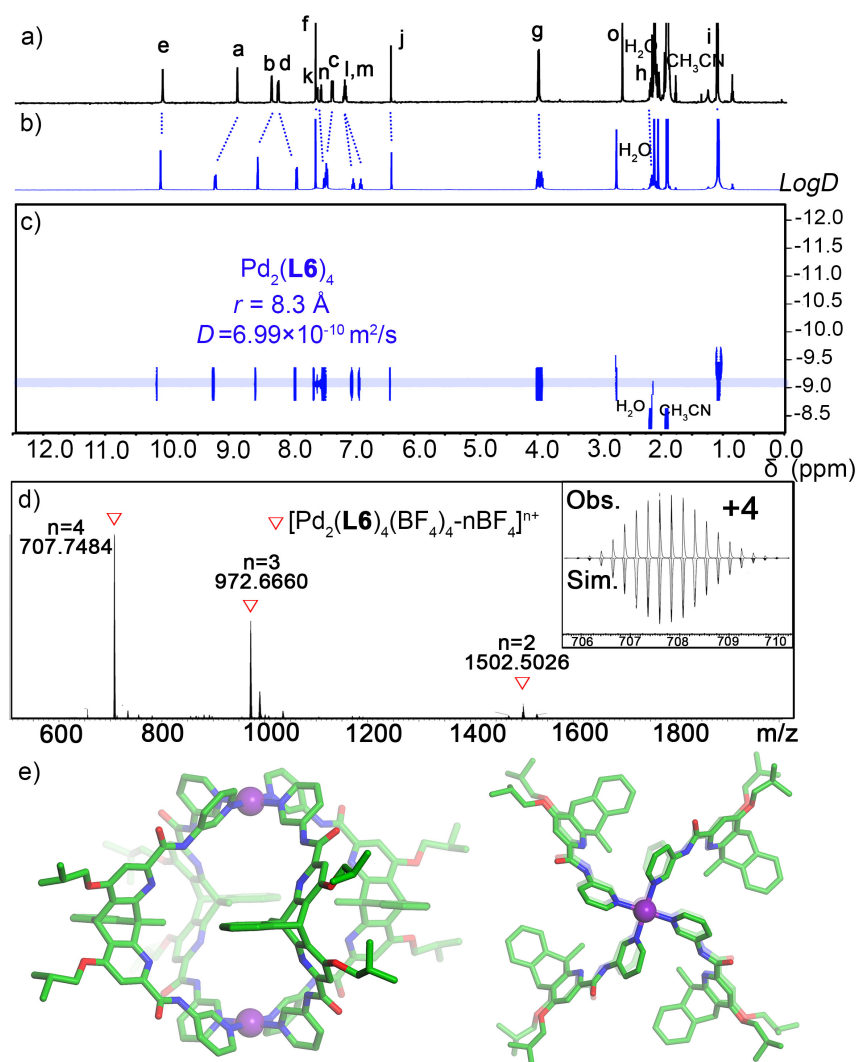


Figure 4.02 ^1H NMR spectra (500 MHz, CD_3CN , 298 K) of ^1H NMR spectra of a) **L6** and b) its self-assembly product $\text{Pd}_2(\text{L6})_4$. c) the DOSY spectra of $\text{Pd}_2(\text{L6})_4$. d) ESI-TOF-MS for $\text{Pd}_2(\text{L6})_4$ as its BF_4^- salt. Inset shows the comparison of the observed isotopic pattern with the simulated spectrum. e) X-ray crystal structure of $\text{Pd}_2(\text{L6})_4$ with views along (left) and perpendicular (right) the Pd-Pd axis. Protons, solvent molecules and counterions are omitted for clarity.

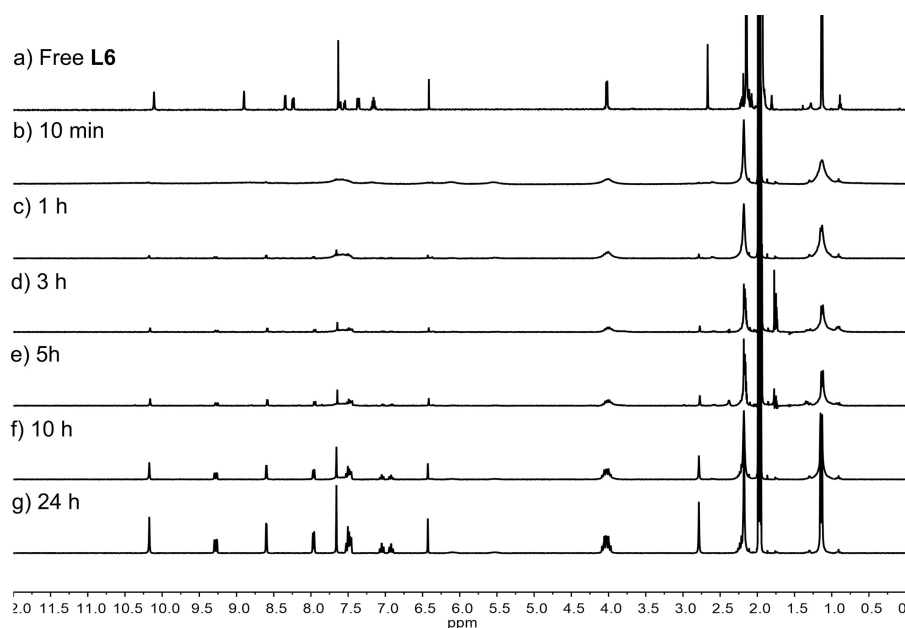
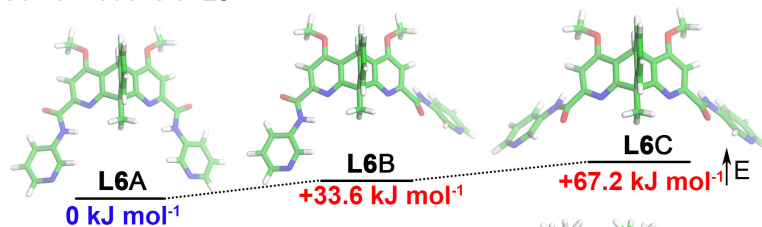


Figure 4.03 ^1H NMR spectra of time-dependent self-assembly of ligand **L6** with 0.5 equivalent $\text{Pd}(\text{CH}_3\text{CN})_4(\text{BF}_4)_2$ in CD_3CN at room temperature.

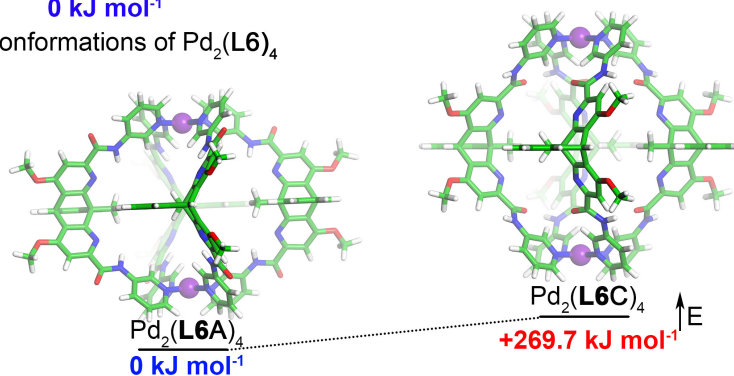
Density functional theory (DFT) computational studies (B3LYP/6-31g*) support that the *anti*-conformation(**L6A**) between the amides of ligand **L6** (possible ligand isomers, **L6A**, **L6B**, and **L6C**) should be favored by almost 30 kJ/mol in the self-assembly solvent (CH_3CN), Figure 4.04. Similar DFT computational studies (B3LYP/def2SVP) on the other potential M_2L_4 cage conformations also suggest that this preference should be maintained in the complex, Figure 4.04. Still, the lack of planar symmetry in the ligands could result in four different $\text{Pd}_2(\text{L6})_4$ isomers (A-D) with different *cis/trans* relationships between the 9,10-bridging groups. However, the additional curvature in the ligands, perpendicular to the bend angle curvature, should allow for good shape complementarity that directs single isomer formation in order to avoid steric interactions. Indeed, additional DFT studies comparing the four isomers estimated that isomer A, where the curves of the ligands are oriented in the same orientation, should be the most stable by ~40 kJ/mol. The higher energy for the three other isomers is likely resulting from steric interactions between nearby benzene rings in the diazatriptycene backbones

based on the calculated structures.

a) Conformations of L6



b) Conformations of $\text{Pd}_2(\text{L6})_4$



c) Isomers of $\text{Pd}_2(\text{L6})_4$

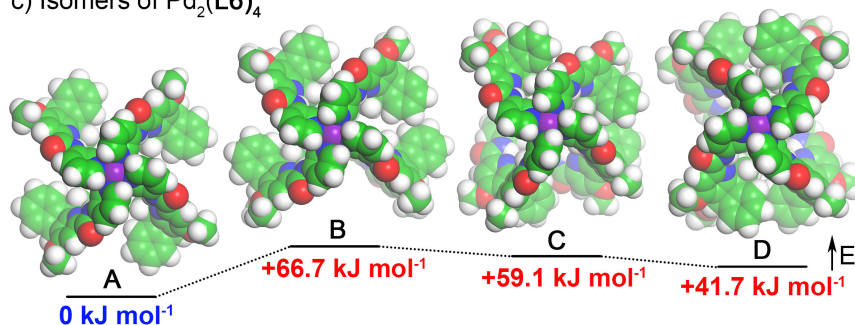


Figure 4.04 Density functional theory (DFT) calculated structures and relative energies(B3LYP/6-31g* for ligands and B3LYP/def2SVP for cages) of a) three possible conformations of ligand **L6** (**L6A**, **L6B** and **L6C**), b) $\text{Pd}_2(\text{L6})_4$ cage with two representative ligand conformations, and c) four possible steric isomers of $\text{Pd}_2(\text{L6})_4$ cage

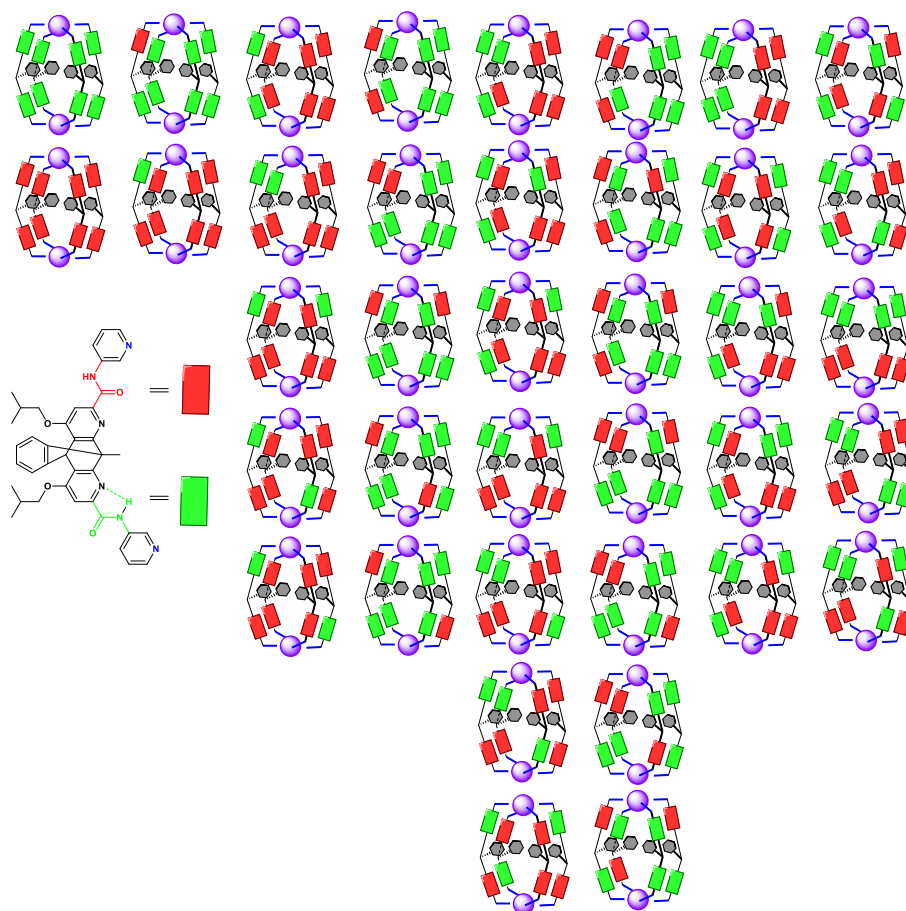


Figure 4.05 Schematic representation of up to 38 possible conformational isomers derived from amide conformations in isomer A of $\text{Pd}_2(\text{L6})_4$ cage.

Further support for the formation of isomer A came from its solid-state structure. Single crystals of $\text{Pd}_2(\text{L6})_4(\text{BF}_4)_4$ could be obtained and were studied by X-ray diffraction, Figure 4.02. The crystal structure of the complex shows two palladium ions, each in a square planar N_4 coordination environment, bridged by four units of **L6** with a Pd^{2+} to Pd^{2+} 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 carbonyls are all *anti* to the endocyclic nitrogens of the diazatriptycene units. Relative to

our previously reported Pd₂(**L1**)₄ cage in the last chapter, which had overall D_{4h} symmetry, the directionality of the triptycene units used for Pd₂(**L6**)₄ leads to a decrease in the symmetry of the cage to C_{4h}.

Motivated by the high selectivity observed with ligand **L6**, 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 **L7** was reacted with 0.5 equivalent Pd²⁺ (NO₃⁻, BF₄⁻, CF₃SO₃⁻, or PF₆⁻ salt) in D₆-DMSO or D₇-DMF, similar to self-assembly with **L6**, the ¹H NMR spectrum showed a single set of resonances distinct from the starting ligand, Figure 4.06. As expected, DOSY studies on this species suggested the formation of a larger structure ($D = 7.32 \times 10^{-11}$ m²/s; $r = 13.8$ Å). Similarly, self-assembly was followed up at room temperature by time-dependent ¹H NMR that confirmed the high selectivity of self-assembly leads to the formation of single species, Figure 4.07. However, as opposed to the M₆L₁₂ or M₁₂L₂₄ cages obtained previously with the analogous planar ligand **L2** in the previous chapter, ESI-TOF-MS analysis showed isotopic patterns consistent with the formation of an M₄L₈ assembly with the formula Pd₄(**L7**)₈(BF₄)₈.

This M₄L₈ composition was further confirmed by X-ray diffraction studies, and the crystal structure shows a deep crown-like double-walled metallomacrocyclic, Figure 4.06. The four palladium ions are found in the same plane and can be seen as occupying the four corners of an imaginary 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.

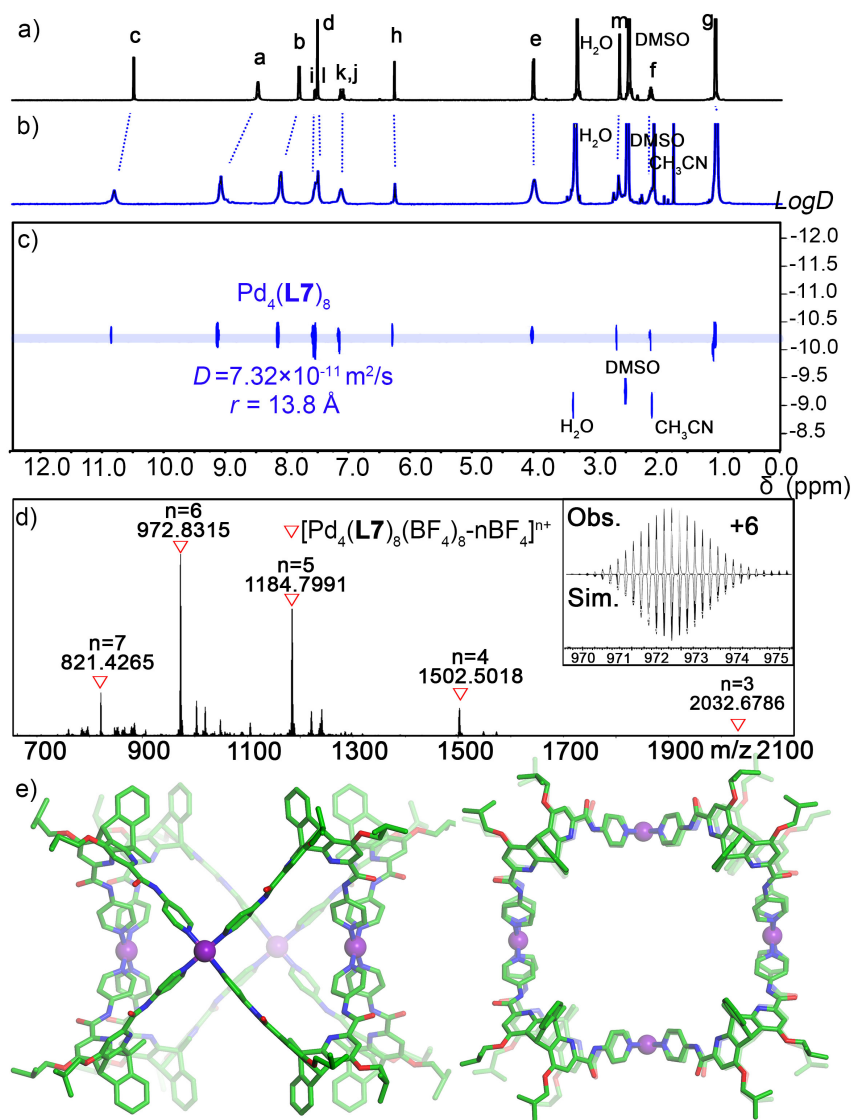


Figure 4.06 ^1H NMR spectra (500 MHz, $\text{DMSO}-d_6$, 298 K) of ^1H NMR spectra of a) L7 and b) its self-assembly product $\text{Pd}_4(\text{L7})_8$. c) the DOSY spectra of $\text{Pd}_4(\text{L7})_8$. d) ESI-TOF-MS for $\text{Pd}_4(\text{L7})_8$ as its BF_4^- salt. Inset shows the comparison of the observed isotopic pattern with the simulated spectrum. e) X-ray crystal structure of $\text{Pd}_4(\text{L7})_8$ with side view (left) and top view (right). Protons, solvent molecules and counterions are omitted for clarity.

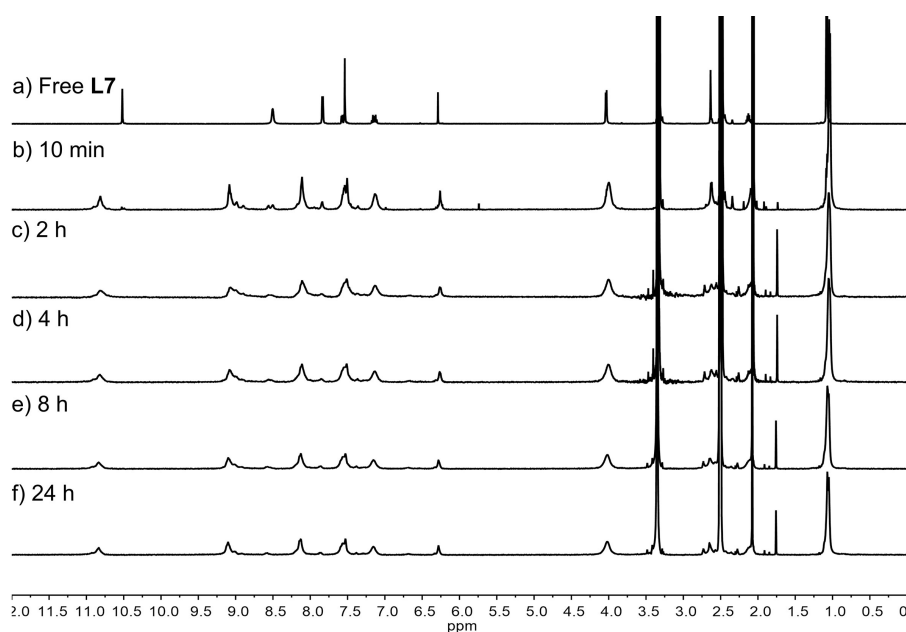


Figure 4.07 ^1H NMR spectra of time-dependent self-assembly of ligand **L7** with 0.5 equivalent $\text{Pd}(\text{CH}_3\text{CN})_4(\text{BF}_4)_2$ in $\text{DMSO}-d_6$ at room temperature.

Interestingly, the bend angle for the ligands in the crystal structure of $\text{Pd}_4(\text{L7})_8$ is $\sim 70^\circ$, while the same bend angle in the DFT optimized structure of the free ligands was found to be 64° . In the previous chapter, 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.^[12] For example, M_6L_{12} and $\text{M}_{12}\text{L}_{24}$ structures, which require ideal bend angles around 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 $\text{Pd}_4(\text{L7})_8$ towards a larger $\text{Pd}_6(\text{L7})_{12}$ 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 structure in most M_6L_{12} octahedra containing eight adjacent 3-fold symmetry axes, with the dual curvature ligand **L7**, make it impossible for the ligands to be arranged in a way where they are all pointing away from each other, something that does occur with $\text{Pd}_4(\text{L7})_8$, Figure 4.08. Interestingly, no close contacts of the

complementary shapes, as seen in the isomers of $\text{Pd}_2(\text{L6})_4$, are observed in a PM6 model of a $\text{Pd}_6(\text{L7})_{12}$ octahedron. 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 M_6L_{12} structure may limit its stability.

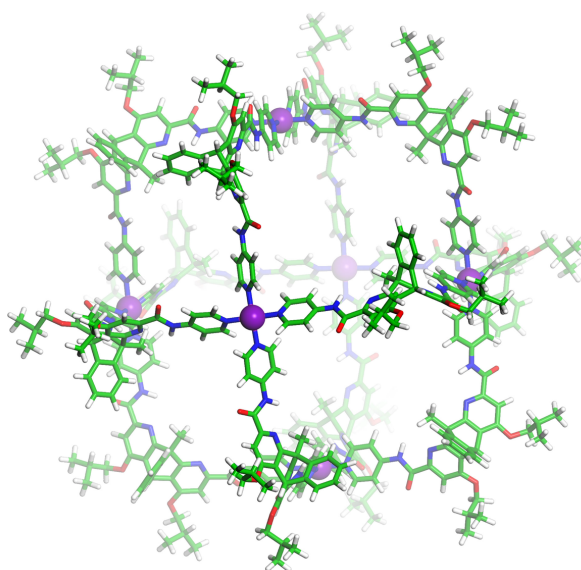


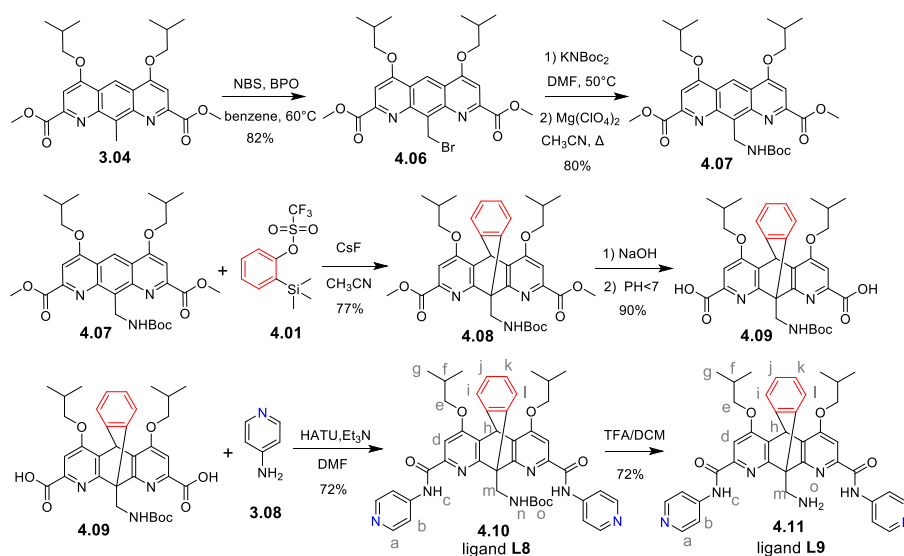
Figure 4.08 Optimized $\text{Pd}_6(\text{L7})_{12}$ cage PM6 model balancing steric hindrance and conformation with low-symmetry ligand **L7**.

4. Cage functionalization

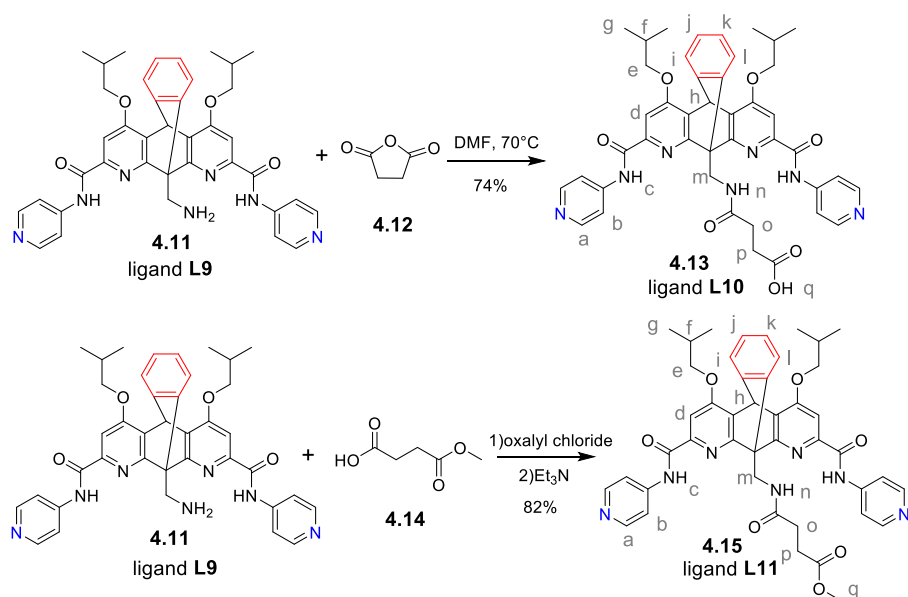
4.1 Acid-base functionalization

While the smaller cavity in $\text{Pd}_2(\text{L6})_4$ limits the potential for having both endohedral functionalization and guest binding, the larger M_4L_8 structure is an intriguing scaffold for designing functional groups lined cavities 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 **L10** bearing a carboxylic acid function of high interest for self-assembly of functional supramolecular catalyst was synthesized as shown in Scheme 4.02-4.03. According to reported procedures,^[14] the 9-methyl in the precursor 1,8-diazaanthracene-2,7-dicarboxylate ester **3.04** can be easily functionalized into a Boc-protected 9-methylamino diazaanthracene derivative **4.07**. Based on this Boc-protected 9-methylamino diazaanthracene derivative, the pyridine coordination sites were installed in a manner analogous to **L7**, i.e., saponification followed by HATU coupling with 4-aminopyridine. Subsequent amine deprotection and reaction with succinic anhydride allowed the incorporation of a flexible chain with a terminal carboxylic acid group for **L10** and a protected methyl carboxylate group for **L11**. The intermediate product of compound **4.10** (ligand **L8**) and compound **4.11** (ligand **L9**) that formed during the acid functionalization process can also be used as base functionalization.



Scheme 4.02 Synthetic procedures for compound **4.10** (ligands **L8**) and compound **4.11** (ligand **L9**).



Scheme 4.03 Synthetic procedures for compound **4.13** (ligands **L10**) and compound **4.15** (ligand **L11**).

The endohedral carboxylic acid may compete with metal-ligand interactions during self-assembly. This group has been reported to be a good ligand for metal complexes, metal-organic cages, and metal-organic frameworks.^[3b, 15] Nevertheless, self-assembly proceeded without any problems. Upon reaction of **L10** with Pd²⁺ (NO₃⁻, BF₄⁻, CF₃SO₃⁻, or PF₆⁻ salt), in a 2:1 molar ratio in D₆-DMSO or D₇-DMF, similar changes as for self-assembly with **L7**, i.e., a single set of signals shifted relative to the free ligand, are seen by ¹H NMR, Figure 4.09-4.10. Given the similar bend angles expected for **L7** and **L10**, self-assembly with the functionalized ligand should also lead to an M₄L₈ structure. This was supported by DOSY studies ($D = 7.55 \times 10^{-11} \text{ m}^2/\text{s}$; $r = 13.4 \text{ \AA}$), which suggested the formation of a complex with a size similar to parent Pd₄(**L7**)₈.

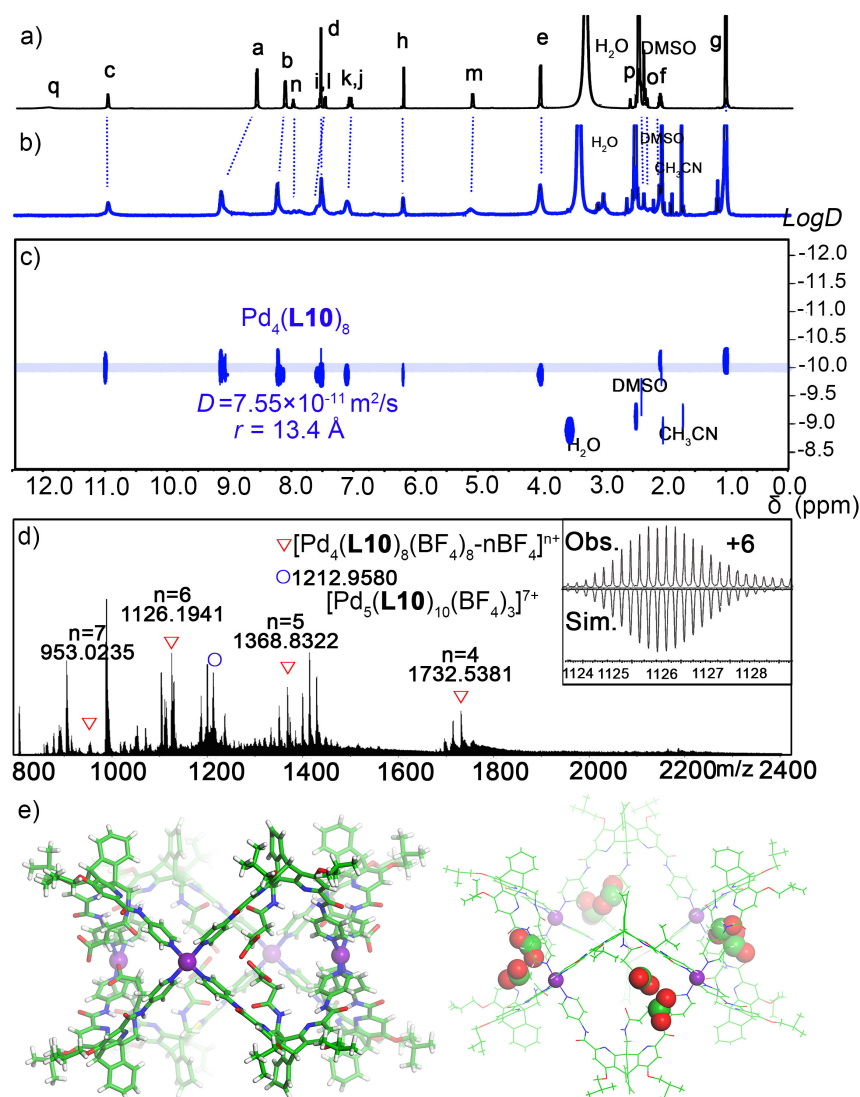


Figure 4.09 ^1H NMR spectra (500 MHz, $\text{DMSO}-d_6$, 298 K) of ^1H NMR spectra of a) L10 and b) its self-assembly product $\text{Pd}_4(\text{L10})_8$. c) the DOSY spectra of $\text{Pd}_4(\text{L10})_8$. d) ESI-TOF-MS for $\text{Pd}_4(\text{L10})_8$ as its BF_4^- salt. Inset shows the comparison of the observed isotopic pattern with the simulated spectrum. e) X-ray crystal structure of $\text{Pd}_4(\text{L10})_8$ with side views (left) and highlight the 9-position endohedral carboxylic acids (right). Protons, solvent molecules and counterions are omitted for clarity.

The $\text{Pd}_4(\mathbf{L10})_8(\text{BF}_4)_8$ formula was further confirmed by ESI-TOF-MS, though minor signals for an M_5L_{10} structure could also be observed. The presence of the more bulky group on the 9-position of **L10** relative to **L7** may lead to this minor formation of some of the larger macrocycles.^[16] Still, the X-ray crystal structure of $\text{Pd}_4(\mathbf{L10})_8$ did not show any apparent distortions and was highly similar to the $\text{M}_4(\mathbf{L7})_8$ structure, Figure 4.09. 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, which will be discussed later in this chapter.

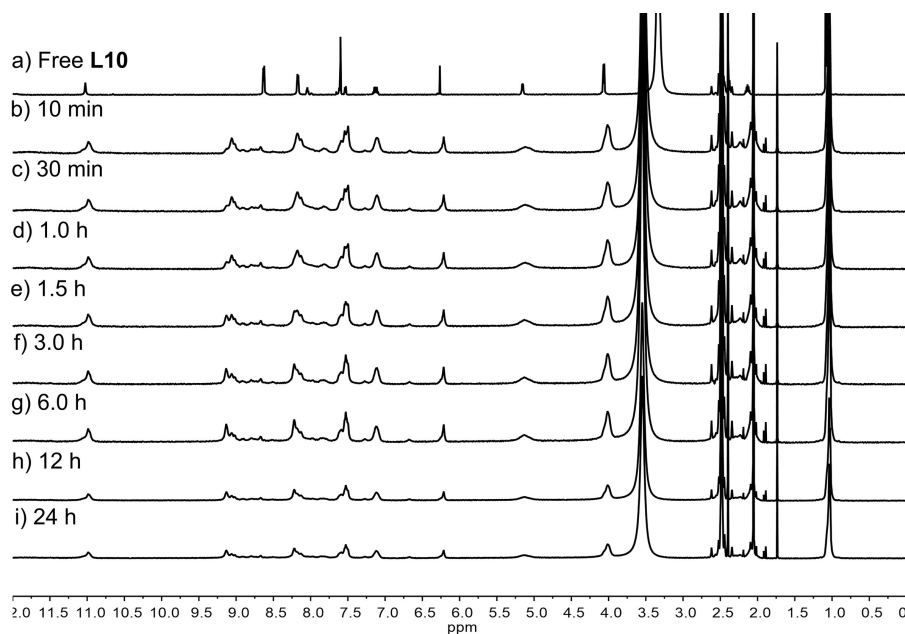


Figure 4.10 ^1H NMR spectra of time-dependent self-assembly of ligand **L10** with 0.5 equivalent $\text{Pd}(\text{CH}_3\text{CN})_4(\text{BF}_4)_2$ in $\text{DMSO}-d_6$ at room temperature.

Similar to parent ligand **L7** and acid-functionalized ligand **L10**, the self-assembly of ligand **L11** with a protected methyl carboxylate group was studied.

As expected, upon the reaction of **L11** with Pd^{2+} (NO_3^- , BF_4^- , CF_3SO_3^- , or PF_6^- salt), in a 2:1 molar ratio in D_6 -DMSO or D_7 -DMF results in a single set of signals shifted relative to the free ligand in ^1H NMR, Figure 4.11. ESI-TOF-MS confirmed the formula of the assembly was $\text{Pd}_4(\text{L11})_8(\text{BF}_4)_8$, Figure 4.12. Still, minor signals for an M_5L_{10} structure could also be observed in ESI-TOF-MS as the same possible effect of the endohedral bulky group.

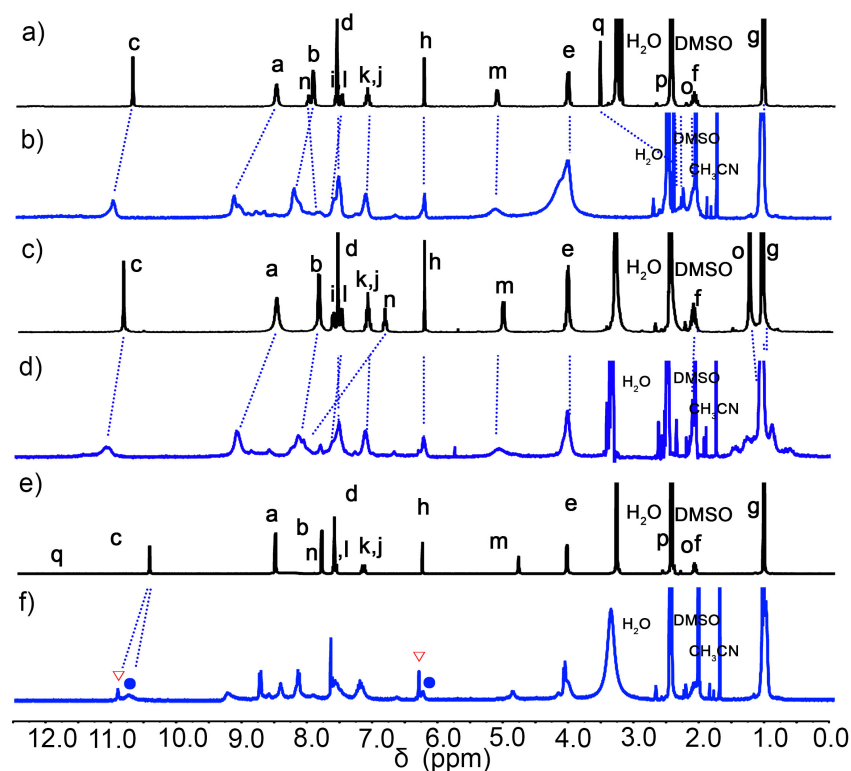


Figure 4.11 ^1H NMR spectra (500 MHz, $\text{DMSO}-d_6$, 298 K) of a) ligand **L11** and b) $\text{Pd}_4(\text{L11})_8$, c) ligand **L8**, d) $\text{Pd}_4(\text{L8})_8$, e) ligand **L9** and f) the self-assembly of **L9** with 0.5 equivalent $\text{Pd}(\text{CH}_3\text{CN})_4(\text{BF}_4)_2$.

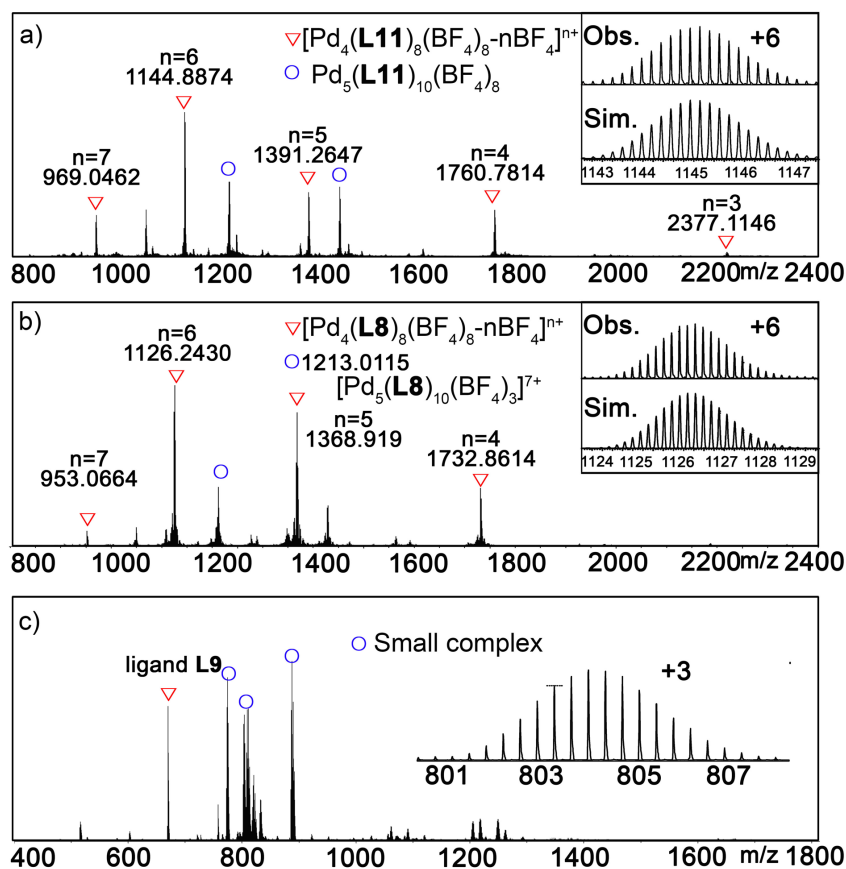


Figure 4.12 ESI-TOF-MS for M_4L_8 as their BF_4^- salt. a) $Pd_4(L11)_8$, b) $Pd_4(L8)_8$, c) the product of ligand **L9** with 0.5 equivalent $Pd(CH_3CN)_4(BF_4)_2$ showing no large assembly formed.

The successful self-assembly with these two functionalized ligands inspired our further interest in base-functionalized ligands **L8** and **L9**. Interestingly, self-assembly of the Boc protected ligand **L8** with Pd^{2+} (NO_3^- , BF_4^- , $CF_3SO_3^-$, or PF_6^- salt) under the same conditions used for the functionalized ligands **L10** and **L11** is still possible and also results in a single set of signals shifted relative to the free ligand in 1H NMR, Figure 4.11. As expected, DOSY studies on this species suggested the formation of a larger structure ($D = 7.24 \times 10^{-11} \text{ m}^2/\text{s}$; $r = 13.9 \text{ \AA}$) with the same size as its parent

cage $\text{Pd}_4(\text{L7})_8$ and acid functionalized $\text{Pd}_4(\text{L10})_8$. ESI-TOF-MS confirmed the formula of the assembly as $\text{Pd}_4(\text{L8})_8(\text{BF}_4)_8$ with again minor signals of $\text{Pd}_5(\text{L8})_{10}(\text{BF}_4)_{10}$. Importantly, we successfully obtained its X-ray crystal structure that unambiguously confirmed the $\text{Pd}_4(\text{L8})_8$ structure, Figure 4.13. Still, the BOC groups, the anions and solvent molecules are very disordered and tricky to refine.

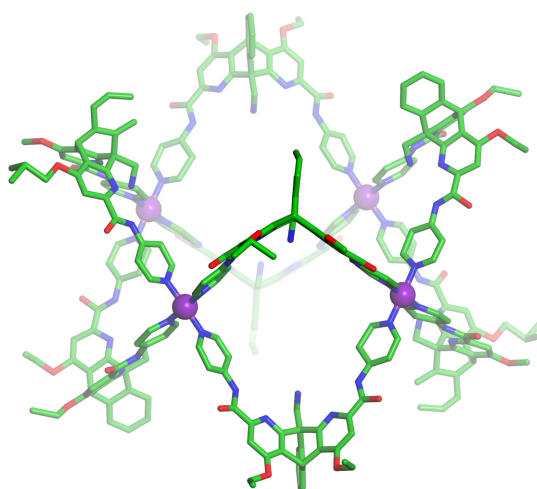
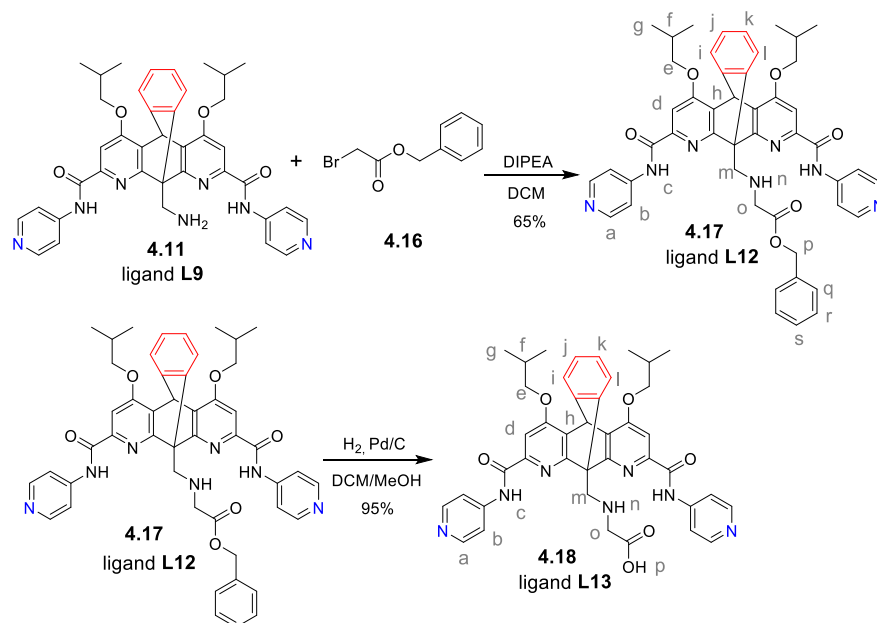


Figure 4.13 The preliminary X-ray crystal structure of $\text{Pd}_4(\text{L8})_8$, the BOC groups, the anions and solvent molecules are very disordered and their positions are still being refined. Protons, solvent molecules and counterions are omitted for clarity.

However, the self-assembly of free amino-functionalized ligand **L9** is more complicated. After self-assembly with Pd^{2+} (NO_3^- , BF_4^- , CF_3SO_3^- , or PF_6^- salt), there are two sets of apparent signals in ^1H NMR, Figure 4.11. Both of them are shifted relative to the free ligand indicating the formation of Pd(II) complexes. One is relatively broad and similar to the parent and functionalized M_4L_8 assemblies that are temporarily assigned to the $\text{Pd}_4(\text{L9})_8$ structure. The other is much narrow with higher intensity, with a possibility of a highly symmetrical smaller structure. An attempt with ESI-TOF-MS to confirm the formula of the $\text{Pd}_4(\text{L8})_8(\text{BF}_4)_8$ failed and no mass peaks related to M_4L_8 or larger structures could be found based on valence and isotope analysis,

Figure 4.12. In the ESI-TOF-MS, peaks related to small Pd(II) complexes were obvious, but we are still unable to ensure the formula with only mass results. This different self-assembly behavior from the other similar ligands can potentially be attributable to the competitive effects of the amino groups on the coordination of pyridine with Pd²⁺ ions. Indeed, similar amino groups were reported as classic ligands for Pd(II) metal-organic assemblies. For instance, ethylenediamine was extensively used as a co-ligand with Pd(II) ions to self-assemble metal-organic macrocycles and cages.^[17]

Although the self-assembly with free amino-functionalized proved to be incompatible in our systems, the promising results with Boc protected ligand **L8** indicated that partial amino protection may still allow the formation of base-functionalized assemblies. If this is the case, it will enable more interesting acid-base multifunctional active sites in our metal-organic architectures. For instance, the rigidity of the assemblies should give a platform for isolation and prevent self-quenching of the acid-base functional groups, which is a current challenge in the design of multifunctional catalysts. Two ligands, **L12** and **L13**, were designed and synthesized for this purpose, Scheme 4.04. Starting from the free amino-functionalized ligand **L9** with benzyl 2-bromoacetate as an alkali reaction lead to form the compound **4.17** (ligand **L12**) in one step. After the reaction, the free amino group was partially protected by introducing the carboxylic acid precursor group. Indeed, after one more reduction reaction with hydrogen and Pd/C catalyst, the compound **4.18** (ligand **L13**), with acid-base functionalization in the same ligand, was obtained in high yield and used for self-assembly.



Scheme 4.04 Synthetic procedures for compound **4.17** (ligands **L12**) and compound **4.18** (ligand **L13**).

Using the same conditions for self-assembly and following it by NMR, both ligands **L12** and **L13** result in complex ^1H NMR spectra similar to free amino-functionalized ligand **L9** with two sets of signals, Figure 4.15. Similarly, the ESI-TOF-MS could not detect any species that relate to M_4L_8 or larger structures, but small unknown Pd(II) complexes were obvious, Figure 4.16. These results indicated that partial amino protection is still competitive for coordination-driven self-assembly with Pd^{2+} ions. The bulky group of Boc may also play an important role in enabling the self-assembly with ligand **L8**. Due to the time limitation of this thesis, we did not figure out the self-assembled structures of the other base-functionalized related ligands (**L11**, **L12** and **L13**), thus limiting their studies for supramolecular catalysis.

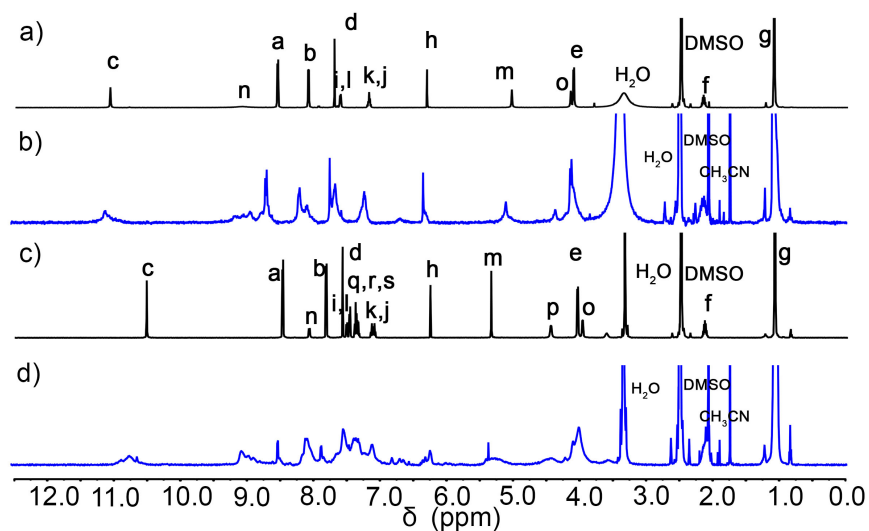


Figure 4.15 ^1H NMR spectra (500 MHz, $\text{DMSO}-d_6$, 298 K) of ligands a) **L13** and c) **L12**, the self-assembled products of b) **L13** and d) **L12** with 0.5 equivalent $\text{Pd}(\text{CH}_3\text{CN})_4(\text{BF}_4)_2$.

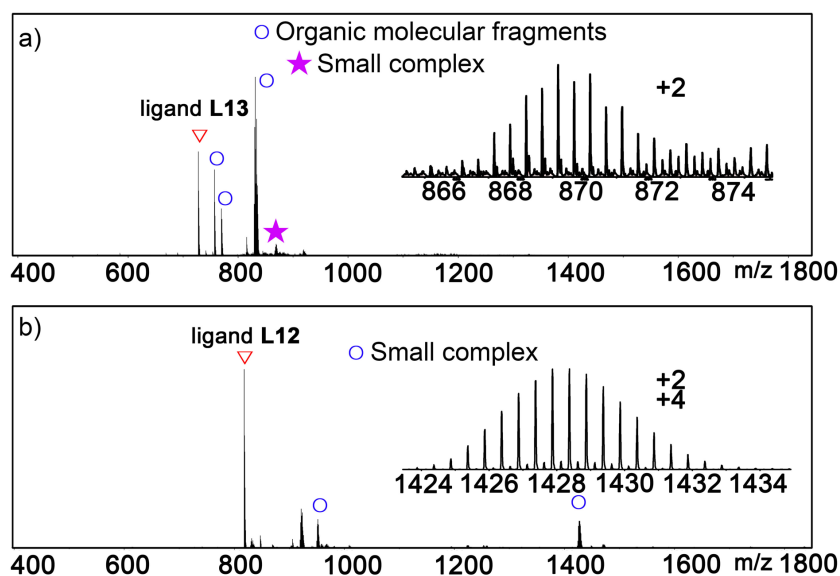


Figure 4.16 ESI-TOF-MS for the self-assembled products of a) **L13** and b) **L12** with 0.5 equivalent $\text{Pd}(\text{CH}_3\text{CN})_4(\text{BF}_4)_2$.

4.2 Steric effect of endohedral groups

During the attempts to diversely functionalize our cage, an interesting phenomenon was that the bulky groups could lead to the self-assembly of the M_4L_8 structures with a small amount of larger M_5L_{10} structure. This indicates that our self-assembled structures can be sensitive to the endohedral groups in the cavity. Another important aspect of studying this steric effect is decreasing the size of endohedral groups to look at the effect for controlling self-assembly. This can offer particular importance to our systems because the methyl in the 9-position of the diazaanthracene units was preferentially used to prevent the coordination of central nitrogen atoms to the Pd^{2+} ions. However, whether this methyl is necessary is still ambiguous. The possibility to remove this bulky group could give potential access to more cavities that are promising for host-guest chemistry, especially for the application of M_2L_4 cages. As shown in Figure 4.17, the density functional theory (DFT) calculated structures (B3LYP/6-31g*) of monomer precursors of the ligands, the endohedral groups can be decreasing in size from methyl, chlorine and hydrogen. Thus, in addition to the initial design with a methyl group, the other two monomer precursors with chlorine and hydrogen would offer a platform to understand the endohedral steric effect on self-assembly and outcomes.

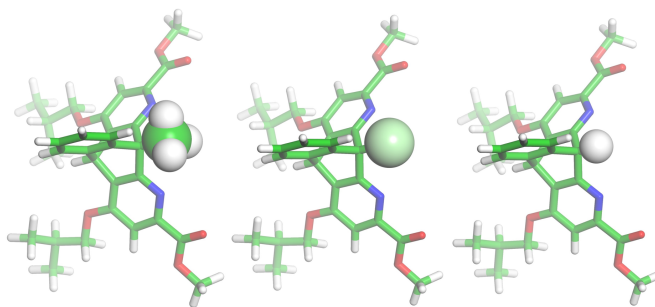
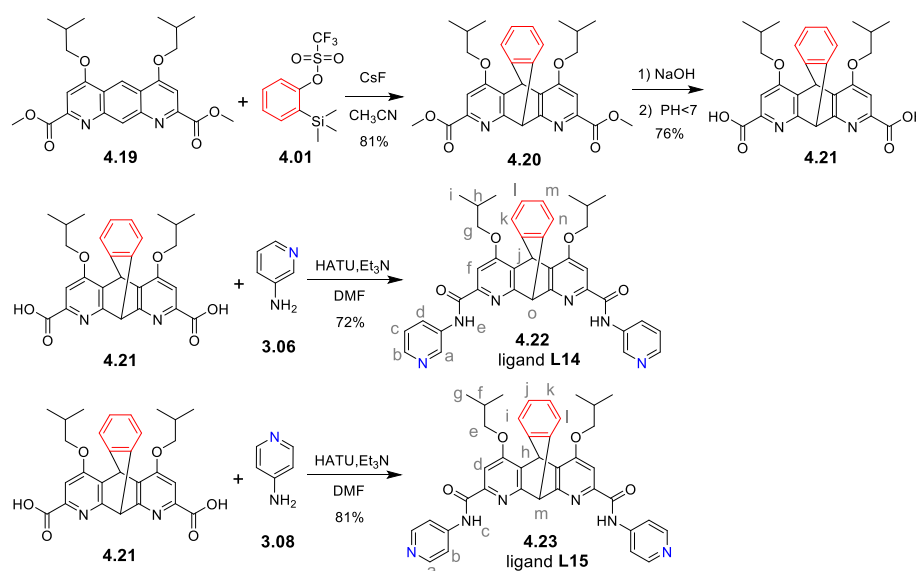


Figure 4.17 Density functional theory (DFT) calculated structures (B3LYP/6-31g*) of monomer precursors of the ligands, spheres highlight the size decrease in the 9-position group from methyl to chlorine to hydrogen.

Firstly, two ligands, **L14** and **L15**, with the 9-position hydrogen atom were

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designed and synthesized, Scheme 4.05. Both ligands were easily obtained in high yields following the same established synthetic routes for the parent ligands **L6** and **L7**.



Scheme 4.05 Synthetic procedures for compound **4.22** (ligands **L14**) and compound **4.23** (ligand **L15**).

Interestingly, both ligands **L14** and **L15** were capable of coordination-driven self-assembly, Figure 4.18-4.19. While the behavior of ligand **L15** is similar to the other analogs, allowing simple self-assembly into the corresponding M₄L₈ structures. However, the self-assembly with ligands **L14** and Pd²⁺ (NO₃⁻, BF₄⁻, CF₃SO₃⁻, or PF₆⁻ salt) is more complicated. Two sets of signals are observed in the ¹H NMR spectra. ESI-TOF-MS indicates that they are a mixture of two species with the formulas of Pd₂(**L14**)₄(BF₄)₄ and Pd₄(**L14**)₈(BF₄)₈. Based on the bend angle and shape of ligand **L14**, it should be less likely to form structures other than the M₂L₄ cage. Rather than Pd₄(**L14**)₈, another possibility is that two Pd₂(**L14**)₄ could come together to form the dimer [Pd₂(**L14**)₄]₂. Whether it is interlocked or resulting from aggregation, the nature of this dimer still needs further study. However, the observation of the dimer by MS suggests that the two units are strongly

associated with each other.

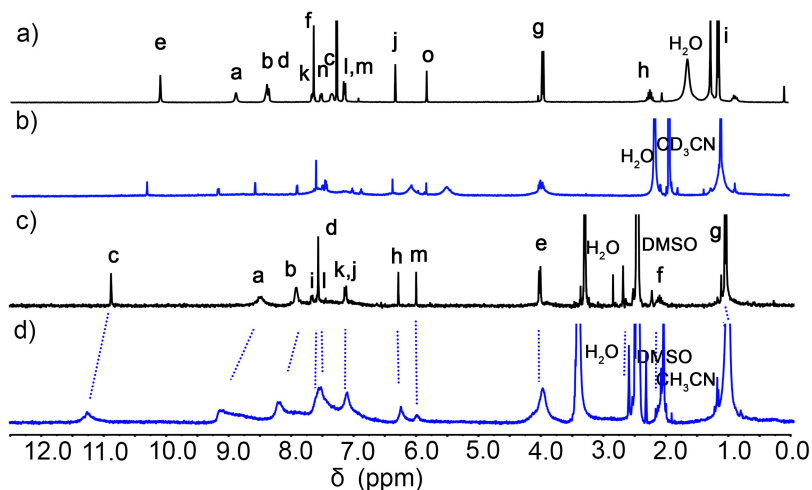


Figure 4.18 ^1H NMR spectra (500 MHz, 298 K) of a-b) ligand **L14** in CDCl_3 and $\text{Pd}_2(\text{L14})_4$ with dimer $[\text{Pd}_2(\text{L14})_4]_2$ in CD_3CN , c-d) ligand **L15** and $\text{Pd}_4(\text{L15})_8$ in $\text{DMSO}-d_6$.

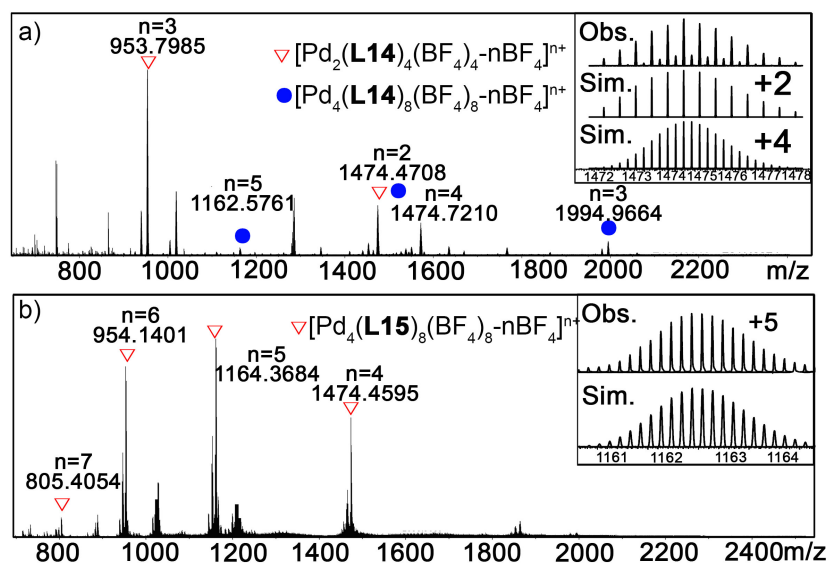
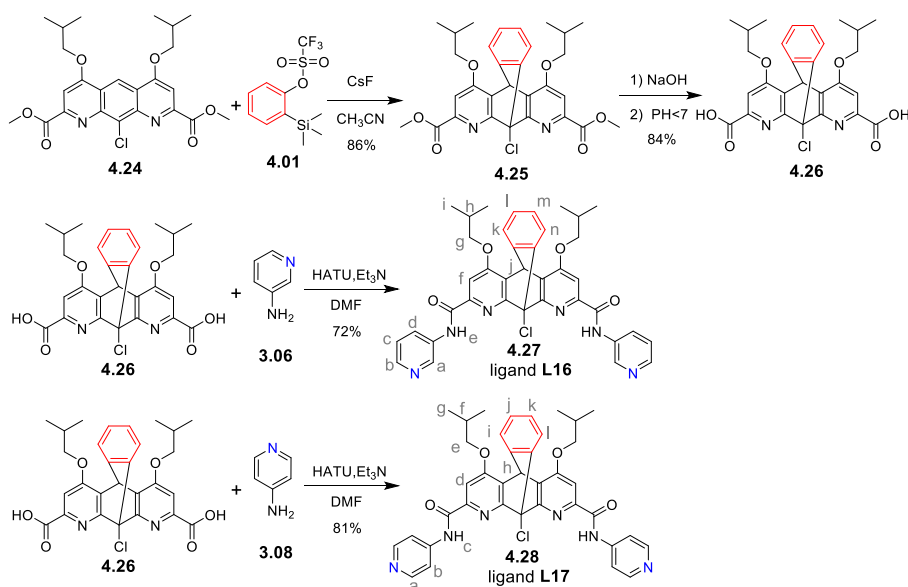


Figure 4.19 ESI-TOF-MS for a) a mixture of $\text{Pd}_2(\text{L14})_4$ and dimer $[\text{Pd}_2(\text{L14})_4]_2$, and b) $\text{Pd}_4(\text{L15})_8$ as their BF_4^- salt.

Indeed, it seems that the self-assembly is sensitive to the size of the

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endohedral group, especially for the M_2L_4 cage with a smaller cavity. To better look at this sensitivity related to steric effects between the 9-position group and the self-assembled outcomes, the middle-sized chloride group (intermediate between methyl and hydrogen atom) would also be interesting for this purpose. Two ligands, **L16** and **L17**, with the 9-position chlorine atom were designed and synthesized, Scheme 4.06. Similarly, both ligands were easily obtained in high yields following the same established synthetic routes for the parent ligands **L6** and **L7**.



Scheme 4.06 Synthetic procedures for compound **4.27** (ligands **L16**) and compound **4.28** (ligand **L17**).

The simple replacement of the 9-position hydrogen atom to a middle-sized chlorine atom in ligands **L16** and **L17** can restore the simple self-assembly and form M_2L_4 and M_4L_8 structures with high selectivity, respectively. This high selectivity of self-assembly with ligands (**L16** and **L17**) and Pd^{2+} (NO_3^- , BF_4^- , CF_3SO_3^- , or PF_6^- salt) are comparable to the parent ligands **L6** and **L7**, resulting in a single set of signals shifted relative to their free ligand in ^1H NMR, Figure 4.20. ESI-TOF-MS confirmed the formulas of the assemblies are $\text{Pd}_2(\text{L16})_4(\text{BF}_4)_4$ and $\text{Pd}_4(\text{L17})_8(\text{BF}_4)_8$, Figure 4.21. Importantly, for the self-

assembly of ligand **L16**, no dimerization was observed by either ^1H NMR or ESI-TOF-MS. This indicates that the outcomes of self-assembly with highly similar ligands **L14** and **L16**, differing just by the size of a single atom on the ligands, can be controlled by the steric effect of endohedral groups. These high sensitivities of the cavities in the structures and the potential to tune the internal environment can make these cages of great potential interest for use in host-guest chemistry, especially for the further development of sensors.

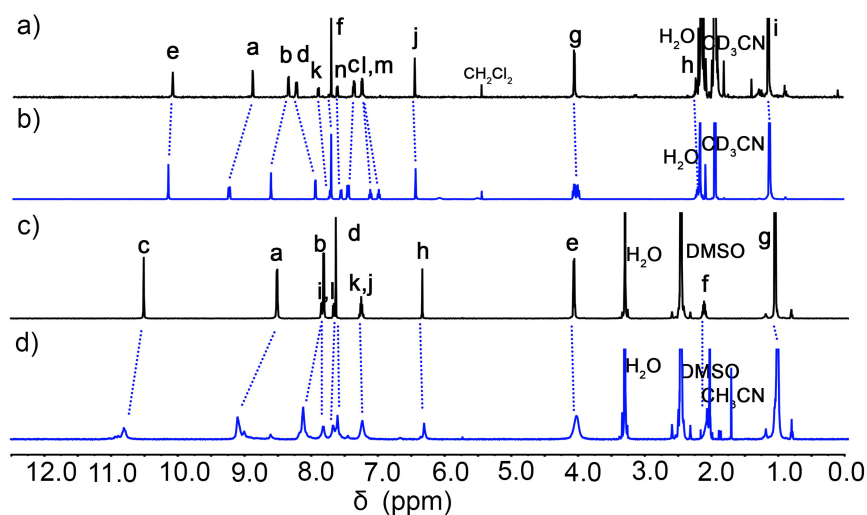


Figure 4.20 ^1H NMR spectra (500 MHz, 298 K) of a-b) ligand **L16** and $\text{Pd}_2(\text{L16})_4$ in CD_3CN , c-d) ligand **L17** and $\text{Pd}_4(\text{L17})_8$ in $\text{DMSO}-d_6$.

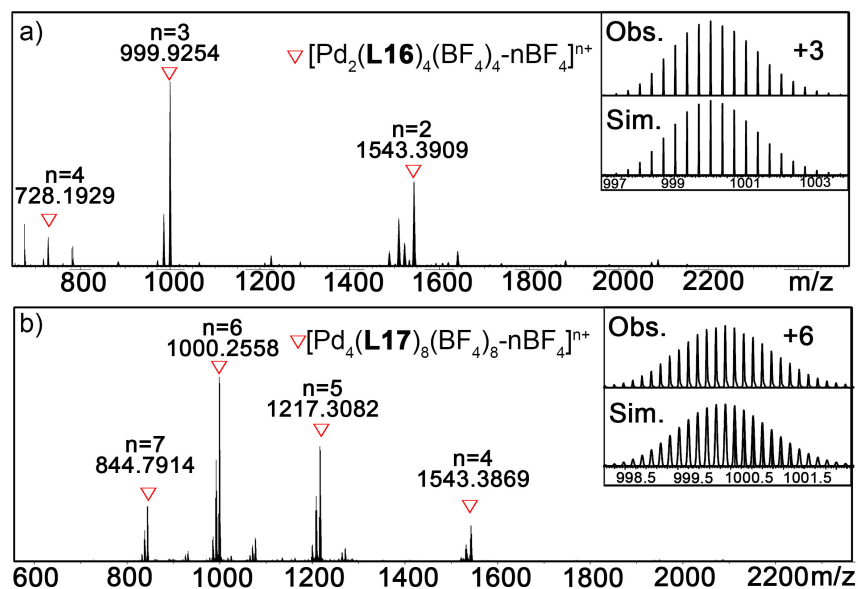
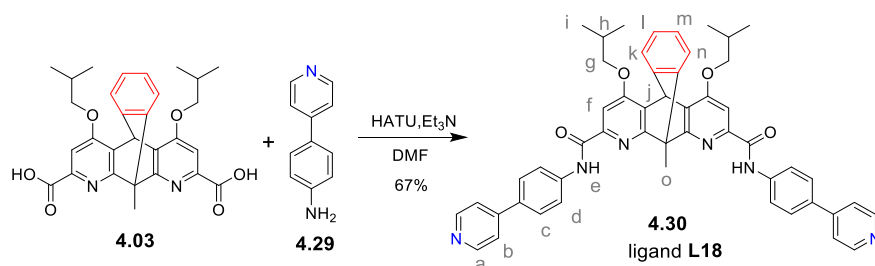


Figure 4.21 ESI-TOF-MS for a) $\text{Pd}_2(\text{L16})_4$ and b) $\text{Pd}_4(\text{L17})_8$ as their BF_4^- salt.

4.3 Tuning size of the cavity

Based on the exciting structures obtained with the triptycene ligands, we were further interested in being able to tune different parameters of the structures. We have already discussed the internal functionalization, but it can also be interesting to modify the cavity sizes. Notably, obtaining larger cavities can be helpful for binding larger guests.^[18] An attractive strategy for this purpose is to lengthen the initial building blocks, thereby increasing the cavity for larger and more complex objects. In order to look at the effectiveness of this strategy in our system, a ligand **L18** with a larger size was designed and synthesized for self-assembly of the M_4L_8 structure, Scheme 4.07. Ligand **L18** was obtained following the same procedure used for parent ligand **L7**, using 4-(pyridin-4-yl)aniline **4.29** as a reagent instead of 4-aminopyridine **3.08**.



Scheme 4.07 Synthetic procedures for compound **4.30** (ligands **L18**).

Interestingly, the increased ligand size has little effect on self-assembly and enables the formation of an M_4L_8 structure with a larger size. Self-assembly of **L18** with $Pd(CH_3CN)_4(BF_4)_2$ was performed under the same conditions as for **L7**. Similar changes were found in 1H NMR, i.e., a single set of signals shifted relative to the free ligand, Figure 4.22. Importantly, DOSY studies suggested the formation of one kind of species with a larger size ($D = 5.30 \times 10^{-11} \text{ m}^2/\text{s}$; $r = 19.0 \text{ \AA}$) versus $Pd_4(L7)_8$ ($D = 7.32 \times 10^{-11} \text{ m}^2/\text{s}$; $r = 13.8 \text{ \AA}$). ESI-TOF-MS analysis showed isotopic patterns consistent with the formation of an M_4L_8 assembly with the formula $Pd_4(L18)_8(BF_4)_8$. As the calculated models of ligands and M_4L_8 structures are shown in Figure 4.23, the ligand lengthening strategy effectively tunes the cavities. This is important for more complex functionalization and applications of our self-assembled systems in the future.

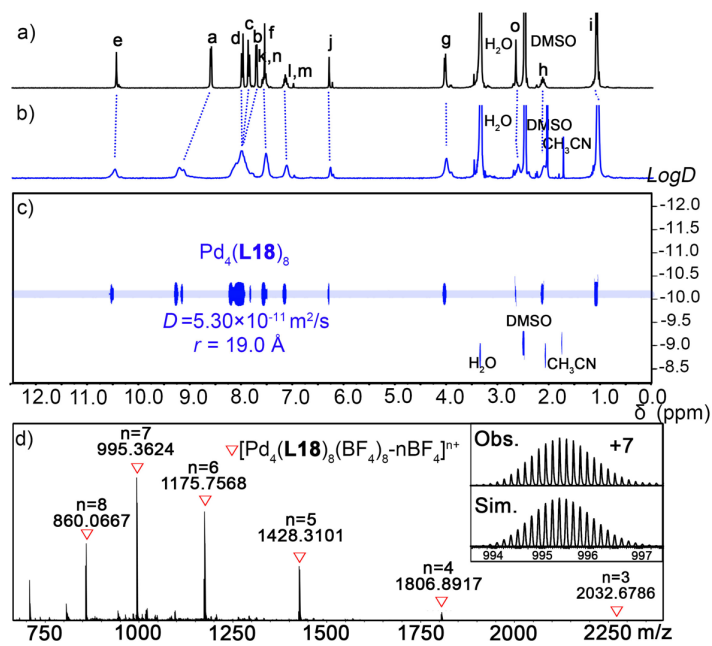


Figure 4.22 ^1H NMR spectra (500 MHz, $\text{DMSO}-d_6$, 298 K) of a) **L18** and b) $\text{Pd}_4(\text{L18})_8$. c) the DOSY spectra of $\text{Pd}_4(\text{L18})_8$. d) ESI-TOF-MS for $\text{Pd}_4(\text{L18})_8$ as its BF_4^- salt. Inset shows the comparison of the observed isotopic pattern with the simulated spectrum.

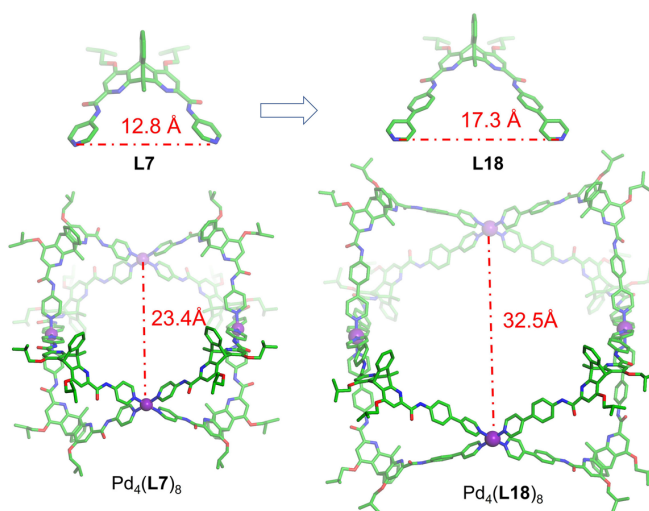


Figure 4.23 Calculated structures of ligands (B3LYP/6-31g*) and M_4L_8

metallomacrocycles (PM6) show that lengthening ligand leads to a significantly enlarged cavity.

5. Self-sorting studies

Based on the above results in this chapter that proved non-covalent interactions and complementary shapes of ligands are able to control self-assembly with one kind of ligand and achieve more complex structures and functionality. We next supposed that these steric and conformational constraints of dual curvature ligands may also be important to promote self-sorting when mixing two different ligands. Three ligands, **L6**, **L7** and **L10**, differing in bend angle or endohedral groups, were selected to study self-sorting. All three ligands have been proven to control the self-assembly of M_2L_4 or M_4L_8 metal-organic architectures and should thus simplify the characterization of self-sorting outcomes. In order to look at how strongly the non-covalent interactions present in the ligand structures control their bend angle, self-sorting studies were performed with ligands **L6** and **L7**. 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 angles. While this could potentially allow the self-assembly of structures containing both ligands **L6** and **L7**, this does not appear to be favored. Indeed, upon reacting a 1:1 mixture of **L6** and **L7** with $Pd(CH_3CN)_4(BF_4)_2$ in D_7 -DMF, two distinct sets of signals were observed by 1H NMR, as verified by the COSY and DOSY spectra, corresponding to the $M_2(L6)_4$ and $M_4(L7)_8$ species as described above, Figure 4.24-4.25. ESI-TOF-MS analysis also showed only a mixture of M_2L_4 and M_4L_8 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 narcissistic self-sorting based on bend angle, something only previously reported for more ridged ligands.^[19]

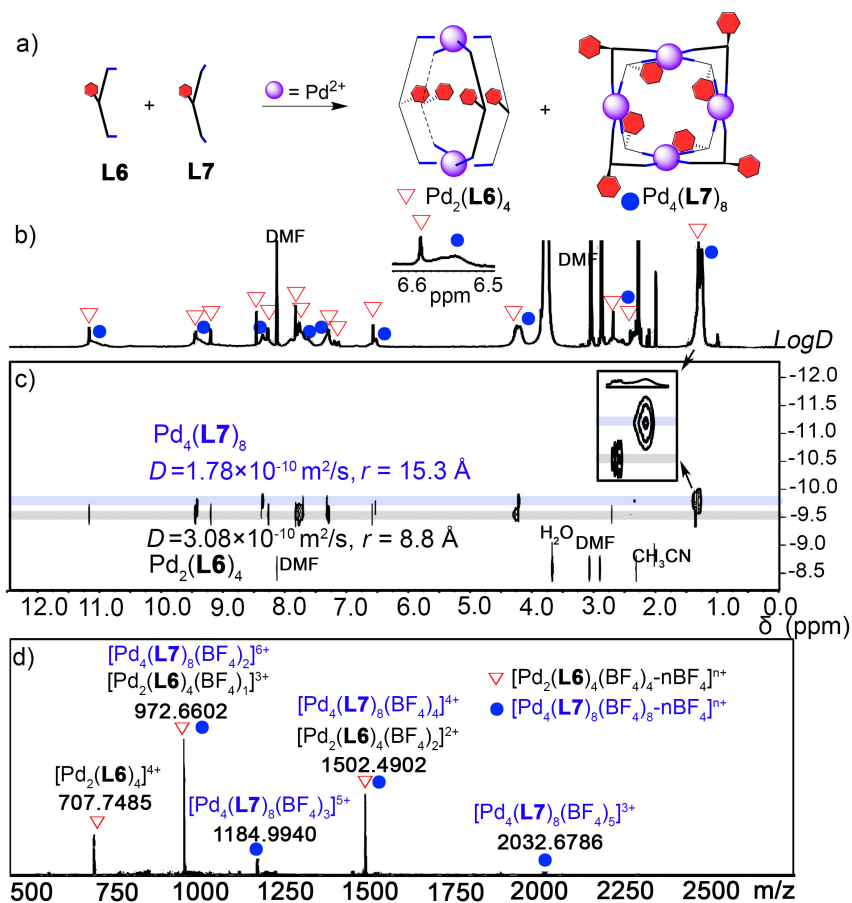


Figure 4.24 a) Narcissistic self-sorting of M_2L_4 and M_4L_8 architectures from mixed ligands **L6** and **L7**, b) ^1H NMR spectra (500 MHz, DMF-d_7 , 298 K), c) DOSY spectra and d) ESI-TOF-MS of self-sorting outcomes, a mixture of $\text{M}_2(\text{L6})_4(\text{BF}_4)_4$ and $\text{M}_4(\text{L7})_8(\text{BF}_4)_8$ species.

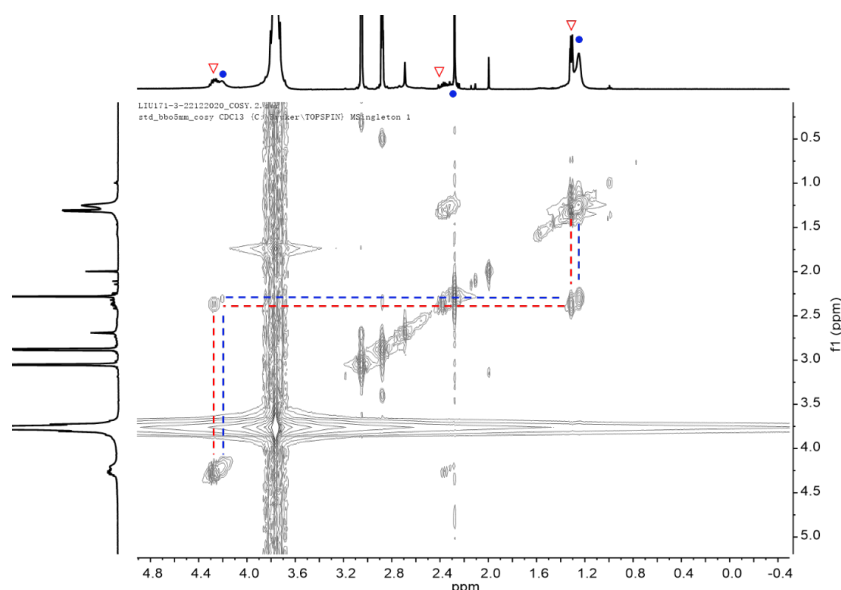


Figure 4.25 ^1H - ^1H COSY NMR (500 MHz, $\text{DMF-}d_7$) spectrum of mixed-ligands (**L6**:**L7**: Pd^{2+} =1:1:1) narcissistic self-sorting of $\text{Pd}_2(\text{L6})_4$ and $\text{Pd}_4(\text{L7})_8$.

For the self-assembly study with ligand **L10**, we observed a short distance between neighboring carboxylic acid groups in the crystals of $\text{Pd}_4(\text{L10})_8$ suggesting hydrogen bonds between ligands. As mentioned before, these interactions could be interesting to understand their preference for self-sorting. However, self-assembly with mixtures of **L7** and **L10** resulted in statistical mixtures of M_4L_8 species with different ratios of the two ligands, Figure 4.26-4.27. The ^1H NMR shows two kinds of resonances of ligands in the assemblies, and all the signals have the same diffusion coefficient ($D = 6.16 \times 10^{-11} \text{ m}^2/\text{s}$; $r = 16.3 \text{ \AA}$) for the M_4L_8 structure obtained from the DOSY spectrum. Importantly, the ESI-TOF-MS analysis also confirmed the statistical mixtures of M_4L_8 species with the formula of $\text{Pd}_4(\text{L7})_n(\text{L10})_{8-n}(\text{BF}_4)_8$, $n=0-8$, indicating that, similar to most reported examples with mixed highly symmetrical and rigid ligands, the difference between endohedral groups was still not enough to control the self-sorting outcomes in our systems.^[20] Nevertheless, similar studies using **L6** and **L10** did show self-sorting into $\text{M}_2(\text{L6})_4$ and $\text{M}_4(\text{L10})_8$ based on the different bend angles, Figure 4.28-4.29.

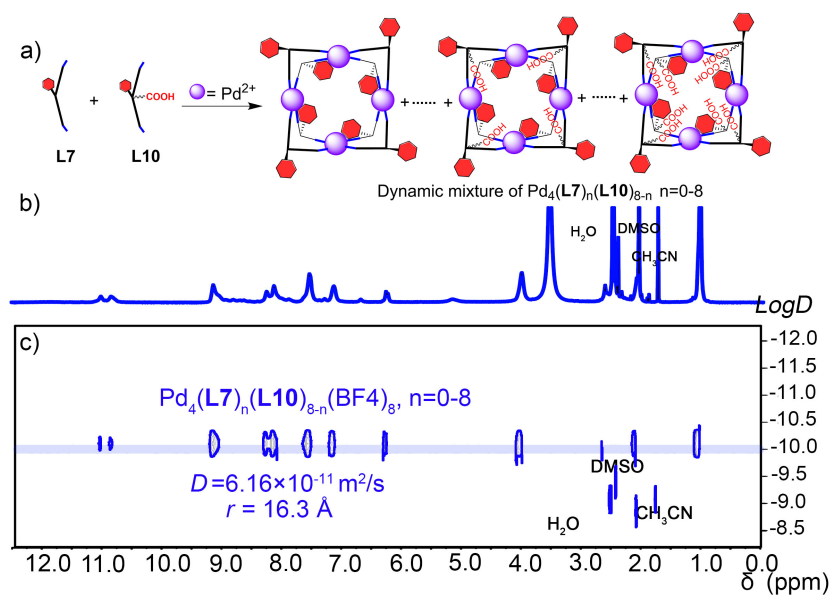


Figure 4.26 a) non-sorted scrambled dynamic mixtures from mixed ligands **L7** and **L10**, b) ^1H NMR spectra (500 MHz, $\text{DMF-}d_7$, 298 K) c) the DOSY spectra of the mixtures $\text{Pd}_4(\text{L7})_n(\text{L10})_{8-n}(\text{BF}_4)_8$, $n=0-8$.

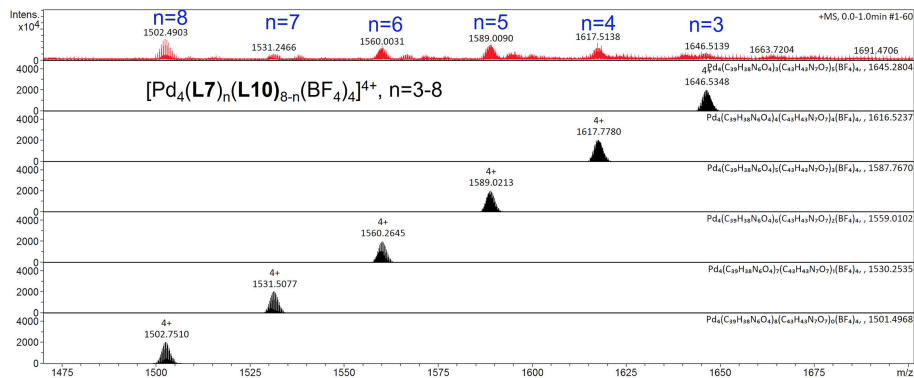


Figure 4.27 ESI-TOF mass expanded spectrum for the charged species of $[\text{Pd}_4(\text{L7})_n(\text{L10})_{8-n}(\text{BF}_4)_4]^{4+}$, $n=3-8$, observed (above) and simulated isotopic distribution (below).

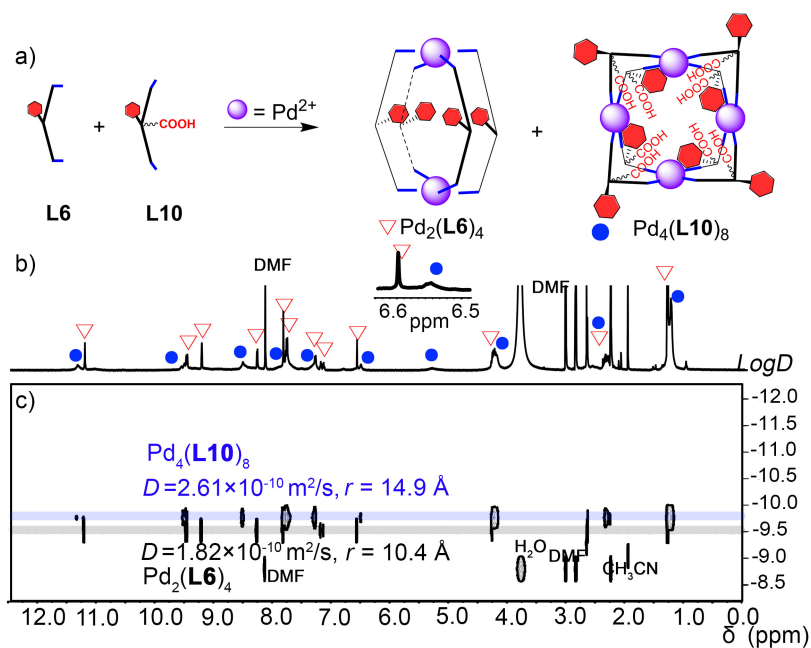


Figure 4.28 a) Narcissistic self-sorting of M_2L_4 and M_4L_8 architectures from mixed ligands **L6** and **L10**, b) ^1H NMR spectra (500 MHz, $\text{DMF-}d_7$, 298 K), c) the DOSY spectra in a mixture of $\text{M}_2(\text{L6})_4$ and $\text{M}_4(\text{L10})_8$ species.

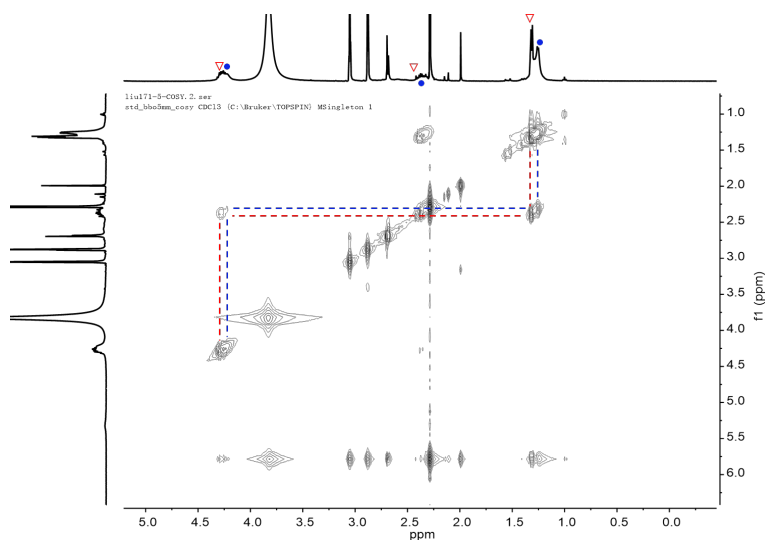


Figure 4.29 ^1H - ^1H COSY NMR (500 MHz, $\text{DMF-}d_7$) spectrum of mixed-ligands (**L6**:**L10**: Pd^{2+} = 1:1:1) self-sorting of $\text{Pd}_2(\text{L6})_4(\text{BF}_4)_4$ and $\text{Pd}_4(\text{L10})_8(\text{BF}_4)_8$.

6. Supramolecular catalysis

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.^[5f, 21] Based on the carboxylic acid functions in ligand **L10**, we were interested in studying the reactivity of the endohedral functionalized M_4L_8 structures. For this, we chose to look at a tandem reaction sequence involving hydrolysis of the dimethyl acetal of benzaldehyde followed by amination 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.^[22] Importantly, both steps of the reaction sequence can be catalyzed by either Lewis or Brønsted acids, and the latter step was also reported to be highly efficient with rate enhancements inside the cavity of metal-organic cages.^[23] These make the endohedral acid functionalization in the $Pd_4(L10)_8$ and the parent $Pd_4(L7)_8$ structures highly interesting as potential supramolecular catalysts for promoting product formation, Figure 4.30.

Initially, the acetal hydrolysis and amination formation steps were studied separately. In all cases, the reactions were performed using the substrates at concentrations of ~40mM in the presence of either 3.1 mol% $Pd_4(L10)_8$ or $Pd_4(L7)_8$, or 24.8 mol% **L10** or **L7** as a catalyst and the reactions followed by 1H NMR using an internal standard, Figure 4.30-4.33. Acetal hydrolysis to benzaldehyde in wet DMSO occurs rapidly with $Pd_4(L10)_8$ at room temperature, giving 90% product formation in 12 h, Figure 4.30-4.31. By contrast, the same reaction with $Pd_4(L7)_8$ is less efficient. Less than 50% aldehyde formation was observed after 12 h and even after 24 h, conversion to the product was only around 60%. The stark difference between the two otherwise similar cages highlights the importance of the endohedral functionalization in $Pd_4(L10)_8$ for this initial step.

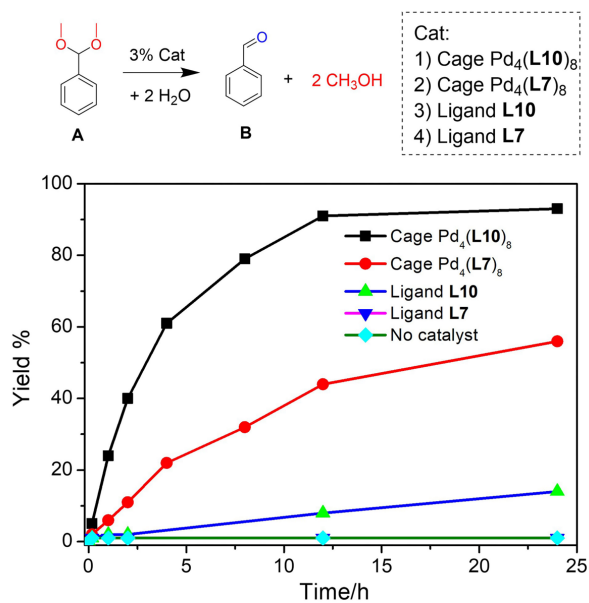


Figure 4.30 Supramolecular catalysis of benzaldehyde dimethyl acetal hydrolysis with different catalysts at room temperature, with 3.1 % cage or 24.8% ligand.

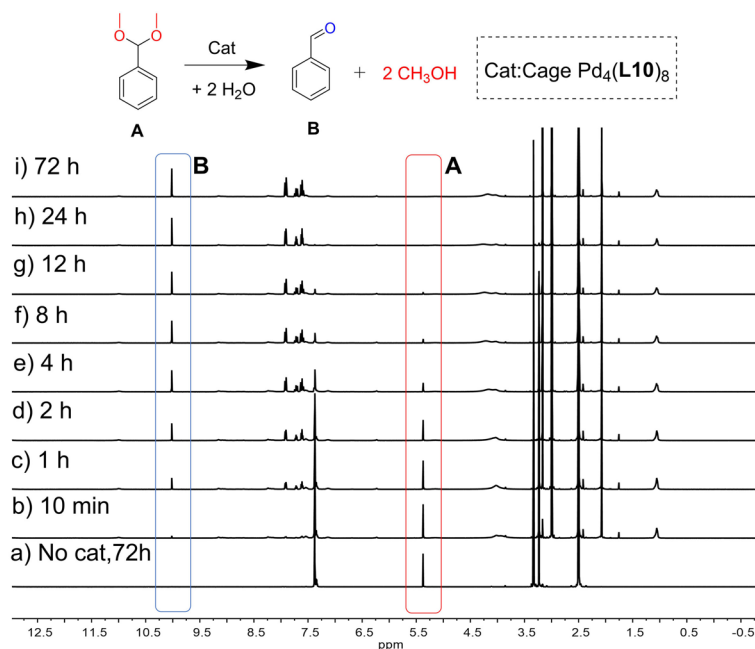


Figure 4.31 ¹H NMR (500 MHz, DMSO-*d*₆) spectra of benzaldehyde dimethyl

acetal hydrolysis at room temperature with 3.1 % $\text{Pd}_4(\text{L10})_8(\text{BF}_4)_8$ and without catalyst.

Still, the carboxylic acid groups alone are not sufficient. When **L10** was used as the catalyst for the reaction in quantities where the concentration of carboxylic acid groups was constant versus $\text{Pd}_4(\text{L10})_8$ or $\text{Pd}_4(\text{L7})_8$, the aldehyde yield was lower (<20% yield) than for either cage. While the increased reactivity of $\text{Pd}_4(\text{L10})_8$ could be rationalized by a potential decrease in the pKa of the carboxylic acid groups in the cationic environment of the cavity, the results with $\text{Pd}_4(\text{L7})_8$ suggest that the Pd^{2+} ions in the two structures act as Lewis acids to catalyze the reaction. Indeed, this appears to be the case for the amination step, both $\text{Pd}_4(\text{L7})_8$ and $\text{Pd}_4(\text{L10})_8$ performed similarly, giving almost 90% dihydroquinazolinone formation in only a few hours. **L10**, while moderately active for this step, was substantially slower and 75% yield was observed after 12h, Figure 4.32-4.33. Of note, using **L7** or no catalyst for either the acetal hydrolysis or amination steps gave only trace product formation after 24h.

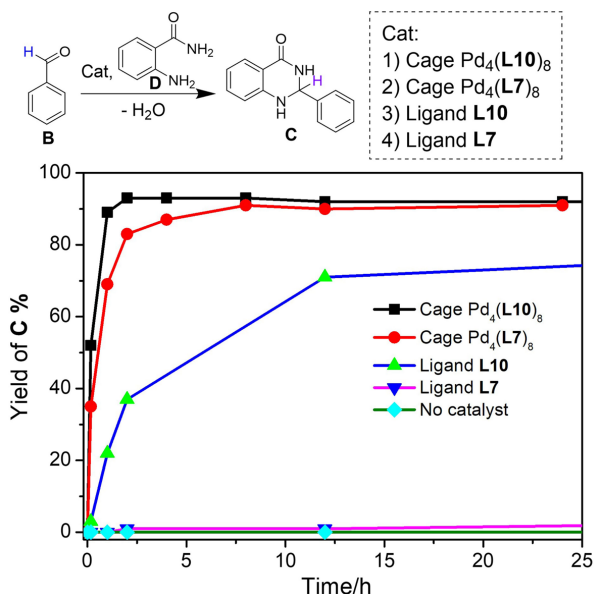


Figure 4.32 Supramolecular catalysis of condensation and cyclization of anthranilamide with benzaldehyde using different catalysts (3.1% cages or

24.8% ligands) at room temperature.

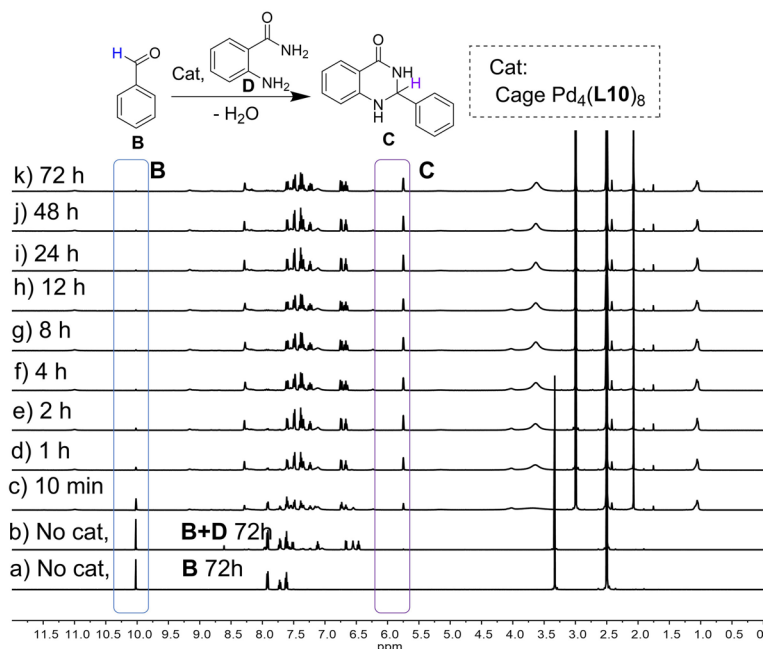


Figure 4.33 ^1H NMR (500 MHz, $\text{DMSO}-d_6$) spectra of condensation and cyclization of anthranilamide with benzaldehyde at room temperature using 3.1 % cage $\text{Pd}_4(\text{L}10)_8(\text{BF}_4)_8$ and without catalyst.

Next, the tandem reaction of benzaldehyde dimethyl acetal with anthranilamide in wet DMSO using the same catalysts was attempted and again followed by ^1H NMR, Figure 4.34-4.35. In the absence of any catalyst, only trace product formation was observed even after 72 h. By contrast, when $\text{Pd}_4(\text{L}10)_8$ was used as the catalyst, the starting acetal disappears almost completely within 24 h, coinciding with >90% formation of the product. The same reaction with the $\text{Pd}_4(\text{L}7)_8$ assembly lacking the carboxylic acid groups also leads to >80% product formation. However, the reaction rate is slower than for $\text{Pd}_4(\text{L}10)_8$, consistent with the results obtained for the individual steps of the reaction. Using just the free ligands, product formation was also substantially slower, with the carboxylic acid functionalized **L10** eventually giving almost 30% conversion after 72 hours and less than 5% product

formation observed with **L7** over the same period. In all cases, only minor amounts of the aldehyde were ever observed. While this can correspond with the slower kinetics observed for 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 4.36, 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.

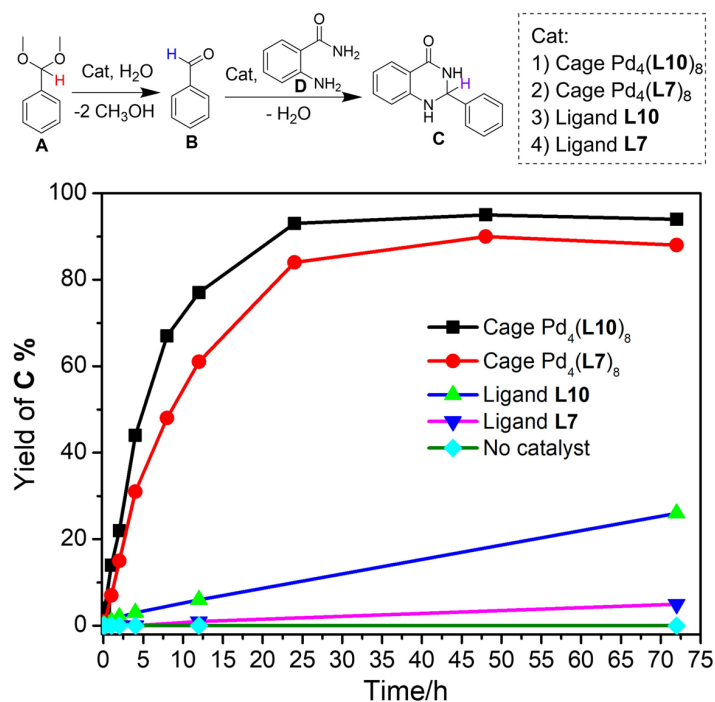


Figure 4.34 Supramolecular tandem three component deacetalization/acetallization of 2-aminobenzamide with benzaldehyde dimethyl acetal at room temperature, 3.1% cages and 24% ligands.

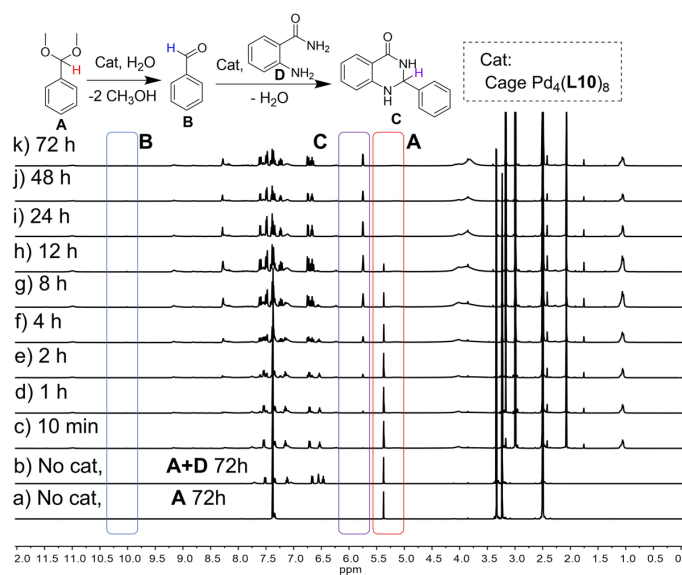


Figure 4.35 ^1H NMR (500 MHz, $\text{DMSO}-d_6$) spectra of tandem three-component deacetalization–acetalization of 2-aminobenzamide with benzaldehyde dimethyl acetal at room temperature during the reaction with 3.1% cage $\text{Pd}_4(\text{L}10)_8(\text{BF}_4)_8$ and without catalyst.

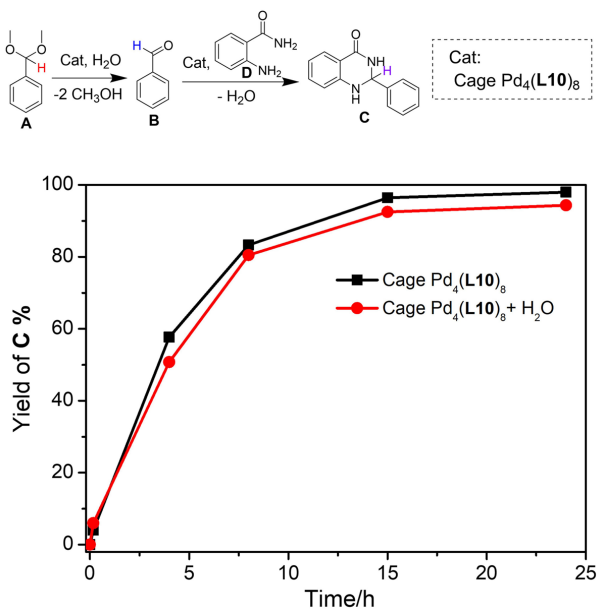


Figure 4.36 Supramolecular tandem three component deacetalization

acetalization of 2-aminobenzamide with benzaldehyde dimethyl acetal at room temperature, 3.1% $\text{Pd}_4(\text{L10})_8(\text{BF}_4)_8$ and with an additional 10 equivalents H_2O .

In order to further examine the efficiency of these catalysts, the catalysis reactions with $\text{Pd}_4(\text{L3})_8$ were set up with different ratios of catalyst to substrate. Increasing or decreasing the substrates by 10-fold lead to different catalyst loadings of 0.31%, 3.1% and 31% versus substrate, then the reaction was followed by ^1H NMR using an internal standard. For the acetal hydrolysis, as shown in Figure 4.37-4.38, even with the lowest catalyst ratio, 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, a lower catalyst:substrate ratio (0.31%) leads to a significant decrease in the reaction rate. Still, the starting reagents disappear almost completely within 48 h, coinciding with >90% formation of the product. Surprisingly, only minor changes are observed between the two other conditions (3.1% and 31%).

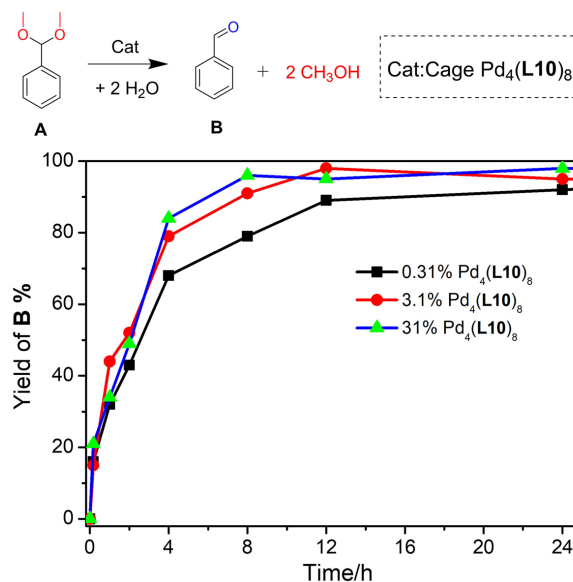


Figure 4.37 Supramolecular catalysis of benzaldehyde dimethyl acetal with different relative loading of $\text{Pd}_4(\text{L10})_8(\text{BF}_4)_8$ (0.31%, 3.1% or 31%.) versus

substrate concentration.

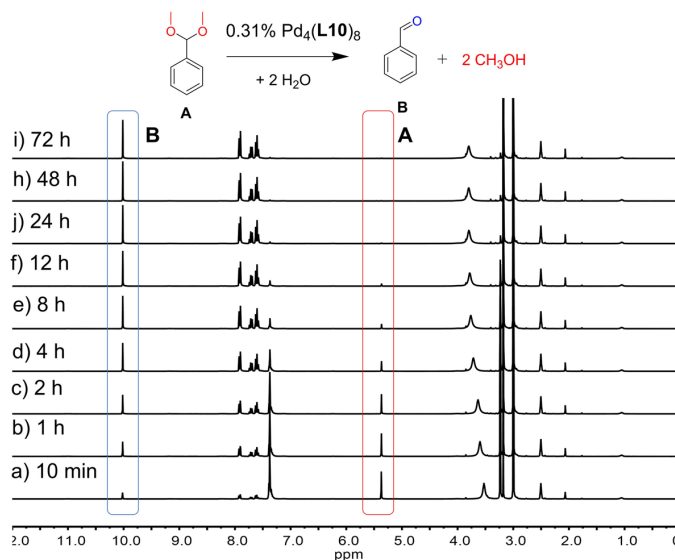


Figure 4.38 ^1H NMR (500 MHz, $\text{DMSO}-d_6$) spectra of benzaldehyde dimethyl acetal hydrolysis at room temperature with a 10-fold excess of a substrate (0.31% cage $\text{Pd}_4(\text{L10})_8(\text{BF}_4)_8$ as a catalyst).

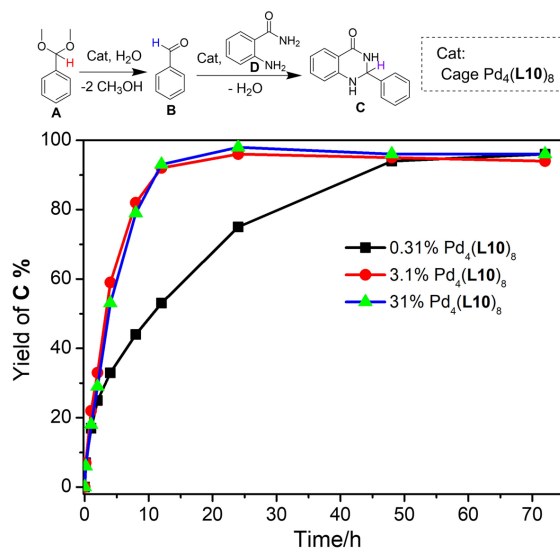


Figure 4.39 Supramolecular tandem reaction of benzaldehyde dimethyl acetal with anthranilamide at room temperature with different concentrations of

substrates lead to 0.31%, 3.1% and 31% $\text{Pd}_4(\text{L10})_8(\text{BF}_4)_8$.

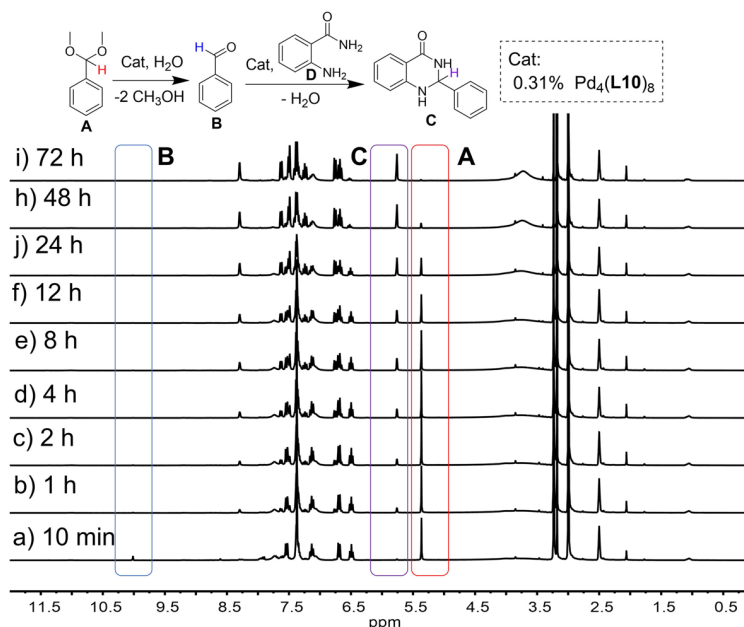


Figure 4.40 ^1H NMR (500 MHz, $\text{DMSO}-d_6$) spectra of tandem reaction of benzaldehyde dimethyl acetal with anthranilamide at room temperature with a 10-folds excess substrates lead to 0.31% cage $\text{Pd}_4(\text{L10})_8(\text{BF}_4)_8$ as a catalyst.

7. Conclusions

This chapter provided an effective strategy for controlling self-assembly in more complex systems by combining the endohedral non-covalent interactions in aromatic amides with additional shape complementarity brought by dual curvature in the ligands. A Diels-Alder reaction was used to break the symmetry of the ligands and incorporate additional steric constraints and complementary shapes that allowed designing and synthesizing a series of dual curvature ligands (**L6-L18**). The self-assembly studies of the parent ligands **L6-L7** showed these constraints are able to highly control the self-assembly of the ligands with Pd^{2+} towards a single M_2L_4 cage or M_4L_8 double-walled metallomacrocyclic out of hundreds of possible isomers. Moreover, the

high modularity of the amide ligands allows ready access to different functional group modified ligands (**L8-L17**) for self-assembly. With larger groups (**L8-L11**), an increased possibility to generate larger double-walled metallomacrocyclic (i.e., M_5L_{10}) was observed. However, if the size of endohedral groups (**L12-L17**) decreases, the self-assembly behavior can also be potentially different (i.e., dimerization of M_2L_4). The ligand lengthening strategy (**L18**) also proved to be able to tune the cavity of M_4L_8 structures effectively. Moreover, the non-covalent interactions provide sufficient control to allow narcissistic self-sorting based on bend angle in mixed flexible ligands. Finally, the acid-functionalized M_4L_8 structures with deep cavitands are able to perform tandem catalysis with significant rate enhancements and product selectivity. These results advanced the knowledge of coordination-driven self-assembly with more complex building blocks for extending structural and functional complexity and give promising new designs for supramolecular applications.

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Chapter V

Adaptation and post-modification of metal-organic assemblies

1. Introduction

Self-assembly has provided the foundation for significant development across many subdisciplines of chemistry, spanning fundamental investigations concerned with the design and synthesis of new architectures to defining practical applications.^[1] In order to mimic the structures in nature, coordination-driven self-assembly has resulted in the formation of many discrete polygons and polyhedral structures that have demonstrated various functionality.^[2] One of the main design principles in these systems relies on the idea that the shapes and geometries of organic building blocks and distinct coordination modes of transition metals can be used to dictate the final assemblies.^[3] The simplicity of the components in self-assembly is advantageous for this purpose. For instance, rigid and symmetrical building blocks that are used to construct Archimedean and Platonic structures are essential for the high predictability of the self-assembled products and limit the competing processes from conformational changes during self-assembly.^[4] However, these design principles limit the scope for developing more sophisticated systems that use low symmetry or structural flexibility features to exchange between one or more isomers. Apart from well-defined symmetric structures, non-Archimedean/Platonic structures constructed with conformationally flexible and asymmetric building blocks are more close to

proteins and enzymes in nature.^[5] The main challenge in the design of nonclassical architectures is that low symmetry and flexibility in ligands will lead to the formation of isomeric mixtures.^[6] Those isomers are usually tricky to distinguish and purify. In the previous chapters, we successfully used non-covalent interactions to mediate conformational rigidity in ligands and showed that a Diels-Alder reaction could be used to incorporate additional steric constraints for designing aromatic amide-based dual curvature ligands. Importantly, these constraints in the ligands promote self-assembly and self-sorting with reduced symmetry building blocks, showing the remarkably quantitative and highly selective formation of single isomeric species from hundreds of possible isomers. Our results advanced the knowledge of coordination-driven self-assembly and opened the door to control self-assembly with low symmetry and flexible subcomponents. However, like most metal-organic supramolecular structures, covalent reactions are exclusively used to synthesize and modify ligands before self-assembly. Thus, the outcomes have only functional groups already present in the initial building blocks, and adding or removing any functional groups of the assemblies must be designed and synthesized from the beginning.

Interestingly, another practical approach, covalent post-modification, has been reported to allow tuning of the properties of metal-organic architectures and allow a single-parent structure to increase various functions after self-assembly.^[7] Still, covalent post-modification is less common in discrete metal-organic architectures, as many of these supermolecular assemblies are observed to decompose under the conditions required to form covalent bonds.^[8] Thus, the covalent reactions used for post-modification should be achievable under mild conditions and proceed in near-quantitative yields to avoid the need for further purification of self-assembled complexes. Some highly efficient covalent reactions have gained popularity for this purpose, such as azide-alkyne cycloadditions,^[9] nucleophile-isocyanate,^[7h] Diels-Alder reactions,^[10] etc. Based on our success in controlling the complexity and functionality of metal-organic assemblies with pre-synthesized Diels-Alder

adduct ligands, we are interested in the possibility of achieving the same types of structures by using the Diels-Alder reactions for covalent post-modification in this chapter. This approach should give a shorter alternative pathway to achieve similar complex structural and functional diversity and provide unique access to novel supramolecular structures and functions that are unable to be realized through self-assembly.

2. Design and synthesis of ligands

Indeed, a highly active covalent reaction under mild conditions will be ideal for the covalent post-modification of metal-organic architectures, especially in our systems with complex flexibility and symmetry properties. The synthesis of ligands in the previous chapter showed high selectivity and excellent conversion for the Diels-Alder reaction with the diazaanthracene units. This makes this reaction potentially interesting for the post-modification of our metal-organic architectures containing these units. However, the high activity of benzyne as a dienophile in the Diels-Alder reaction leads it to an unstable compound that needs to be generated in situ by heating it in the presence of excess cesium fluoride. These limitations can potentially decompose the metal-organic assemblies making benzyne not an ideal dienophile for use in the Diels-Alder reaction for covalent post-modification of metal-organic architectures. Indeed, our attempts at this failed, and even attempts to generate the benzyne via diazonium formation from anthranilic acid did not give promising results. Thus, in this chapter, we look at the use of two other dienophiles, 4-Phenyl-1,2,4-triazoline-3,5-dione **5.01** and 1-Methyl-1H-pyrrole-2,5-dione **5.03**, to design new ligands and optimize conditions for covalent post-modification, Figure 5.01.

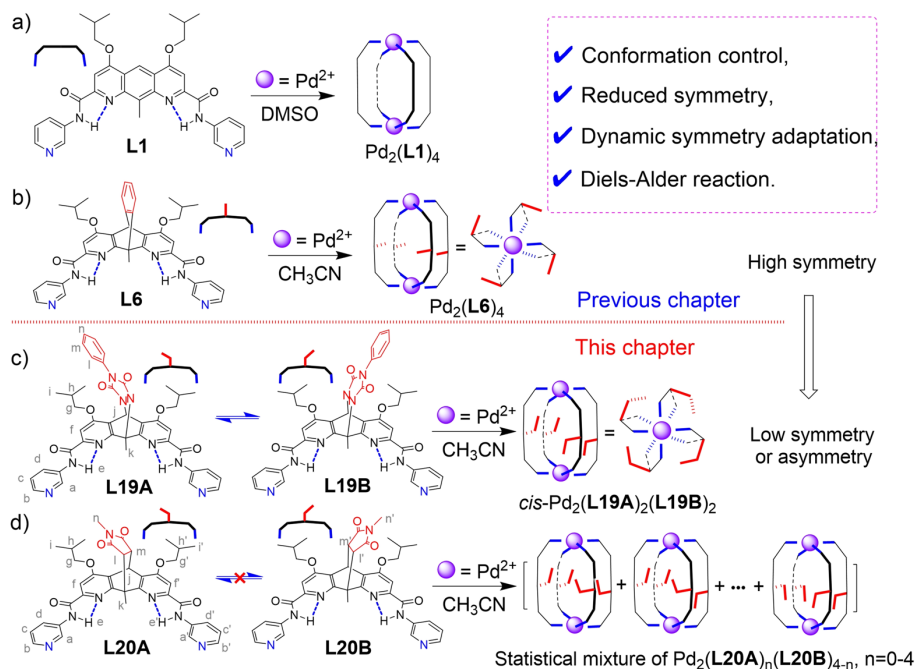


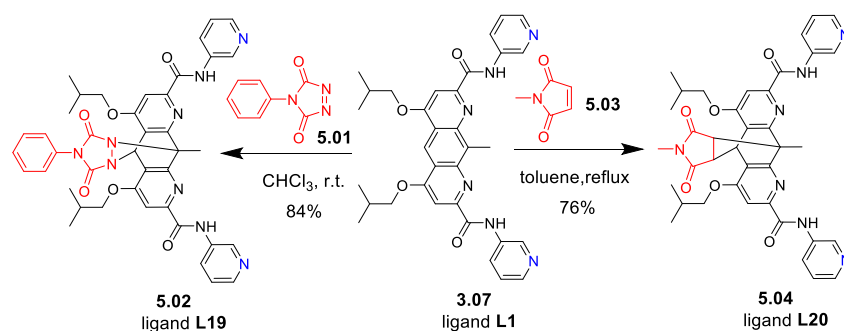
Figure 5.01 Design of new ligands **L19-L20**, showing the continuous reduction in symmetry by Diels-Alder reaction, a) conformation controlled high symmetry ligand **L1**, Diels-Alder reaction with b) symmetrical benzene in ligand **L6**, c) ligand **L19** with an equilibrium between its two enantiomers (**L19A** and **L19B**) and d) ligand **L20** existing in two stable two enantiomers (**L20A** and **L20B**). Cartoon representations of the products of their self-assembly with Pd^{2+} are shown at the right.

Our previous study proved that the Diels-Alder reaction is an efficient strategy to break the symmetry of ligands, leading to more complex self-assembly behavior. Different from ligand **L6**, the two pre-synthesized ligands **L19** and **L20** are less symmetric, possessing chirality due to the single bond nature of the 9,10-bridging units. Because of this, we initially set out to understand their self-assembly properties and potential to form conformational and asymmetrical metal-organic isomers. In addition, the dynamic structural properties of these two ligands are significantly different. Ligand **L19** can readily equilibrate between its two enantiomers (**L19A** and **L19B**), while ligand

L20 is cannot. This can also give a chance to understand how the ligands adapt to self-assembly outcomes in a complex system. We reasoned that the dynamic adaptation of building blocks in self-assembly could be an additional controlling factor in promoting the convergence of isomeric mixtures into a single isomer and simplifying the characterization of the complex systems. This hypothesis is based on reported examples where neighboring ligands in the metal-organic assemblies could communicate, directing the dissociation and rearrangement of components.^[11] For instance, the chiral communication of ligands in metal-organic cages is widespread.^[12] As shown in Figure 5.01, when self-assembled with Pd²⁺ salts, ligand **L19** with its adaptable symmetry properties can efficiently transform into its M₂L₄ cage, revealing a highly symmetrical system in solution based on its ¹H NMR signals and a single cis-configurational Pd₂(**L19A**)₂(**L19B**)₂ isomer in solid-state. This indicates that the highly active dienophile, 4-Phenyl-1,2,4-triazoline-3,5-dione **5.01**, can be interesting for covalent post-modification of our metal-organic architectures at room temperature. The classic 1-Methyl-1H-pyrrole-2,5-dione **5.03** was also able to form its Diels-Alder ligand **L20**, but self-assembly with Pd²⁺ salts led to a mixture of Pd₂(**L20A**)_n(**L20B**)_{4-n}, n=0-4 products.

The synthesis of new compound **5.02** (ligands **L19**) and compound **5.04** (ligands **L20**) was efficiently achieved in one step by Diels-Alder reaction of the diazaanthracene-unit in our previous compound **3.07** (ligand **L1**) with 4-Phenyl-1,2,4-triazoline-3,5-dione **5.01** and 1-Methyl-1H-pyrrole-2,5-dione **5.03** as the selected dienophiles, scheme 5.01. 4-phenyl-1,2,4-triazoline-3,5-dione **5.01** is an interesting dienophile that can typically undergo Diels-Alder reactions and retro-Diels-Alder reactions close to room temperature. Thus, the compound **5.02** (ligands **L19**) could be quantitatively formed (as seen by ¹H NMR) under mild conditions just by mixing of 4-phenyl-1,2,4-triazoline-3,5-dione **5.01** and compound **3.07** (ligand **L1**) at room temperature in CHCl₃. By contrast, the same reaction with the more classic dienophile 1-Methyl-1H-pyrrole-2,5-dione **5.03** needs somewhat harsher conditions, requiring >12h of refluxing in toluene with **L1** to have a good conversion and still requires

chromatographic purification after the reaction.



Scheme 5.01 Synthetic procedures for ligands **L19** and **L20**.

3. The properties of ligands

Four heteroaromatic amide-based ligands **L1**, **L6**, **L19** and **L20**, that differ in the composition of their central backbones, were used in this study, Figure 5.02 and carefully selected with different symmetry and structural adaptation properties. All ligands contain non-covalent interactions and conjugation between the amides and aromatic units that mediate their conformational rigidity. The first-generation ligand **L1** is highly symmetric due to the flat structure of the diazaanthracene central unit. The symmetry in the other three ligands, **L6**, **L19** and **L20**, is reduced due to disruption of the aromaticity of the central ring of the diazaanthracenes as a result of the Diels-Alder reaction. However, different from the ligand **L6**, where the anthracene adduct is a stable triptycene without the possibility for isomers, the symmetry of the Diels-Alder adducts of ligands **L19** and **L20** is lower as the single bond nature of the 9,10-bridging unit leads to it bending to one side of the adduct. This results in the formation of two enantiomers of which, because of their random formation, should exist in equal amounts. As shown in Figure 5.03, this bent structure and the presence of both enantiomers can be seen in the crystal structure of the Diels-Alder adduct of the central monomer in ligand **L19**, obtained by Louis Smal in our group during his master thesis.^[13] Still, an important difference between **L19** and **L20** is that the heteroatomic nature of the bridging hydrazine

group in **L19** allows for a pyramidal inversion that allows equilibration between the two enantiomers (**L19A** and **L19B**). As shown in Figure 5.02, this was supported by its high symmetry based on the ^1H NMR signals in CDCl_3 at room temperature. For ligand **L20**, similar to most of the reported Diels-Alder adducts, its enantiomers (**L20A** and **L20B**) are stable and do not undergo dynamic exchange. This stability in ligand **L20** was supported by splitting the proton signals in its ^1H NMR at room temperature. For instance, the amide protons at 10.1 ppm appear as two peaks, corresponding to the proton on the same side as the dienophile and the proton on the opposite side. The DFT calculated structures of the ligands are shown in Figure 5.04 and further highlight the differences in symmetry and structural adaptation.

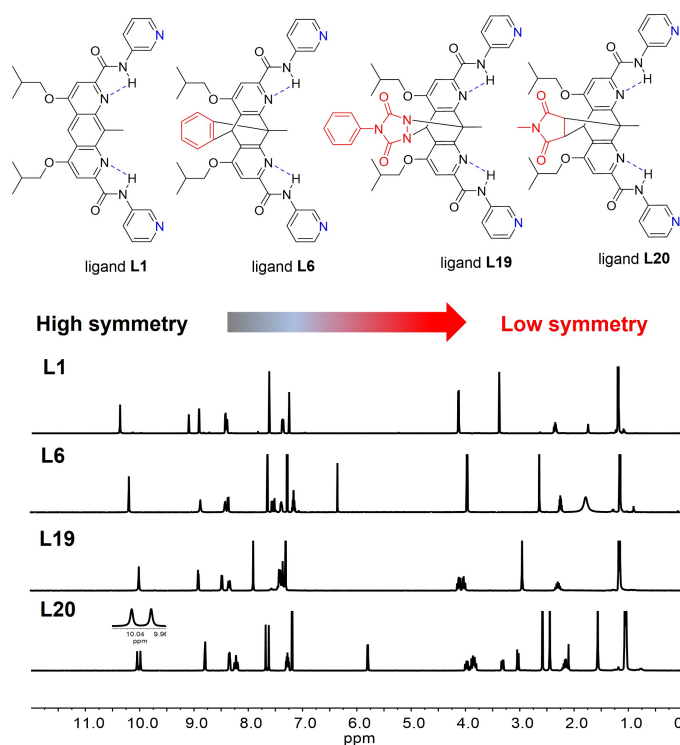


Figure 5.02 ^1H NMR spectra of ligands **L1**, **L6**, **L19** and **L20** from high symmetry to low symmetry.

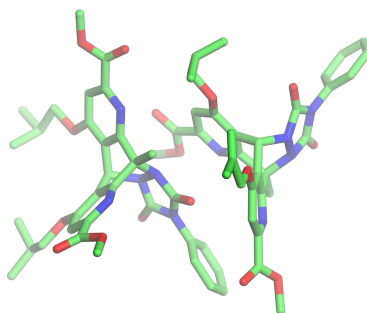


Figure 5.03 X-ray crystal structure of the Diels-Alder adduct of the central monomer in ligand **L19** showing both enantiomers. Protons and solvent molecules are omitted for clarity.

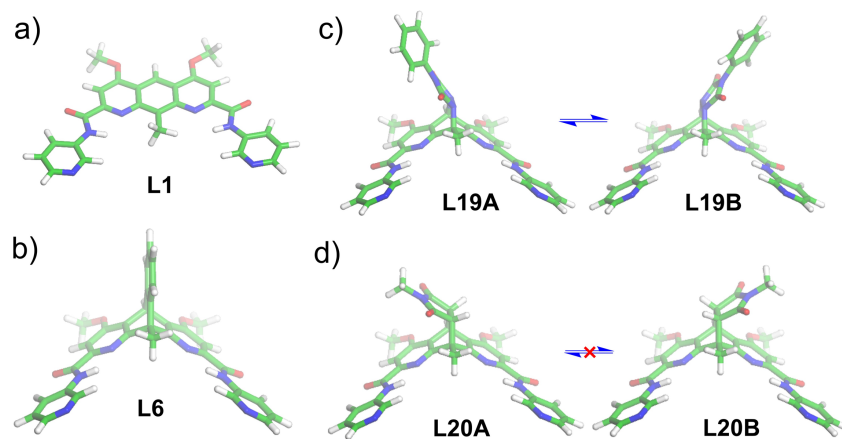


Figure 5.04 DFT calculated structures (B3LYP/6-31G*) of ligands a) **L1**, b) **L6**, c) **L19** and d) **L20** from high symmetry ligand to asymmetric isomers of ligands, c-d) the different adaptation properties of ligands **L19** and **L20**.

4. Self-assembly of M_2L_4 cage

4.1 Self-assembly with ligand **L19**

To initially look at the self-assembly behavior of the ligands and the potential for different stereoisomer formation, the well-studied M_2L_4 cages represent an ideal model due to their relative simplicity. Complexation of **L19** with Pd^{2+} (NO_3^- ,

BF₄⁻, CF₃SO₃⁻ or PF₆⁻ salt) in a 2:1 molar ratio results in a clear yellow CD₃CN solution. Interestingly, although there is the potential for cage formation to inhibit the dynamic exchange between enantiomers, resulting in the formation of multiple diastereoisomers, this does not appear to be the case. Only one set of proton resonances with the same number of signals as the starting ligand was observed by ¹H NMR, Figure 5.05. Compared with the free ligand **L19**, protons resonances of the pyridyl groups were found to be greatly downfield shifted, implying the formation of coordinative pyridyl-Pd(II) bonds. It is similar to the self-assembly behavior of our previous heteroaromatic amide-based ligands **L1** and **L6**. Diffusion-ordered ¹H NMR (DOSY) revealed that all protons resonances had the same diffusion coefficient of $D = 6.99 \times 10^{-10}$ m²/s, which gives an estimated radius of 8.6 Å using the Stokes-Einstein-Equation, consistent with sizes expected for the desired M₂L₄ cage. Electrospray ionization time-of-flight mass spectra (ESI-TOF-MS) also suggest a complex with the formula Pd₂(**L19**)₄(BF₄)₄ is formed. Finally, its single-crystal X-ray structure unambiguously confirmed the precise composition of the self-assembly outcome. Each of the Pd²⁺ ions in the M₂L₄ structure was found in a square planar N₄ coordination environment comprised of four pyridine units. Four ligands bridge the two Pd²⁺ ions with the same orientation of the curved pseudo-triptycene structure of the ligands, similar to what was observed for our Pd₂(**L6**)₄ cage. In the solid state, both enantiomeric forms (**L19A** and **L19B**) of the ligand were integrated into the cage structure. Notably, this means that the benzene rings of the 4-phenyl-1,2,4-triazoline-3,5-dione units could be oriented in one of two directions (up and down) relative to the axis between the two Pd²⁺ ions. In the solid-state, two enantiomers were found oriented up and two down in a *cis*-configurational arrangement, *cis*-Pd₂(**L19A**)₂(**L19B**)₂. Density functional theory (DFT) calculations (B3LYP/def2SVP) suggested that this *cis*-isomer might be slightly thermodynamically favored ($\Delta E = -4.12$ kJ/mol) compared to the *trans*-isomer, Figure 5.06. However, it should be noted that this small value could also easily be within the margin of error for DFT calculations. Nevertheless, the

observation of the *cis*-configuration in the solid-state raises the interesting question of whether the same configuration could be preferred using a ligand where the dynamic exchange between enantiomers was not possible. To explore this idea, we decided to study the palladium-based self-assembly of the similar ligand, **L20**, which has two stable non-equilibrating enantiomeric forms.

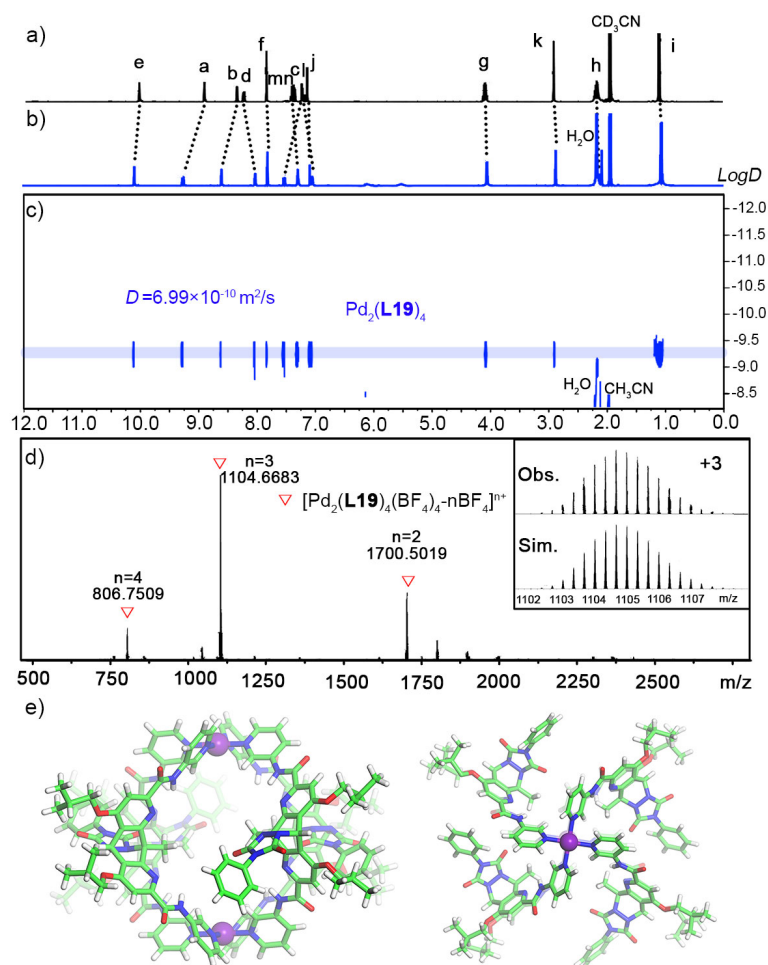


Figure 5.05 ^1H NMR spectra of a) **L19** and b) its self-assembly product $\text{Pd}_2(\text{L19})_4$. c) the DOSY spectra of $\text{Pd}_2(\text{L19})_4$. d) ESI-TOF-MS for $\text{Pd}_2(\text{L19})_4$ as its BF_4^- salt. Inset shows the comparison of the observed isotopic pattern

with the simulated spectrum. e) X-ray crystal structure of $\text{cis-Pd}_2(\text{L19A})_2(\text{L19B})_2$ with views along (left) and perpendicular (right) the Pd-Pd axis. Solvent molecules and counterions are omitted for clarity.

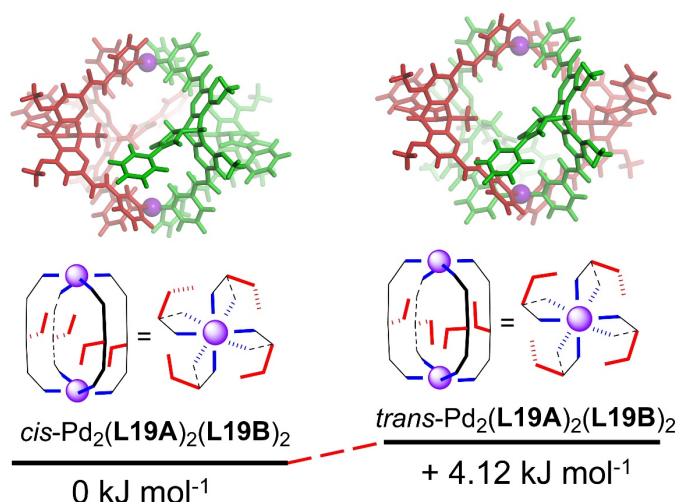


Figure 5.06 DFT calculated structures (B3LYP/def2SVP) of trans and cis conformational isomers of cage $\text{Pd}_2(\text{L19A})_2(\text{L19B})_2$ with relative energies.

4.2 Self-assembly with ligand L20

With **L19**, the dynamic exchange between the two enantiomers can and does readily occur in solution. This is clear in the high symmetry observed by NMR, which suggests a fast exchange between the up and down orientations of the 4-phenyl-1,2,4-triazoline-3,5-dione units even in the cage structure. With ligand **L20**, this is not the case. Signals for the two halves of the ligand are clearly split in the ¹H NMR spectrum indicating loss of the perpendicular mirror symmetry plane, Figure 5.07. Since the tetrahedral carbon atoms in the 9,10-bridging unit do not allow the inversion process seen for ligand **L19**, the ligand **L20** should be locked into the two stable enantiomeric forms. If we suppose that the formation of the single heteroleptic $\text{cis-Pd}_2(\text{L19A})_2(\text{L19B})_2$ product was indeed favored, self-assembly with the two enantiomers of ligand **20** (**L20A** and **L20B**) and Pd^{2+} ions could also give the same single cis-

configurational outcome. Obtaining a cis-configurational $\text{Pd}_2(\text{L}^{\text{A}})_2(\text{L}^{\text{B}})_2$ type cage in this way would represent a substantially different approach from those described in the literature, which primarily relies on controlling metal coordination aspects (complementary angles, steric bulk, etc.).^[14]

Complexation of **L20** with Pd^{2+} (NO_3^- , BF_4^- , CF_3SO_3^- or PF_6^- salt) in a 2:1 molar ratio in CD_3CN was able to form a clear yellow solution as the same as ligand **L19**. Unfortunately, the ^1H NMR of the solution showed multiple sets of proton resonances. Still, we were pleasantly surprised to see one of these sets of resonances appeared in higher intensity, suggesting it was a major species, Figure 5.07. This species appeared to be highly symmetric; only two amide bond signals were observed, similar to what is seen in the starting ligand but more downfield shifted. As the model structures using density functional theory (DFT) calculations (B3LYP/def2SVP) show in Figure 5.08, if we consider only the possible up/down configurations (**L20A** and **L20B**) of the ligand in an M_2L_4 cage with the curvature of the ligands in the same direction, there are six possible cage isomers (A-F). One could expect that up to four different species could be observed by NMR consisting of a) four up and enantiomer (A and B), b) three up and enantiomer (C and D), and c) cis-two up (E) and d) trans-two up (F). Of these, the cases of a), c), and d) could be expected to show only two amide signals, while b) should show eight different signals. In addition to the major species in ^1H NMR, other lower intensity signals and broad signals are found overlapped with the higher intensity signals and may correspond to the case of b) or isomers derived from different curvature directions of the ligand. Notably, ESI-TOF-MS analysis suggests the composition of this solution was entirely cage isomers with the formula $\text{Pd}_2(\text{L20})_4(\text{BF}_4)_4$. The above results indicate that the self-assembly of ligand isomers **L20A** and **L20B** with Pd^{2+} can still form a preferred major species. However, there still exists a mixture of other isomers, $\text{Pd}_2(\text{L20A})_n(\text{L20B})_{4-n}$, $n=0-4$.

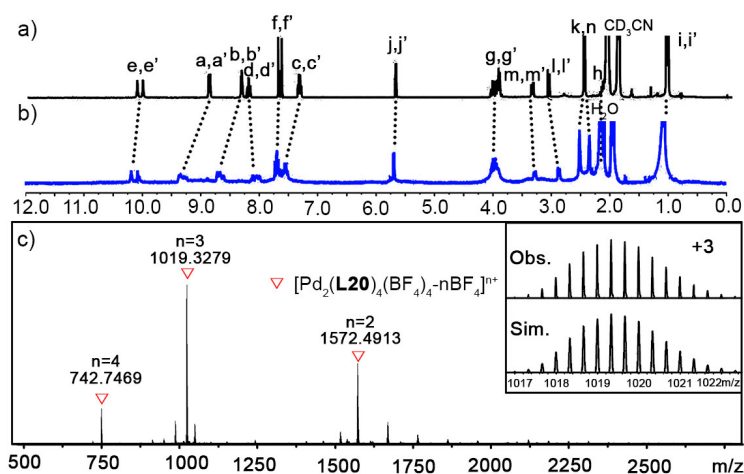


Figure 5.07 ^1H NMR spectra of a) **L20** and b) its self-assembly product $\text{Pd}_2(\text{L20})_4$. c) ESI-TOF-MS for $\text{Pd}_2(\text{L20})_4$ as its BF_4^- salt. Inset shows the comparison of the observed isotopic pattern with the simulated spectrum.

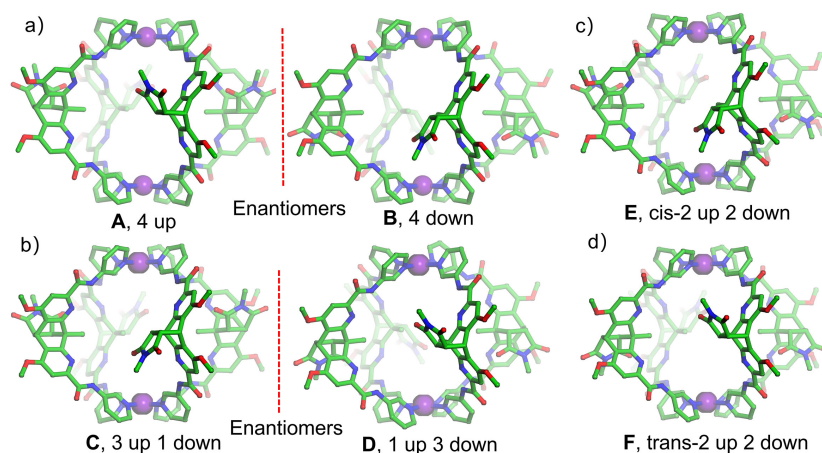


Figure 5.08 DFT calculated structures (B3LYP/def2SVP) of possible isomers (A-F) with up/down configurations of cage $\text{Pd}_2(\text{L20})_4$ in the case that the curvature of the ligands is in the same direction.

To gain better insight into the self-assembly behavior of this ligand **L20**, time-dependent self-assembly was performed at room temperature and compared to **L19**. For **L19**, time-dependent self-assembly was performed at

room temperature, Figure 5.09. Within 10 minutes of mixing **L19** with Pd^{2+} , a clean solution was obtained directly. However, ^1H NMR exhibited relatively broad signals with low intensity. After 1 hour, one set of simple, high symmetry proton resonances began to appear and became the main signals by ^1H NMR, similar to what was observed with our previous $\text{Pd}_2(\text{L6})_4$ cage. As the bridging group on this ligand exchanges, the initial broadness can potentially be attributed to isomers derived from different orientations of the ligand curvature. The ESI-TOF-MS analysis further supports this, suggesting that the solution composition was mainly species with formula $\text{Pd}_2(\text{L19})_4(\text{BF}_4)_4$.

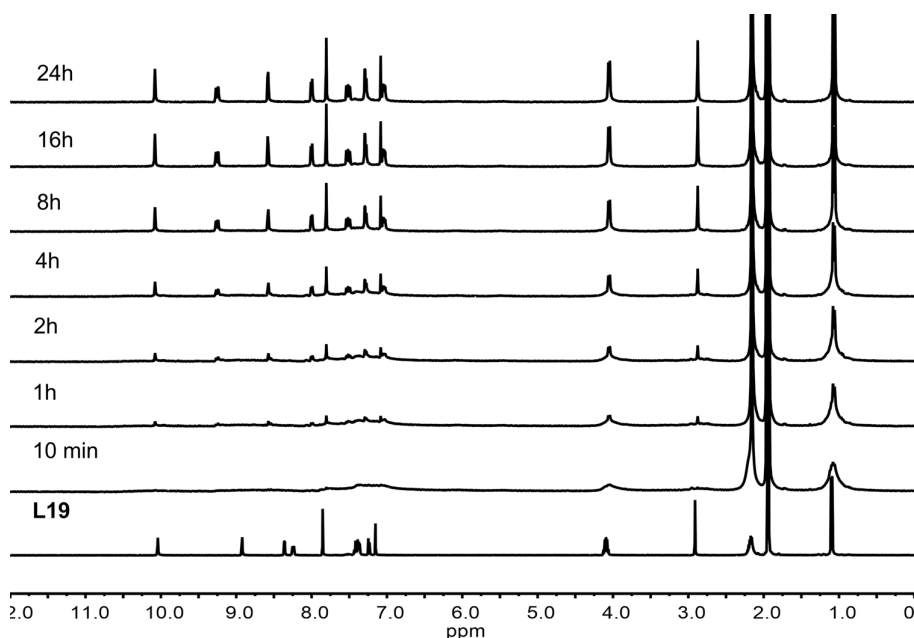


Figure 5.09 ^1H NMR spectra of time-dependent self-assembly of ligand **L19** with 0.5 equivalent $\text{Pd}(\text{CH}_3\text{CN})_4(\text{BF}_4)_2$ at room temperature.

Interestingly, **L20** shows similar behavior in time-dependent self-assembly, Figure 5.10. Within 10 minutes of mixing it with Pd^{2+} , a clean solution was obtained with the ^1H NMR spectrum also showing relatively broad signals with low intensity. After 1 hour, one set of symmetric and straightforward proton resonances began to appear. Still, unlike **L19**, these

simple proton resonances were always with other broad or lower intensity signals, and an increase in intensity or sharpening of the signals did not occur. Moreover, this mixture of cage isomers was relatively stable in the solution. After utilizing more extreme reaction conditions, there was no change, such as extending the time substantially or increasing the temperature. Using methylsulfone as an internal standard, the simple and symmetry proton resonances in the assemblies with ligand **L20** showed that the major species corresponded to only ~48% of the initial ligand concentration, while **L19** represent >92%, Figure 5.11. This suggests that the remaining ligand concentration for the self-assembly with **L20** should be assigned to the other sets of relatively broad signals in ^1H NMR potentially belonging to a more statistical mixture of $\text{Pd}_2(\text{L20A})_n(\text{L20B})_{4-n}$, $n=0-4$ cage isomers including lower symmetry structures.

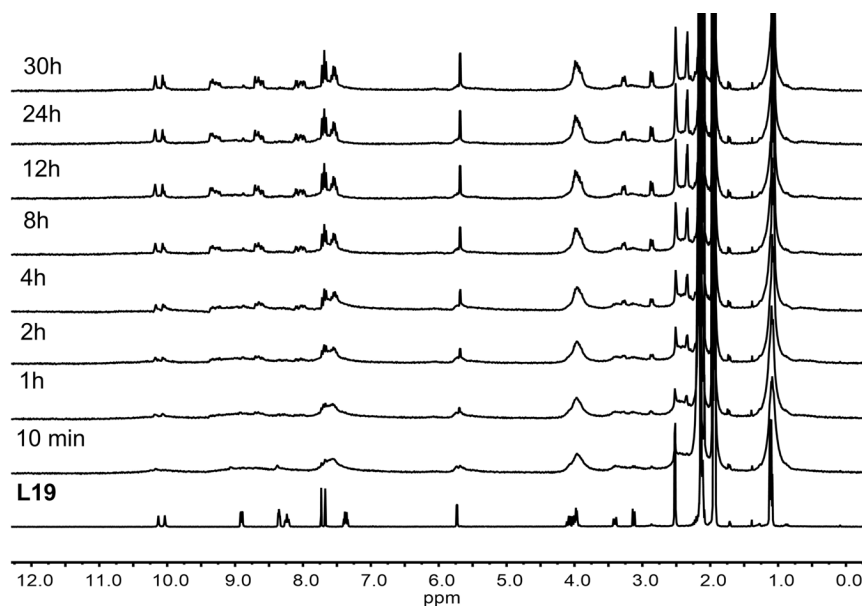


Figure 5.10 ^1H NMR spectra of time-dependent self-assembly with ligand **L20** and 0.5 equivalent $\text{Pd}(\text{CH}_3\text{CN})_4(\text{BF}_4)_2$ at room temperature.

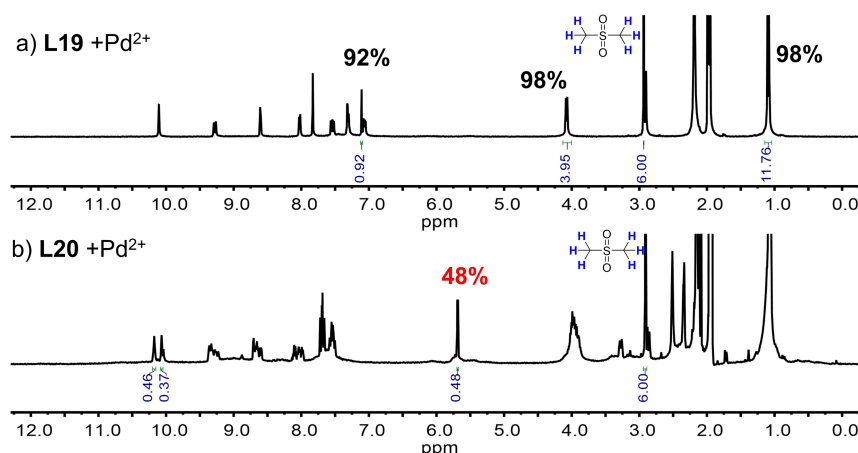


Figure 5.11: ^1H NMR spectra of self-assemblies with methylsulfone as an internal standard (ligand: methylsulfone = 1:1), the yield of simple and symmetry proton resonances determined to a) ligand **L19** correspond to >92% and b) ligand **L20** correspond to ~48% of the initial ligand concentration.

The time-dependent and quantitative NMR studies unambiguously show that the two enantiomers of **L20** (**L20A** and **L20B**) do not converge during self-assembly to a single structural outcome. This different self-assembly behavior of ligand **L20** further supports the role of dynamic adaptation of isomers in ligand **L19** was necessary for the self-assembly of a single cage. Still, by further tuning the structure of the 9,10-bridging group in these ligands, it can be interesting in the future to see if interligand interactions or shape complementarity can also allow the self-assembly of low symmetry cage structures. Heteroatom bridged ligands like **L19** can be interesting for this. The construction of heteroleptic assemblies through self-sorting has been reported to be a practical approach for increasing structural and functional complexity.^[3a,15] However, statistical mixtures are commonly formed during multicomponent self-assembly with two or more ligands, particularly when the ligands are nearly identical such as in the case of enantiomers. In our system, ligands **L19** provide a way to simplify these mixtures allowing easy NMR characterization and crystallization because of the high dynamic exchange between enantiomers. In essence, this will enable us to sample all of the

possible structural conformations of the cage to see what could be the most favored. For instance, observation in the crystal structure of a potential preference for the $\text{cis-Pd}_2(\text{L19A})_2(\text{L19B})_2$ hints at similar possibilities with other ligands.

5. Covalent post-modification

With the understanding obtained for the self-assembly with ligand **L19** and the verification that it forms a single M_2L_4 cage structure, we next looked to the possibility of using the Diels-Alder for the covalent post-modification of the metal-organic cages. Indeed, the Diels-Alder reaction has been reported to be an efficient reaction for post-modification of metal-organic assemblies, polymer and metal-organic frameworks.^[16] However, the use of 4-phenyl-1,2,4-triazoline-3,5-dione **5.01** as the dienophile represents a particularly intriguing option. It is a highly reactive dienophile that enables the quantitative synthesis of ligand **L19** under mild conditions. Moreover, literature reports describing its use for reversible Diels-Alder/retro Diels-Alder exchange with anthracenes under mild conditions make it ideal for post-modification of metal-organic cages where higher temperature can lead to disassembly/assembly mechanisms rather than direct modification. Still, it has not yet been described for this purpose. Therefore, we envisaged that a Diels-Alder reaction using 4-phenyl-1,2,4-triazoline-3,5-dione **5.01** could be adapted to metal-organic cages to offer a rapid and facile approach to tune their structures and functionalities.

To this purpose, the reactivity of 4-phenyl-1,2,4-triazoline-3,5-dione **5.01** and ligand **L1** was first followed by time-dependent ^1H NMR at room temperature. As shown in Figure 5.12, upon mixing ligand **L1** with 4-phenyl-1,2,4-triazoline-3,5-dione **5.01** (1.5 Equiv.) in CDCl_3 , the proton resonances of the target product **L19** began to appear within 10 minutes as a new set of shifted proton resonances. For instance, the amide proton resonances move from 10.3 ppm to 9.9 ppm and the 9-methyl of anthracene units from 3.3 ppm

to 2.9 ppm. This Diels-Alder reaction between 4-phenyl-1,2,4-triazoline-3,5-dione **5.01** and ligand **L1** was highly active, achieving ~50% yield within 1 hour and >90% within 8 hours at room temperature. Importantly, ^1H NMR shows complete conversion of ligand **L1** within 24 hours at room temperature, making it highly valuable for the possibility of covalent post-modification of metal-organic cages by the same Diels-Alder reaction.

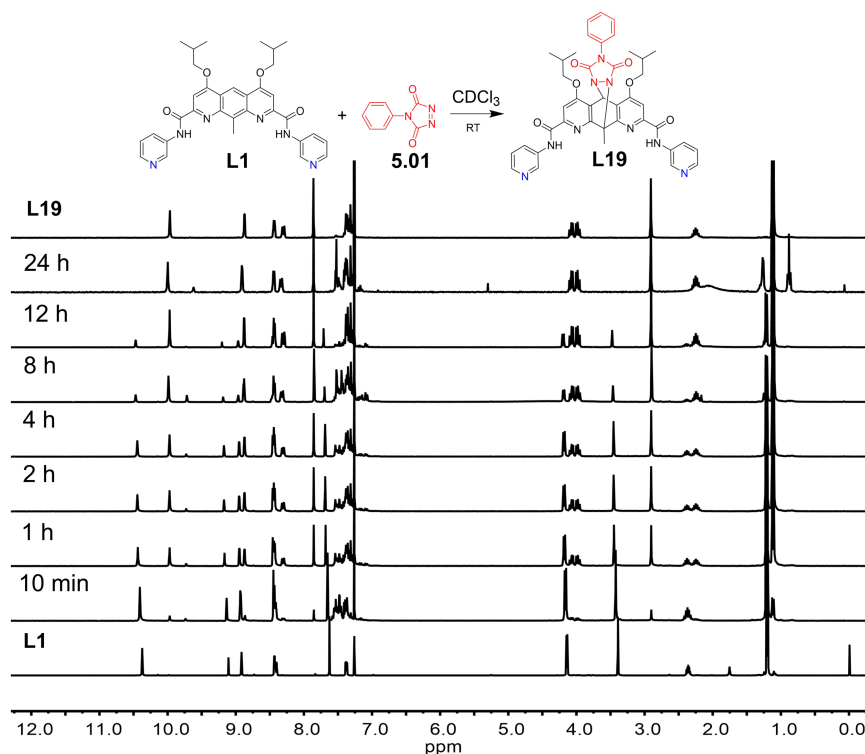


Figure 5.12 ^1H NMR spectra of time-dependent reaction with ligand **L1** and 4-Phenyl-1,2,4-triazoline-3,5-dione **5.01** (1.5 equiv.) at room temperature.

Thus, we next tested the covalent post-modification reaction with 4-phenyl-1,2,4-triazoline-3,5-dione **5.01** using the self-assembled anthracene-containing $\text{Pd}_2(\text{L1})_4$ cage as a model. Due to the solubility of the $\text{Pd}_2(\text{L1})_4$, the solvent was changed from CDCl_3 to a mixture of CD_3CN and $\text{d}^6\text{-DMSO}$ (v/v=20:1). Similar to ligand **L1**, $\text{Pd}_2(\text{L1})_4$ was mixed with 4-phenyl-1,2,4-triazoline-3,5-dione **5.01** (2.0 Equiv. dienophile per ligand) in solution at room

temperature. As verified by ^1H NMR spectra, the cage $\text{Pd}_2(\text{L1})_4$ was wholly converted into another species after 48 hours, Figure 5.13. Evidence of conversion of the anthracene units into the corresponding Diels-Alder adducts was clear based on the differences in chemical shifts for the ligand resonances. Notably, the characteristic proton resonances of the 10-position proton in the diazaanthracene units in $\text{Pd}_2(\text{L1})_4$ were shifted from 8.9 ppm to 7.1 ppm in its adducts, consistent with chemical shifts seen in **L19**. Also, similar to ligand **L19**, the 9-methyl resonance for the diazaanthracenes in $\text{Pd}_2(\text{L1})_4$ was found to be shifted from 3.6 ppm to 2.9 ppm after the reaction. These results indicate that the dienophile 4-phenyl-1,2,4-triazoline-3,5-dione **5.01** was able to covalently modify the $\text{Pd}_2(\text{L1})_4$ cage through a Diels-Alder reaction. Based on the self-assembly studies with **L19** and the dynamic nature of the bridging unit, we expected that the most favored Diels-Alder adduct of the $\text{Pd}_2(\text{L1})_4$ cage should be the same as for the $\text{Pd}_2(\text{L19})_4$ assembly formed with the pre-synthesized ligand **L19**. However, although the proton resonances observed in the ^1H NMR of the cage clearly indicate the formation of the Diels-Alder adducts of the ligands, they do not exactly match the previously formed $\text{Pd}_2(\text{L19})_4$ cage, Figure 5.13. Rather, a new set of proton resonances is obtained, indicating the formation of a new cage, a different isomer of cage $\text{Pd}_2(\text{L19})_4$, or potentially a change in the occupation of the cage cavity. This needs further confirmation. Notably, single-crystal X-ray structure analysis could help confirm the structure of the $\text{Pd}_2(\text{L1})_4$ Diels-Alder adduct.

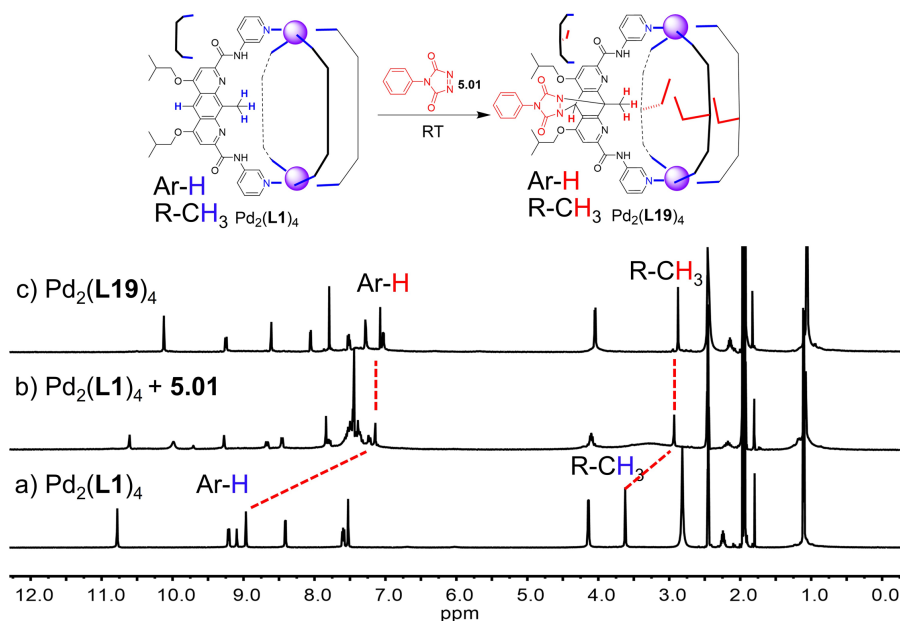


Figure 5.13 ^1H NMR spectra in CD_3CN and $\text{d}^6\text{-DMSO}$ ($v/v=20:1$) of a) $\text{Pd}_2(\text{L1})_4$, b) $\text{Pd}_2(\text{L1})_4$ with 8.0 equiv 4-phenyl-1,2,4-triazoline-3,5-dione **5.01** after 48 hours at room temperature and c) $\text{Pd}_2(\text{L19})_4$.

6. Conclusion

This chapter has potentially offered a method to expand the complexity and functionality of metal-organic architectures through covalent post-modification using Diels-Alder reactions to change the shape of the ligands. Two dienophiles, 4-Phenyl-1,2,4-triazoline-3,5-dione **5.01** and 1-Methyl-1H-pyrrole-2,5-dione **5.03**, with different reactivity and conditions for the Diels-Alder reaction, which would offer a rapid and facile approach to tune structures and functionalities. We successfully designed and synthesized ligands **L19** and **L20**, which were used to study their self-assembly behavior and optimize conditions for covalent post-modification. The ligand **L19** allows for a pyramidal inversion that allows equilibration between the two enantiomers (**L19A** and **L19B**). This property of dynamic adaption simplified the self-assembled mixtures, allowing easy NMR characterization and crystallization

due to the high dynamic exchange between enantiomers. Based on these promising results, we next attempted to covalently post-modify the metal-organic architectures at room temperature using 4-phenyl-1,2,4-triazoline-3,5-dione **5.01** as a highly active dienophile for the Diels-Alder reaction and found that a new cage species could be formed. However, the nature of this cage species still requires further study. As the Diels-Alder reactions between anthracene derivatives and N-phenyl-1,2,4-triazoline-3,5-dione are also readily reversible, it may be possible to extend this post-modification in a reversible way in the future, for instance, using a diene scavenger to recover the original anthracene-containing ligands and metal-organic cages.^[17] This could allow switching between two different structures for use in, for example, controlled guest release.

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Chapter VI

Foldamers based novel architectures

Based on the results and experience from the coordination-driven self-assembly in the previous chapters, in this chapter, we studied a new concept of using multiple helix formation of aromatic oligoamide foldamers as a driving force for self-assembly of higher-ordered architectures. Two kinds of ligands were designed with central linkers differing in bend angles and rigidity. An optimized synthetic method was established and allowed us to obtain two ligands, **L22** and **L23**, successfully. Importantly, NMR and MS studies for ligand **L22** showed promising results suggesting it can assemble into larger structures, providing a proof of concept for our idea.

1. Introduction

Self-assembly systems using synthetic molecules typically rely on only a handful of specific point interactions, provided by the small “primary” structures of the molecules, to drive the assembly of different units together. For example, metal-ligand coordination,^[1] hydrogen bonding,^[2] or dynamic covalent bond formation^[3] were driving forces. This poses a challenge when one expands on the complexity of structures possible due to limited orthogonality. For instance, hydrogen bond acceptors can also act as ligands for metals.^[4] Indeed, competition between different interactions can result in complex mixtures of self-assembled structures that are difficult to analyze. As such, most self-assembled structures are derived primarily from only one main driving force that brings together the different units. Nevertheless, these approaches have successfully allowed the construction of numerous

impressive discrete supermolecular structures that have been found in a wide range of applications, as discussed in the previous chapters and the introduction.^[5] Still, expanding on the variety of driving forces that can be used together in a particular orthogonal way can allow greater diversification of molecular assemblies. It could significantly advance our ability to precisely control the self-assembly of complex structures at the molecular level, similar to what is achieved by biological systems.

Importantly, many of the most complex self-assembled structures in nature do not rely on single-point interactions but instead on a collection of interactions spread across large surfaces formed from secondary, tertiary, or quaternary structures.^[6] The diversity in shape and electrostatic surfaces on these units gives high orthogonality due to shape complementarity and permits the formation of various highly asymmetric structures necessary for biological functions.^[7] Driving forces that mimic these sorts of significant surface area interactions could allow similar complex self-assembly with synthetic systems. Foldamers, or more precisely, aromatic oligoamide foldamers(AOF), are intriguing tools for this purpose.^[8] As discussed in the introduction, foldamers are molecules that adopt stable secondary or higher-ordered structures in solution through the same non-covalent interactions that control folding in biopolymers. These higher-ordered structures are ideal scaffolds for generating large functional group arrays over broad surface areas. Notably, AOF possesses excellent and complimentary self-organization and self-assembly properties.^[9]

As previously described, the secondary structures of AOF are the result of intramolecular non-covalent interactions between the aromatic monomers and the amide bonds that control local conformational preferences.^[8c,10] The collection of these local conformational preferences can be programmed through synthetic modification of the monomers to allow the formation of a range of different structural motifs, including sheets, zig-zag, linear strands, and, most importantly, helices.^[11] Numerous helical structures have been described in different aromatic units such as quinolines, pyridines,

naphthyridines, resorcinols, and diazaanthracenes.^[12] Mixing monomers with different sizes or stereochemical relationships between amine or carboxyl groups have even been used to form helical molecular capsules reported for encapsulation and recognition of guest molecules.^[8b,13] However, one of the most exciting properties of these foldamers is the ability of some sequences to self-assemble into multiple helices.

Since the report by Lehn and Huc in 2000 that pyridine oligomers could spontaneously dimerize into double helices, numerous multi-helical AOF sequences have been discovered over the last two decades.^[14] This multi-helix formation has been reported to be stabilized primarily by interstrand aromatic-aromatic interactions between the heterocyclic monomer rings of each strand. As such, the double-helix formation of the strands exhibits a chain-length dependence, with an increase in chain length generally leading to greater double helix formation.^[14b,14d,15] Additionally, the stability of the double-helix can also be enhanced by replacing the pyridine units with larger aromatic monomers, such as diazaanthracenes or quinolines.^[14a,16] Solvent effects have also been reported for their stability, though the self-association of strands are most commonly entropically unfavorable, with partial or complete dissociation occurring at higher temperatures.^[14e] Importantly, the above effects allow tuning of the association constants by changing the length or composition of the sequence and self-association constants ranging from 3×10^4 to $7 \times 10^5 \text{ M}^{-1}$ have been reported.^[14d] As sequence chirality or shape could also be used to direct self-sorting, the use of AOF multi-helix formation to assemble molecular building blocks could represent a powerful new driving force for the construction of larger molecular architectures. It could have high orthogonality both with different AOF sequences as well as with other established methods for self-assembly.

2. Concept and design of AOF based self-assembled structures

The previous chapters showed that aromatic oligoamide based ligands could be used for self-assembly with Pd^{2+} to form different metal-organic architectures. For these, the non-covalent interactions in the ligands controlled their conformation and the metal-ligand interaction acted as the driving force for the large structure formation more or less independently. In this chapter, we aim to study how AOF multiple helix formation can be used in the absence of metals to form discrete supramolecular assemblies and potentially more complex foldamer-based higher-ordered architectures. This would open up new exciting possibilities for self-assembly. However, no examples of using AOF multi-helix formation to generate discrete cage-like supramolecular structures with a well-defined cavity between their secondary subunits have been reported. Thus, we have set out to develop a proof of concept for studying this idea.

Our initial designs were based on ideas taken from the use of ditopic ligands in coordination-driven self-assembly. By incorporating two double helix forming sequences into a larger molecular structure that could be used to control their orientation, we expected that the bend angle between the helices could be used in a similar fashion to predict the final structure. As shown in Figure 6.01, a pentameric sequence of pyridines was chosen as the initial AOF sequence because of its ease of synthesis.^[14d] Its lower affinity for double helix formation could also promote the dynamic exchange needed for the self-assembly of targeted higher-ordered polygon structures. Relative to metal-based self-assembly, this unit would function like the formation of metal-ligand bonds. It was then envisaged that these sequences could be connected to two different central linkers that would position the AOF sequences at approximately 0° or 120° to each other. Based on the concepts from coordination-driven self-assembly, these could result in either a simple two-component macrocycle or a larger multi-component hexagon. The flexibility

versus rigidity of the central linkers is also different. While the linker for the larger structure relies on a highly rigid benzene unit, the central linker for the smaller structure is based on a more flexible pyridine amide unit. Still, as seen in the previous chapters, the non-covalent interactions in this unit should help promote the formation of the targeted discrete dimer rather than a polymer. For simplicity, and in relation to the other chapters, the structures containing the two double helix forming sequences will be referred to as ligands, Figure 6.01.

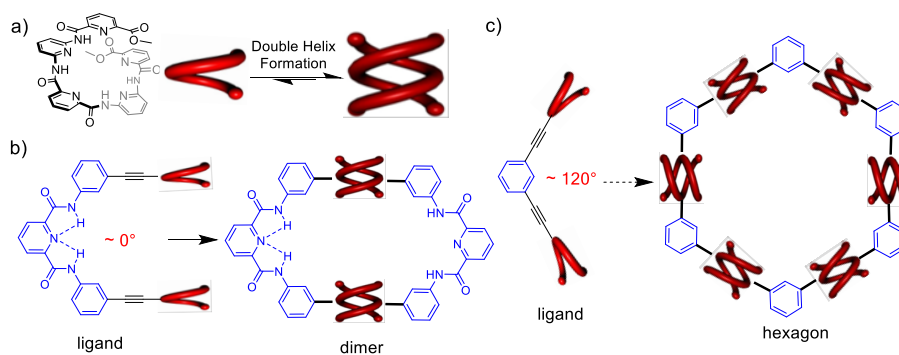
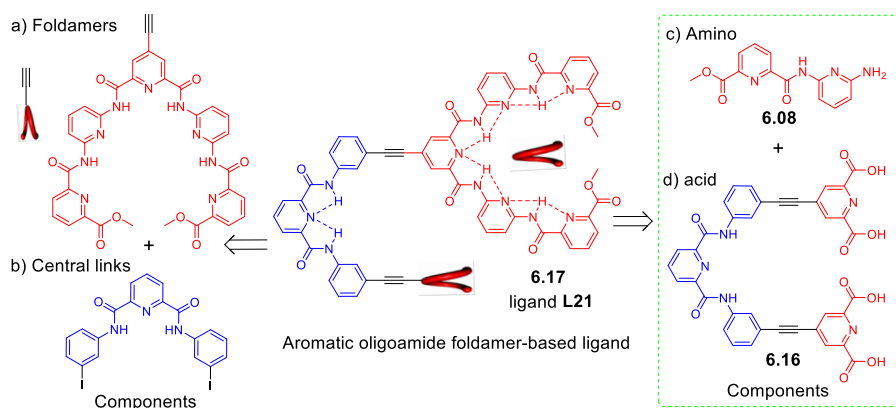


Figure 6.01 a) Pentameric sequence of pyridines and its double helix formation, b-c) the design of two types of aromatic oligoamide foldamer-based ligands differing in the bend angle and flexibility versus rigidity of central linkers and their potential self-assembly to higher-ordered polygon structures.

3. Synthesis of ligands and self-assembly

One of the main challenges, and a potential drawback, for using AOF in self-assembly is that the synthesis of the large units can be time-consuming for developing the initial systems. Still, once an ideal system is found, the high modularity of AOF should make diversification more easy and rapid. As shown in Scheme 6.01, the ligands consist of three main components: the foldamer sequence, the central linker, and the attaching method. From a synthetic standpoint, the critical step relates to covalently attaching multiple double helixes forming sequences to a central linker. Indeed, for the formation of the

foldamer units, the chemistry is well-established and relies on simple amide bond formation.



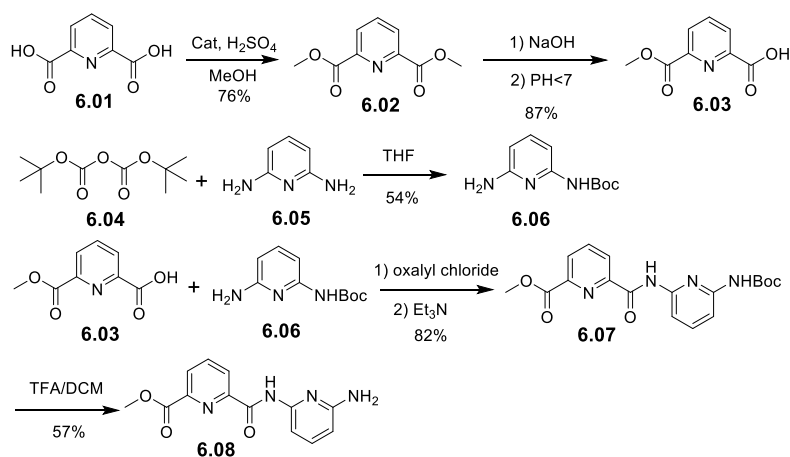
Scheme 6.01 The retrosynthesis for the target initial aromatic oligoamide foldamer-based ligand **21**. a-b) Sonogashira coupling reactions of foldamers and central links, c-d) amide coupling of components.

In the retrosynthesis, the target AOF ligand can split in multiple different ways, Scheme 6.01. The first (a&b) is an intuitive way that directly uses Sonogashira coupling of the aromatic oligoamide sequences and central linker. However, the risk of this method is that once the pentameric sequence of pyridines is formed, double helix formation with the intermediate may lead to difficulties in purification and affect subsequent Sonogashira coupling reactions. Another pathway (c&d) was also envisaged where the pentameric sequence of pyridines was synthesized in the last step through the amide coupling reaction. This would be a standard synthetic method for aromatic oligoamide foldamer synthesis, and while the formation of four amides could be challenging. Several examples of such reactions have been described in the literature.^[14d] Thus, with the formation of the pentameric sequence in the last step, this latter approach was chosen as the initial synthetic route.

3.1 Initial synthesis

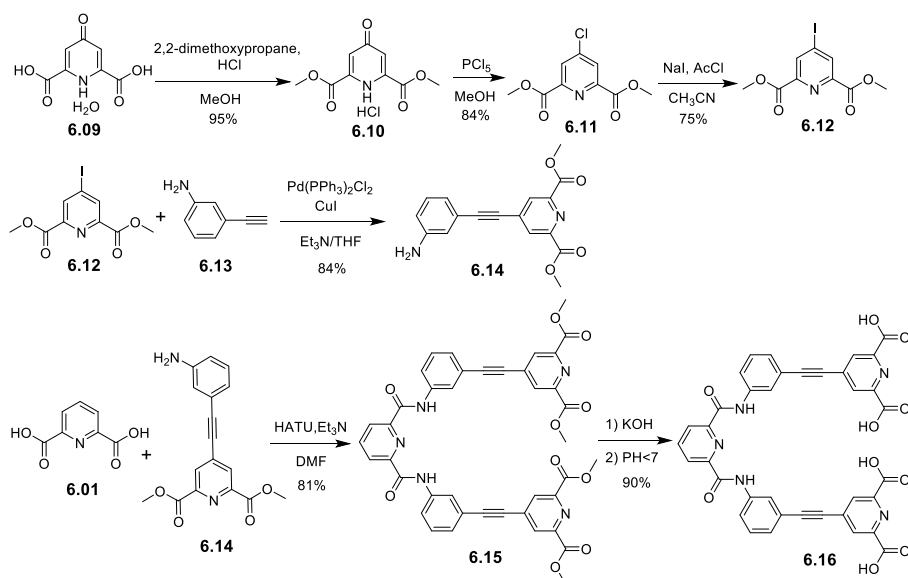
For the synthesis of the pentamer, the component precursors, a pyridine dimer amine and a pyridine dicarboxylic acid can be synthesized as shown in

Scheme 6.02-6.04. The pyridine dimer amine **6.08** can be obtained in seven steps, Scheme 6.02. It started from commercially available 2,6-pyridinedicarboxylic acid **6.01** and 2,6-diaminopyridine **6.05**, following reported procedures related to protection and deprotection methods of the carboxyl and amino groups and the amide coupling reaction.^[17]



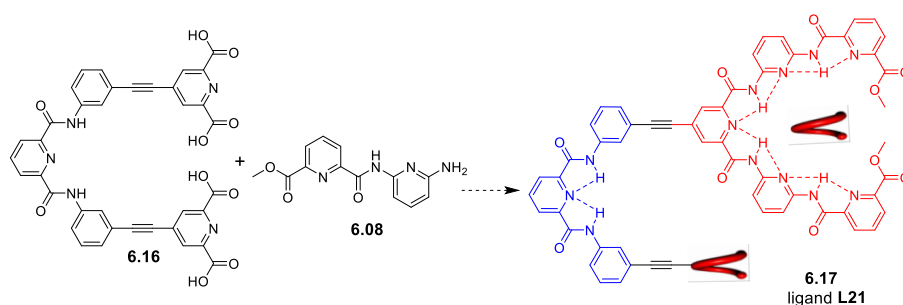
Scheme 6.02 The synthetic route for the pyridine dimer amine **6.08**.

Next, the tetra acid-linked central unit **6.16** was synthesized in six steps with an overall 37% yield starting from chelidamic acid **6.09**, Scheme 6.03. For the Sonogashira coupling, **6.09** was converted into 4-iodo diester **6.12**. After the esterification of chelidamic acid, PCl₅ was used to generate the 4-chloro derivative **6.11** initially. This could then be transformed into 4-iodo diester **6.12** in 75% yield by sonication with sodium iodide and acetyl chloride in acetonitrile. The more highly reactive **6.12** was then used for the Sonogashira coupling with 3-ethynylaniline **6.13**, yielding 84% of compound **6.14**. With compound **6.14** in hand, the central component of compound **6.16** was successfully synthesized via standard 1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate (HATU) coupling with pyridine dicarboxylic acid followed by saponification to give the tetra acid-linked central unit **6.16**.



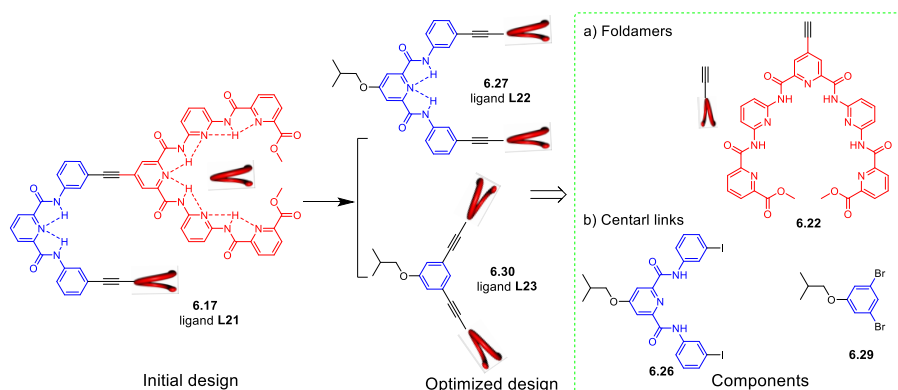
Scheme 6.03 The synthetic route for the tetra acid-linked central unit **6.16**.

After successfully obtaining the precursor components **6.08** and **6.16**, the target aromatic oligoamide foldamer-based ligand, compound **6.17** (Ligand **21**), was planned to be accessed by amide coupling, Scheme 6.04. The amide coupling was set up in DMF under basic conditions, and HATU was again used as the coupling agent. However, the crude product was insoluble in common solvents, thus limiting the purification and characterization of the product. Some other amide condensation methods (PyBOP, acid chloride, etc.) were also tried and were found to form similar insoluble products. Since the starting component with the amino group disappeared, the amide coupling should have been worked. However, the outcomes were limited by characterization to confirm its target product **6.17**. This may be attributed to the tetra acid compound **6.16** and potential intermediates in the reaction having intrinsically low solubility. The need to generate four amide bonds simultaneously can also be leading to the target product **6.17** mixing with some partially formed components resulting in significantly decreased reactivity. Therefore, we looked to change the synthetic pathway to optimize the synthesis of the ligands.



Scheme 6.04 The initial synthetic route for aromatic oligoamide foldamer ligand compound **6.17** (Ligand **21**).

3.2 Optimized synthesis and self-assembly

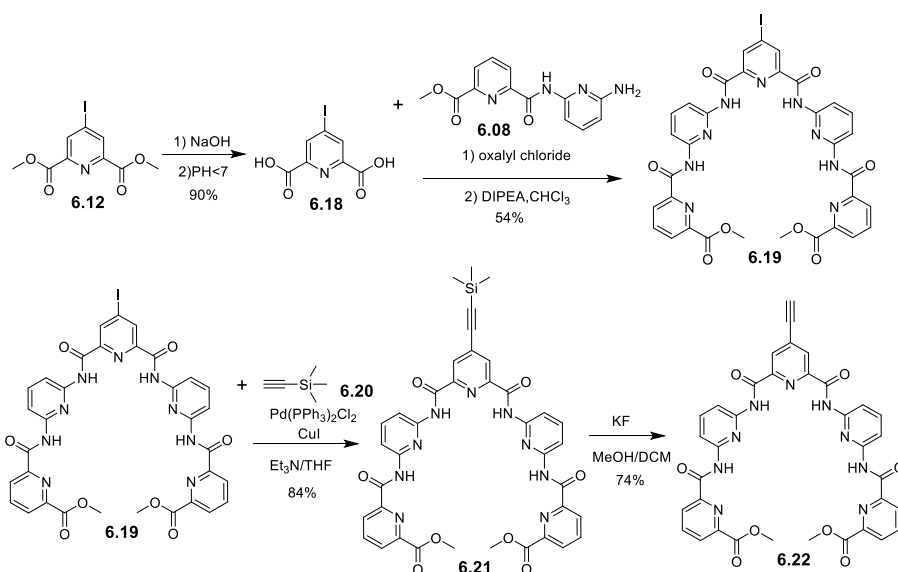


Scheme 6.05 The initial and optimized design of the target foldamer-based ligands and their retrosynthesis by Sonogashira coupling components.

As shown in Scheme 6.05, to overcome the challenges faced in the initial synthesis, the ligand design was slightly modified to include an iso-butoxy group on the central linker. This should have a negligible effect on the double helix formation but can increase the solubility of this unit during subsequent reactions. Additionally, we switched the order of the attachment and amide coupling reactions, looking first to synthesize the foldamer segments and then add them to the central linker via the Sonogashira coupling. This would have the advantage of only forming two chemical bonds simultaneously instead of four with the previous approach.

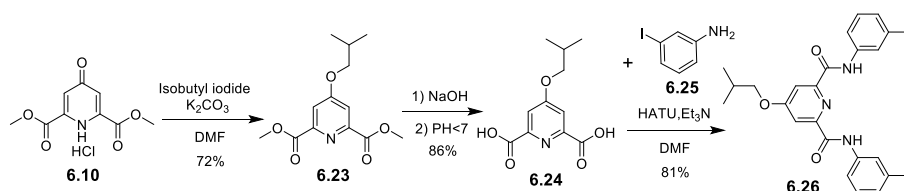
Chapter VI

Like the initial synthetic route for compound **6.17** (Ligand **L21**), straightforward access to the new ligand **L22** can be possible through a handful of organic synthesis steps, Scheme 6.06-6.08. Indeed, we obtained the target precursor foldamer of the component **6.22** in high yield after amide coupling between pyridine dimer **6.08** and 4-iodopyridinedicarboxylic acid **6.18**, followed by Sonogashira coupling with trimethylsilylacetylene and silyl deprotection, Scheme 6.06.

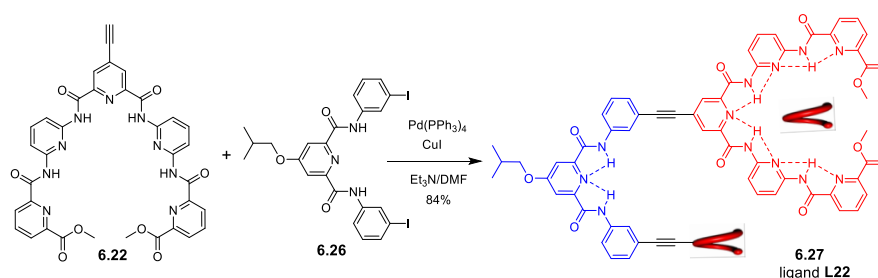


Scheme 6.06 The synthetic route for the precursor foldamer of the component **6.22**.

The central linker compound **6.26** with a bend angle of about 0° was also synthesized from dimethyl chelidamate **6.10**, Scheme 6.07. First, the isobutoxy group was introduced by alkylation with isobutyl iodide. Next, following a similar procedure as compound **6.15**, i.e., saponification and amide coupling with 3-iodoaniline, gave the target central linker **6.26** in 50% yield across three steps.



Scheme 6.07 The synthetic route for the central linker compound **6.26**.



Scheme 6.08 The synthetic route for aromatic oligoamide foldamer ligand compound **6.27**(Ligand **22**).

Finally, a Sonogashira coupling was used to attach the alkynyl functionalized foldamer sequence **6.22** and central linker **6.26**, Scheme 6.08. We were pleasantly surprised by the reaction; the mild conditions do not interfere with the central linker or the foldamer sequence. There did not appear to be any problems of metal coordination inhibiting the reaction. Importantly, the solid obtained after the reaction was well-soluble in chloroform, allowing it to be studied by NMR and MS. After the coupling, we anticipated that compound **6.27** (ligand **L22**) would be formed.

Indeed, ^1H NMR indicated that the alkynyl functionalized foldamer sequence **6.22** and the central linker **6.26** were no longer present, and a more complex NMR spectrum was observed in Figure 6.02. The possibility for different aggregation states due to double helix formation or helix chiralities could be expected to lead to multiple sets of signals, potentially challenging to distinguish from impurities. In the typical case of the pyridine double helix, the single/double helix equilibrium is in fast exchange, resulting in only two sets of amide signals. However, in the case of our ligands, the potential for multi-

valency due to the different connection sites could slow this equilibrium leading to multiple signals. For **L22**, in the case of a monomeric form (ligand itself), if it remains in high symmetry, three amide signals could be expected, two from the foldamer sequence and one from the central linker. If this dimerizes as desired, forming (**L22**)₂, either five or ten amide signals should be observed depending on helix chirality (PP/MM and PM/MP diastereoisomers). Based on the integration of ¹H NMR, two different species are present and temporarily assigned to **L22** and (**L22**)₂, Figure 6.02. For example, protons resonances of the amide groups, appearing between 9.5 to 11.0 ppm, showed one set of higher signals with three peaks. However, another set of overlapping and lower signal with five peaks can also be clearly observed, potentially belonging to the dimeric form. MS analysis proved more promising results to NMR. The formation of compound **6.27** (ligand **L22**) was confirmed and found mixed with its dimer assembly (**L22**)₂, Figure 6.03. The HR-ESI-MS spectrum showed the monomeric ligand **L22** as [M+H]¹⁺ at 1785.5194 along with its sodium adduct [M+Na]¹⁺ at 1806.4954. An additional set of lower intensity signals consistent with the dimer (**L22**)₂ as [M+2H]²⁺ could also be observed at 1785.0162. In all cases, the observed M/z values were <5 ppm from the theoretical values. In addition, a comparison of the observed isotopic patterns for monomer **L22** and dimer (**L22**)₂ with their corresponding theoretical patterns showed a good match. This suggests that the AOF-based ligand **L22** was successfully prepared and can self-assemble to higher-ordered structures.

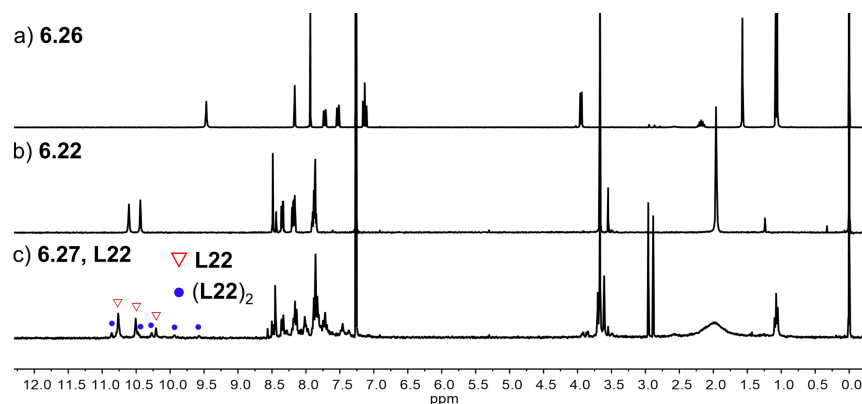


Figure 6.02 ^1H NMR spectra of compounds a) **6.26**, b) **6.22** and c) **6.27**(Ligand **22**) in chloroform.

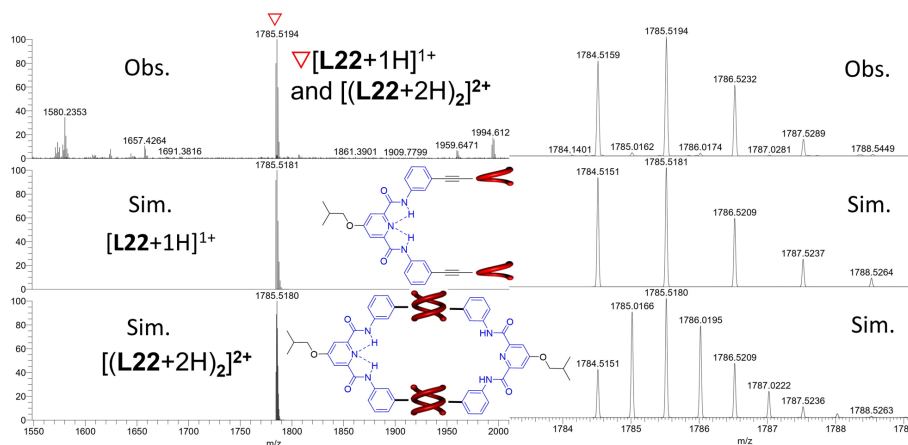
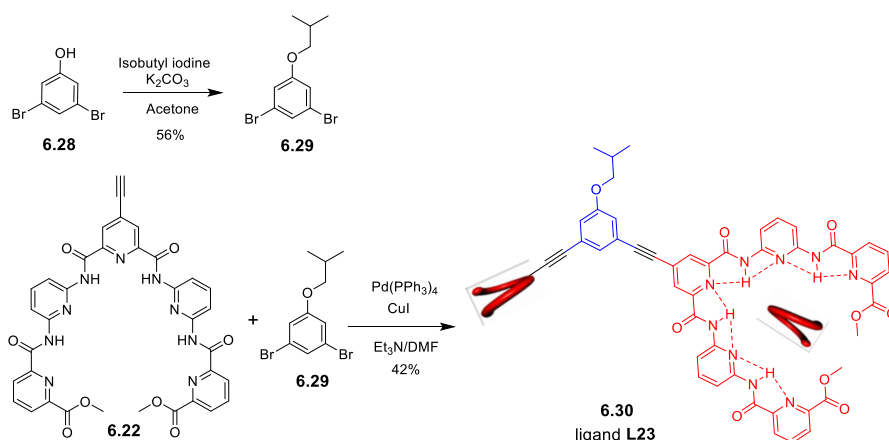


Figure 6.03 HR-MS for ligand **L22** as a mixture of monomer and dimer, the observed isotopic pattern and the simulated spectra are shown on the right.

Still, neither the NMR nor MS allow us to make any conclusions on the structure of the $(\text{L22})_2$ species and more studies are needed to fully confirm the self-assembly, purity, and structure of the product. Ways to push the self-assembly to only a single product rather than a mixture could help with this, as methods prevent self-assembly until desired. Nevertheless, these results are promising and suggest that our design can potentially lead to a new tool for self-assembly.



Scheme 6.09 The optimized synthetic route for aromatic oligoamide foldamer ligand compound **6.30**(Ligand **L23**).

Following similar synthetic procedures for **L22**, we also successfully obtained compound **6.30** (ligand **L23**), Scheme 6.09, where a rigid meta-substituted benzene unit was used as the central linker. This changes the bend angle from $\sim 0^\circ$ to 120° , potentially leading to larger polygons. The ligand **L23** has a high solubility in chloroform, thus enabling us to study the concentration effect of self-assembly. As the double-helix formation was reported to have a concentration dependence, increasing concentration should lead to double helix formation and, ideally, a more self-assembled structure.^[14e] Unfortunately, due to timing, only preliminary studies could be done. Varying concentration showed modest changes in the resonances of ligand **L23** by 1H NMR, Figure 6.04. Still, significant work will need to be done to confirm that any self-assembly has occurred with this ligand **L23**. Although the rigid central linker of this ligand should help promote self-assembly, the self-assembled structure requires a 6-fold double helix formation. With the self-association constants reported for pyridine pentamers, this may be too demanding. Sequences with higher association constants might help this.

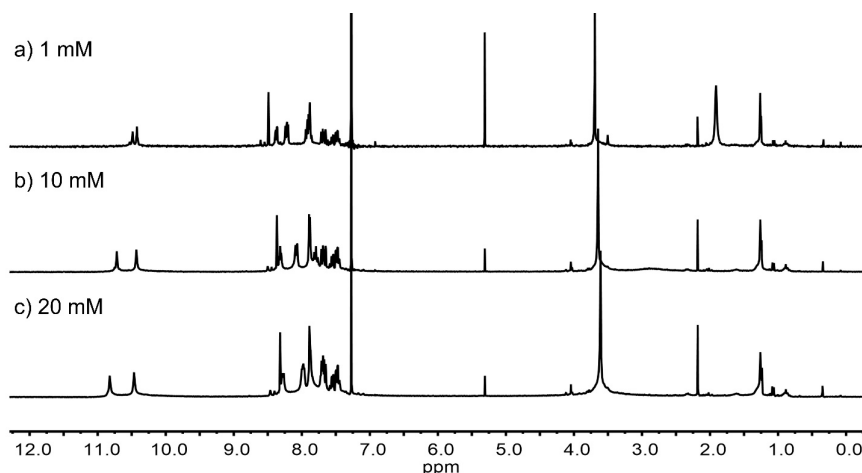


Figure 6.04 ^1H NMR of ligand **L23** with a variable concentration in CDCl_3 , a) 1 mM, b) 10 mM and c) 20 mM.

4. Conclusion

Multiple helix formation based on the secondary structures of aromatic oligoamide foldamers can offer an orthogonal approach for the self-assembly of supramolecular polygons and potentially more complex supramolecular architectures. To study this concept, this chapter designed and synthesized two kinds of ligands with central linkers differing in bend angles and rigidity. After an initial attempt to develop these systems, we were able to find good synthetic routes for the design of two new ligands **L22** and **L23**. Importantly, NMR and MS studies for ligand **L22** showed promising results that suggest it can assemble larger structures. Though the nature of these larger species still needs to be further studied. Nevertheless, more work on the study of self-assembly through double helix formation, additional characterization and X-ray structural analysis are necessary to confirm the self-assembly outcomes unambiguously. As the concept demonstrated in this chapter, the use of multiple helix formation in well-folded synthetic strands for the self-assembly of discrete higher-order assemblies is a bio-inspired approach with the potential to transform the design of the more complex supramolecular systems.

Chapter VI

The ground-up synthesis of these systems, using monomers that are remote from nature, creates prospects for the de novo design of molecules with complexity and reactivity rivaling that of biomolecules, but that make use of the entire range of chemical tools available. A long-term goal from this work is applying this approach, not just towards the designed polygonal structure but more generally for developing a broad range of self-assembled supramolecules or molecular frameworks and materials.

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Chapter VII

Conclusions and Perspectives

1. Conclusions

A primary goal of the research described in this thesis was to advance knowledge in controlling self-assembly with non-covalent interactions and complementary shapes of ligands to achieve more complex structures and functionality. For this, the research work was split into four consecutive aspects.

In the initial research work of this thesis, a series of heteroaromatic amide-based ligands were designed and synthesized with endohedral non-covalent interactions and used for coordination-driven self-assembly of M_nL_{2n} polyhedral cages, Figure 7.01. This approach mimics the behavior in nature, where non-covalent interactions are essential for directing protein folding across multiple intermediates and can even provide access to multiple stable structures with different properties and functions. Two ligands (**L1** and **L2**) whose bend angles are controlled by non-covalent interactions and one ligand (**L3**) lacking the above-mentioned interactions were synthesized and used for self-assembly with Pd^{2+} . Two other ligand designs (**L4** and **L5**) were used as the control for computational chemistry and to study the influence of solubility, respectively. As these weak interactions in the aromatic amide ligands are easily broken, the bend angles have controlled flexibility giving access to $M_2(L1)_4$, $M_6(L2)_{12}$, and $M_{12}(L2)_{24}$ cages. By controlling the self-assembly conditions, this process can be directed in a step-wise fashion. Additionally, the multiple endohedral hydrogen bonding sites on the ligand were found to

play a role in the binding and discrimination of neutral guests.

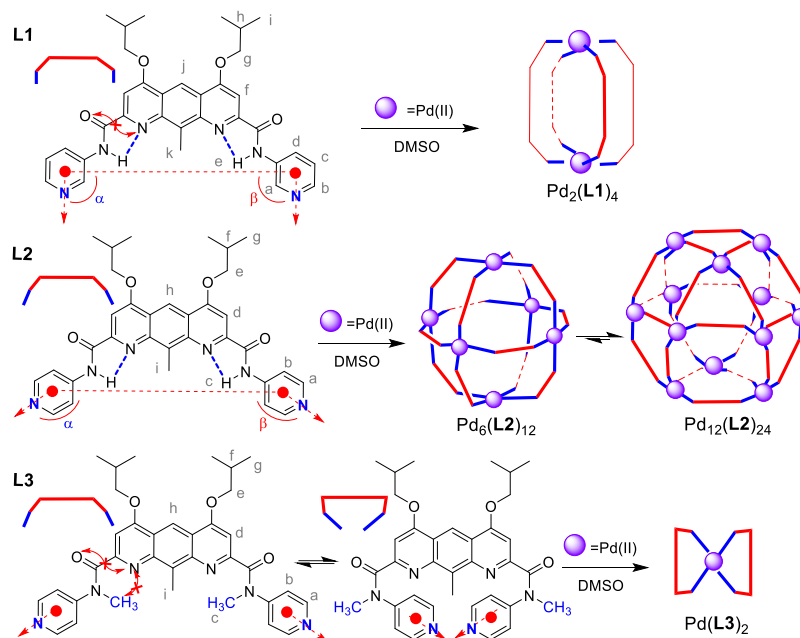


Figure 7.01 Design of ligands **L1-L3**, showing the important non-covalent interactions and the bend angle. Cartoon representations of the products of their self-assembly with Pd^{2+} are shown at the right. The angle between donor atoms on the ligands are calculated as: Bend angle = $(\alpha - 90^\circ) + (\beta - 90^\circ)$.

Based on the success of using non-covalent interactions to mediate conformational rigidity and showing that this provides sufficient control over the bend angles of the ligands to direct self-assembly, the subsequent work studied more complex self-assembly systems. Complex dual curvature ligands (**L6-L18**) were obtained using a Diels-Alder reaction to break the symmetry of the ligands and incorporate additional steric constraints and complementary shapes, Figure 7.02. Importantly, with the ligands **L6-L7**, we showed that these constraints could help direct self-assembly of the ligands with Pd^{2+} towards a single M_2L_4 cage or M_4L_8 double-walled metallomacrocycle out of hundreds of possible isomers.

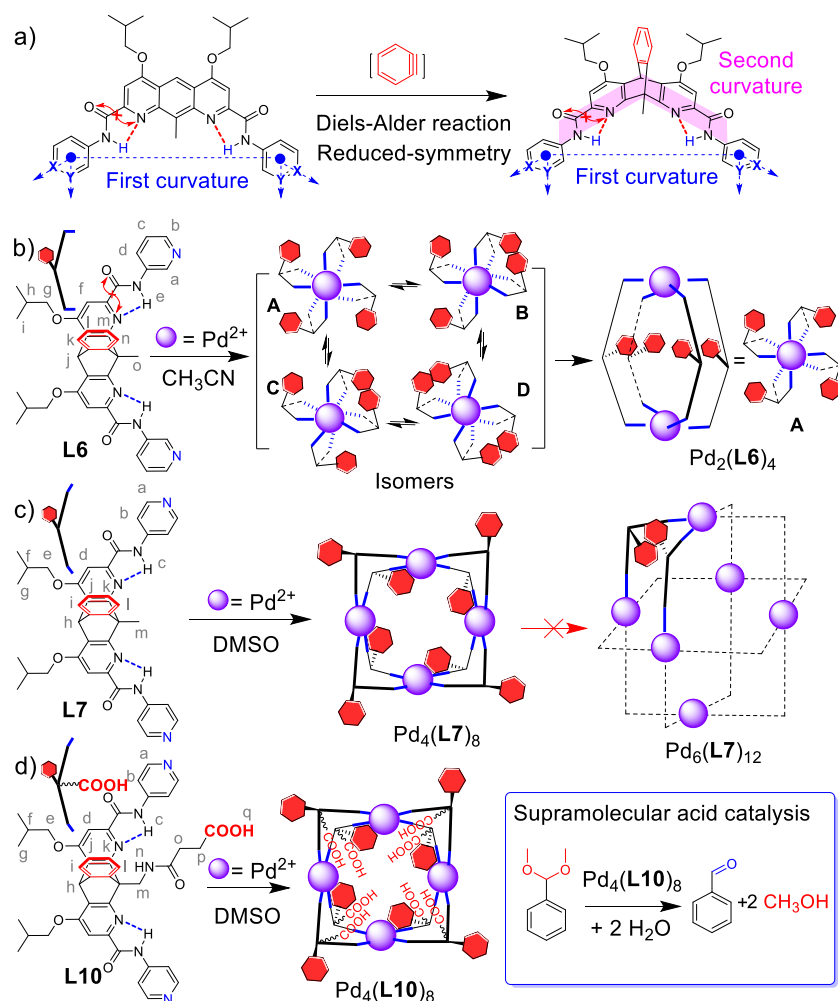


Figure 7.02. a) Reduced-symmetry of the formed triptycene structures by cycloaddition of benzyne into 1,8-diazaanthracenes; b-d) the structure of ligands **L6**, **L7**, **L10** and their self-assembled products.

Moreover, the high modularity of the amide ligands allows ready access to functionalized ligands (**L8-L11**). The acid-functionalized ligands are capable of self-assembling with Pd^{2+} to give deep cavitands with endohedral acid functions that can perform tandem catalysis with remarkable rate enhancements and product selectivity. The self-assembly can also be sensitive to the size of the endohedral groups. With larger endohedral groups (**L8-L11**), there is an increased possibility to generate larger double-walled

metallomacrocyclic (i.e., M_5L_{10}). However, when the size of endohedral groups (**L12-L17**) decreases, the self-assembly behavior can be different, potentially allowing interlocked structure formation to be possible (i.e., dimerization of M_2L_4). Interestingly, the cavity size in the M_4L_8 cages can be easily tuned using the initial size of the ligand (**L18**). This can give greater potential more diverse endohedral functional groups to the M_4L_8 cages for different applications. These results advanced the knowledge of coordination-driven self-assembly and opened the door to control self-assembly with low symmetry and flexible subcomponents closer to those used in nature.

Another limitation of metal-organic architectures is that the covalent reactions are exclusively used to synthesize and modify ligands before self-assembly. Thus, in chapter 5, we studied covalent post-modification as a shorter alternative pathway to achieve similar complex structural and functional diversity. Two dienophiles, 4-Phenyl-1,2,4-triazoline-3,5-dione and 1-Methyl-1H-pyrrole-2,5-dione, with different reactivity and conditions for the Diels-Alder reaction, were successfully used for the design and synthesis of ligands (**L19** and **L20**), which were next studied for self-assembly and optimization of conditions for covalent post-modification. Importantly, the ligand **L19** allows for a pyramidal inversion that allows equilibration between the two enantiomers (**L19A** and **L19B**). This property of dynamic adaption simplified the self-assembled mixtures, allowing easy NMR characterization and crystallization due to the high dynamic exchange between enantiomers. In the solid-state, two enantiomers were found oriented two up and two down in a single isomer in a cis-configurational arrangement of the cage, cis-Pd₂(**L19A**)₂(**L19B**). Based on these promising results, we were able to covalently post-modify the metal-organic architectures at room temperature using 4-phenyl-1,2,4-triazoline-3,5-dione **5.01** as a highly active dienophile for the Diels-Alder reaction and found that a new cage species could be formed. Although the nature of this cage species still requires further study, it demonstrates a rapid and facile approach to tune structures and functionalities of metal-organic architectures through covalent post-modification.

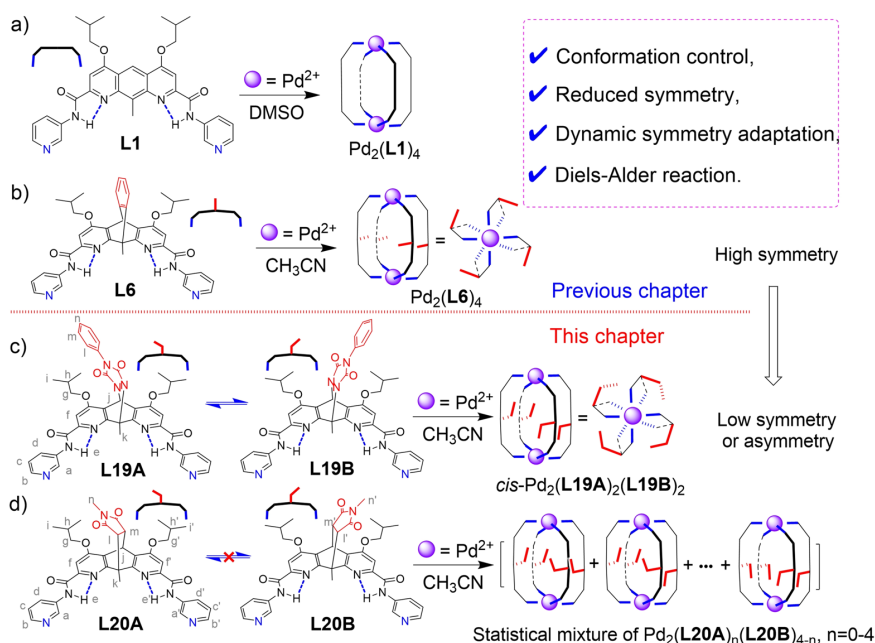


Figure 7.03 Design of new ligands **L19-L20**, showing the continuous reduction in symmetry by Diels-Alder reaction, a) conformation controlled high symmetry ligand **L1**, Diels-Alder reaction with b) symmetrical benzene in ligand **L6**, c) ligand **L19** equilibrium between two of its enantiomers (**L19A** and **L19B**) and d) ligand **L20** existence in two stable enantiomers (**L20A** and **L20B**). Cartoon representations of the products of their self-assembly with Pd^{2+} are shown at the right.

Finally, based on the results and experience from the coordination-driven self-assembly, a new concept of using multiple helix formation of aromatic oligoamide foldamers as a driving force for self-assembly of higher-ordered architectures was studied. Two kinds of ligands were designed with central linkers differing in bend angles and rigidity. An optimized synthetic method was established and allowed us to obtain two foldamer-based ligands, **L22** and **L23**, successfully. Importantly, NMR and MS studies for ligand **L22** showed promising results suggesting it can assemble into larger structures, providing a proof of concept for our idea. Nevertheless, more work on the study of self-assembly through double helix formation, additional characterization and X-

ray structural analysis are necessary to confirm the self-assembly outcomes unambiguously. It is proof of concept that this bio-inspired approach with the potential to transform the design of more complex supramolecular systems.

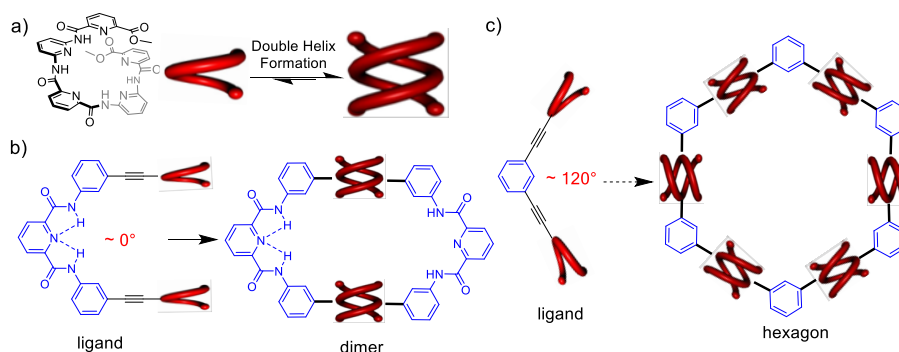


Figure 7.04 a) Pentameric sequence of pyridines and its double helix formation, b-c) the design of two types of aromatic oligoamide foldamer-based ligands differing in the bend angle and flexibility versus rigidity of central linkers and their potential self-assembly to higher-ordered polygon structures.

2. Perspectives

The design and synthesis of novel aromatic amide-based ligands enabled the self-assembly of a series of complex structures and has set up the foundation for further applications. The high modularity of the amide ligands has been shown to give ready access to functionalized ligands. For instance, ligands **L8-L11** with different functional groups. Importantly, the acid-functionalized M_4L_8 cavitands with endohedral acid functions showed promising tandem catalysis. Indeed, another critical aspect in catalysis is chirality, a pervasive structural feature of nature and crucial to the organization and function of nearly all biological systems. Based on the catalytic results with our cages, it should be interesting to extend the functional groups to chiral moieties. This will allow understanding the effect of endohedral chirality on the property of structures. In case endohedral chiral catalyst can be a new supramolecular method to prepare single enantiomeric compounds, which has become an

increasingly important issue in biochemistry and pharmacology. Some novel organic reactivity has been reported through the cooperation between supramolecular hosts and active catalytic sites. Thus, it will be essential to examine the potential as a reliable and efficient strategy for the catalytic synthesis of enantiopure compounds with more experiment results. Due to the significant impact on substrate activation and structures of intermediates and transition states, varying electronic and steric properties of chiral catalysts in cavitands can be used to tailor and tune stereoselectivity in asymmetric catalysis. For instance, the ligand **L24** endohedral chiral proline can be interesting for the initial study, Figure 7.05. This ligand should be obtained in two steps: amide coupling with ligand **L9** and Boc protected proline and follow by Boc deprotection. All reactions and self-assembly can follow similar reactions in this thesis and thus enable the study of supramolecular chiral catalysis.

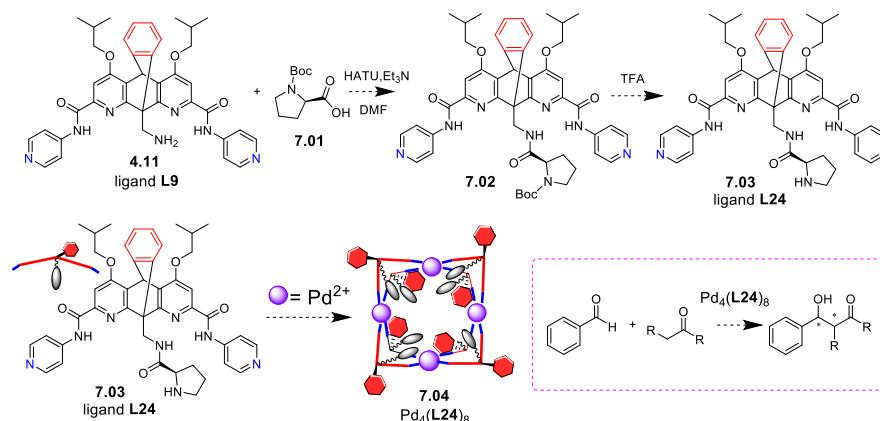


Figure 7.05 The proposed synthetic routes for aromatic amides-based ligand **L24** with chiral groups, and use for self-assembly with Pd²⁺ supramolecular asymmetric catalysis.

Covalent post-modification is another approach to expand the complexity and functionality of metal-organic architectures. After the attempt with more Diels-Alder reactions to optimize conditions for covalent post-modification, we were able to use 4-Phenyl-1,2,4-triazoline-3,5-dione **5.01** as a highly active

dienophile, offering a rapid and facile approach to tune structures and functionalities at room temperature. However, the nature of the formed cage species through covalent post-modification still requires further study. Indeed, the final structure requires confirmation through X-ray crystallography. Additional NMR or mass spectrometry monitoring of the post-modification process can be an important aspect for understanding the different potential mechanisms of the Diels-Alder reactions on free ligands and cages. In addition, these experiments need to be supplemented with a deeper understanding of post-modification. Another attractive property of the Diels-Alder reactions between 4-Phenyl-1,2,4-triazoline-3,5-dione **5.01** and anthracene derivatives is that readily reversible. It can be one main direction of expansion of this work because few examples of reversible covalent post-modification of metal-organic architectures have been reported under mild conditions. Thus, there is still a lack of knowledge on this topic. This reversible property can be helpful for stimulus-response applications. To achieve this, using more active diene scavengers to recover the original anthracene-containing ligands and metal-organic cages can be a good idea to avoid the high temperatures usually required, Figure 7.06.

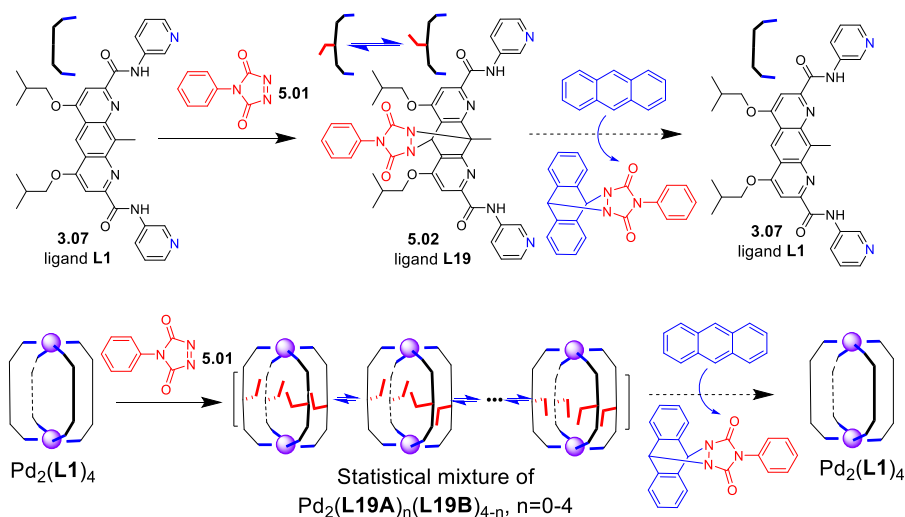


Figure 7.06 A possible extension of this post-modification of ligands and

metal-organic cages to a reversible covalent post-modification.

Another important advance in this thesis is the proof of concept work on the use of multiple helix formation with aromatic oligoamide foldamers as a driving force for the self-assembly of higher-ordered architectures. Thus, self-assembly with aromatic oligoamide foldamer-based building blocks can be another fundamental mechanism to increase the structural diversity of supramolecules and materials. Despite the designed and studied polygonal structures in this thesis, attempts to obtain more complex 3D cage-like structures and framework materials through multiple helix formation of aromatic oligoamide foldamers can be important to look at the potential of this concept. Similarly, the design and synthesis of ligands for these more complex structures can benefit from the work described in this thesis. A primary principle for ligands design is that the shapes of the initial building blocks control the self-assembled outcomes. Exploring new motifs for the central linker in these systems will be the most important control aspect for the shapes of overall ligands. For instance, double helix formation with a tripodal central linker should enable the formation of molecular capsules. However, replacing the tripod central linker with a planar C_3 symmetric unit could lead to framework materials, Figure 7.07. Indeed, this bio-inspired approach is important because the high modification of organic molecules will make use of an extensive range of chemical tools available. Through these works, developing a large class of novel foldamer-based higher-ordered supramolecules and materials are promising for diverse applications.

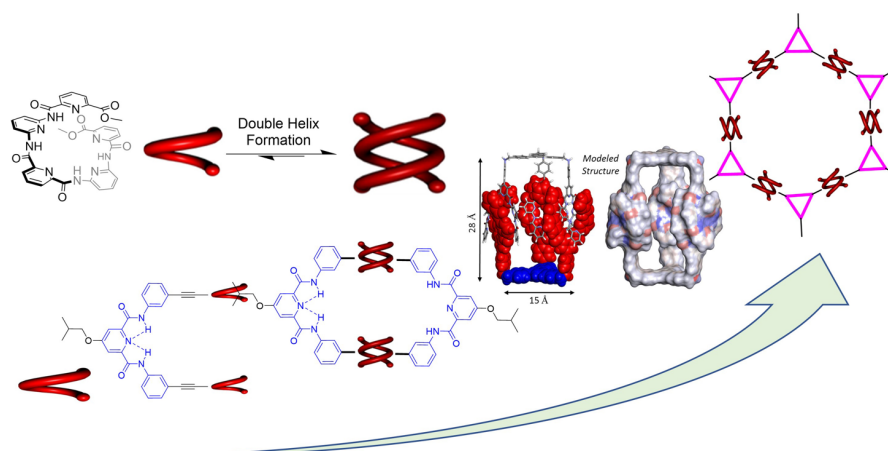


Figure 7.07 Increasing the complexity from aromatic oligoamide foldamers to foldamer-based supramolecules and framework materials through multiple helix formation of aromatic oligoamide foldamers.

Chapter VIII

Experimental section

1. Instrumentation

^1H and ^{13}C nuclear magnetic resonance spectra were recorded on a Bruker Avance II 300 MHz spectrometer (^1H NMR 300 MHz and ^{13}C NMR 75 MHz) or Avance 500 MHz spectrometer (^1H NMR 500 MHz, COSY and ^1H DOSY). ^1H -NMR chemical shifts are reported in ppm and determined with tetramethylsilane (TMS, $\delta = 0$ ppm) or calibrated against residual signals of the deuterated solvents, Chloroform- d ($\delta = 7.26$ ppm), DMSO- d_6 ($\delta = 2.50$ ppm), Methanol- d_4 ($\delta = 3.31$ ppm) and Acetonitrile- d_3 ($\delta = 1.94$ ppm). Deuterated solvents were purchased from Eurisotop. If necessary, the structures were determined by two-dimensional analysis (COSY and DOSY). ^1H NMR spectra are described as chemical shift (multiplicity, coupling constants (Hz), integration). ^{13}C spectra are described as follows: chemical shift. Multiplicity is designed as: s = singlet; d = doublet; t = triplet; q = quartet; qui = quintet; sex = sextet; sep = septet; b = broad; m = multiplet. High-resolution mass spectra (HR-MS) were recorded by Mr. Raoul Rozenberg and Mr. Laurent Collard using VARIAN MATT-44, FINNIGAN MAT-TSQ 7000 and THERMO FISCHER ORBITRAP spectrometers from Mass Spectrometry Service of Université catholique de Louvain (Belgium). Cryo Spray Ionization High-Resolution Mass Spectrometry (CSI-HRMS) and electrospray ionization time-of-flight mass spectra (ESI-TOF-MS) were collected by Mr. Eduard O. Bobylev (University of Amsterdam, The Netherlands) on an HR-TOF Bruker Daltonik GmbH (Bremen, Germany) Impact II, an ESI-TOF MS capable of a

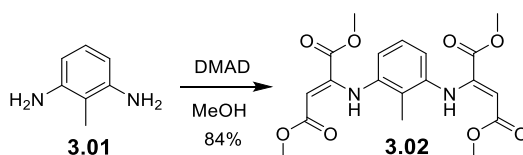
resolution of at least 40000 FWHM, which was coupled to a Bruker cryo-spray unit. Detection was in positive-ion mode and the source voltage was between 4 and 6 kV. The sample was introduced with a syringe pump at a flow rate of 180 $\mu\text{l/hr}$. The drying gas (N_2) was held at $-35\text{ }^\circ\text{C}$ and the spray gas was held at $-40\text{ }^\circ\text{C}$. The machine was calibrated before every experiment via direct infusion of a TFA-Na solution, which provided the m/z range of singly charged peaks up to 3500 Da in both ion modes. Data analysis was conducted with the Bruker Data Analysis software and simulations were performed with the Bruker Isotope Pattern software. Scanning electron microscope (SEM) studies were performed at an accelerating voltage of 1.0 kV on an SEM JEOL 7600F. Samples for SEM were prepared by depositing the diluted DMSO solution of the complexes on a carbon-coated copper grid, and then samples were dried under ambient conditions and in a vacuum overnight. SEM samples were coated with Pt/Pd in an ion coater for 40 s before measurement. Dynamic light scattering (DLS) study was carried out with a Malvern CGS3 device equipped with a He-Ne laser at a wavelength of 632.8 nm. Measurements were performed at 25°C at an angle of 90° . The nanocage solutions were passed through $0,45\text{ }\mu\text{m}$ filters before measurement. Results were analyzed using the CONTIN algorithm to obtain the size distributions. The R_h values indicated in the paper are the averages over ten measurements. X-ray diffraction analysis of compounds was recorded by Dr. Koen Robeyns at the Institute of Condensed Matter and Nanosciences of UCLouvain or recorded by Dr. Brice Kauffmann at the European Institute of Chemistry and Biology in Pessac, France.

2. Synthetic Procedures

Unless otherwise mentioned, all manipulations were performed under an argon atmosphere using standard glassware. Diethyl ether and tetrahydrofuran were distilled on sodium/benzophenone under an argon atmosphere. Dichloromethane, triethylamine and toluene were distilled on calcium hydride under an argon atmosphere. Solvents used for work-ups were of technical grade. Commercial reagents were purchased from Acros, Sigma-Aldrich, ABCR, TCI, Merck or Fluorochem and used as received unless stated otherwise. Thin-layer chromatography (TLC) was performed on Merck Millipore F₂₅₄ silica gel 60 plates (200 μ m thickness, aluminum supported). The plates were visualized using ultra-violet light (254 nm) and stained using alkaline potassium permanganate, vanillin or ninhydrin solution. Flash chromatography was performed with the stated solvents using Sigma-Aldrich silica gel 60 (70–230 mesh).

2.1 Synthesis in chapter 3

Tetramethyl 2,2'-((2-methyl-1,3-phenylene)bis(azanediyl)) difumarate (**3.02**)

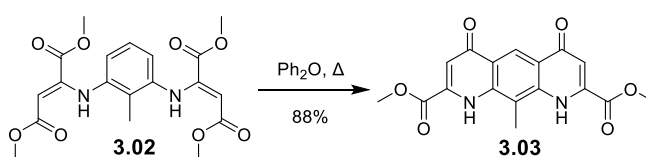


To a solution of diaminotoluene **3.01** (25 g, 205 mmol, 1.0 Equiv.) in 800 mL of methanol in a 1000 mL round-bottomed flask, was added (all at once) dimethyl acetylene dicarboxylate (63.9 g, ca. 55.3 mL, 450 mmol, 2.2 Equiv.). The resulting mixture was heated to 50 °C and stirred for 24 h, after which time a large number of precipitate forms. The solvent was evaporated to ca. 500 mL and the solution was cooled to room temperature. The pale yellow precipitate was collected by filtration, washed with cold methanol (300 mL at -18 °C) and dried under reduced pressure to yield compound **3.02** (69.8 g, 172

Chapter VIII

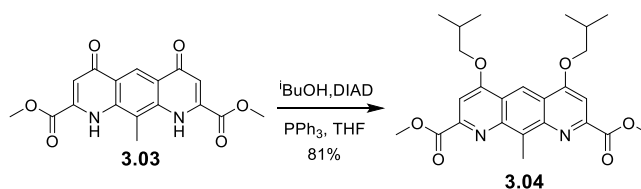
mmol, 84% yield). ^1H NMR (300 MHz, Chloroform-*d*) δ 9.54 (s, 2H), 6.99 (t, J = 8.0 Hz, 1H), 6.59 (d, J = 8.0 Hz, 2H), 5.43 (s, 2H), 3.76 (s, 6H), 3.65 (s, 6H), 2.33 (s, 3H). The characteristic data corresponded with reported literature values.^[1]

Dimethyl 10-methyl-4,6-dioxo-1,4,6,9-tetrahydropyrido[3,2-*g*]quinoline-2,8-dicarboxylate (**3.03**)

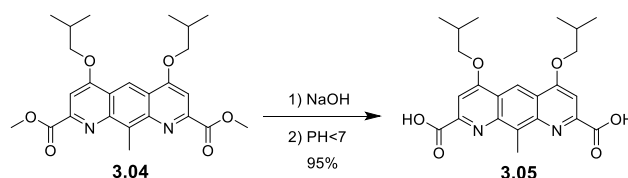


In a 2-liter round-bottomed reactor vessel, 1200 mL of diphenyl ether was heated to boiling 260°C (without stirrer) using a heating mantel. Compound **3.02** (70 g, 172 mmol, 1.0 Equiv.) was added all at once. The mixture was heated for 15-20 minutes. The flask was removed from the heating mantel and allowed to cool down for ~30 minutes. 500 mL petroleum ether was first added to the flask, and then the still-hot mixture was carefully poured into a big Erlenmeyer containing 2000 mL petroleum ether. The precipitate was collected on a fine sintered glass funnel and washed with petroleum ether and then dichloromethane until the liquid coming through the funnel was no longer yellow. After drying under reduced pressure, compound **3.03** was obtained as a sandy yellow solid (52 g, 151.4 mmol, 88%), which was directly used for the next step without purification and characterization.

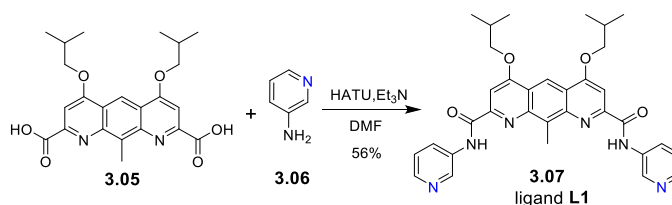
Dimethyl 4,6-diisobutoxy-10-methylpyrido[3,2-g]quinoline-2,8-dicarboxylate (3.04)



In a dry 1000 mL round-bottomed flask, a mixture of compound **3.03** (3.42 g, 10 mmol, 1.0 Equiv.), freshly distilled 2-methyl propanol (1.63 g, 22 mmol, 2.2 Equiv.) and triphenylphosphine (5.78 g, 22 mmol, 2.2 Equiv.) was suspended in 100 mL anhydrous THF. The flask was then hermetically closed and remained under protecting gas during the reaction time. (compound **3.03** is not soluble in THF before the addition of diisopropyl azodicarboxylate). The reaction mixture was cooled to 0°C in an ice bath and DIAD (4.44 g, 22 mmol, 2.2 Equiv.) was then added to this mixture, and the resulting mixture was stirred at 0°C for 30 min and then overnight at room temperature. The solvent was removed by rotary evaporation and the residue was recrystallized from MeOH/CH₂Cl₂ (1:1) by a slow removal of the dichloromethane on the rotovap. Crystals were filtered using a fine sintered glass funnel and washed with cold methanol (-18°C). The product was dried under reduced pressure to yield compound **3.04** as a yellow solid (3.7 g, 8.1 mmol, 81% yield). ¹H NMR (300 MHz, Chloroform-*d*) δ 9.14 (s, 1H), 7.50 (s, 2H), 4.13 (d, *J* = 6.4 Hz, 4H), 4.10 (s, 6H), 3.50 (s, 3H), 2.37 (m, 2H), 1.20 (d, *J* = 6.7 Hz, 12H). The characteristic data corresponded with reported literature values.^[2]

4,6-diisobutoxy-10-methylpyrido[3,2-g]quinoline-2,8-dicarboxylic acid (3.05)

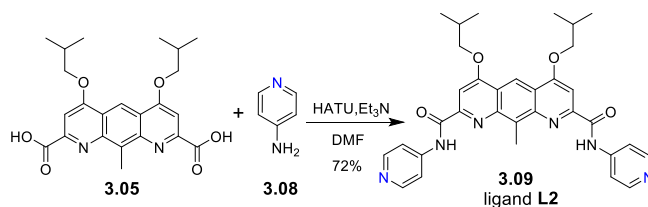
Compound **3.04** (0.5 g, 11.0 mmol, 1.0 Equiv.) was placed in a 50 mL round-bottomed flask and dissolved in 25 mL of CH₂Cl₂: MeOH (1:1). KOH (0.185 g, 33.0 mmol, 3.0 Equiv.) dissolved in MeOH (10 mL) was slowly added to this mixture. The reaction was then stirred at room temperature for 24 hours. The solution was acidified to ~pH 4 with aqueous citric acid and solvent was partially removed on the rotovap to leave a yellow precipitate suspended in water. An additional 100 mL of H₂O was added and the yellow solid is collected by filtration and washed with H₂O. After partially drying on the filter, the solid was suspended in toluene and azeotroped three times with toluene. Afterward, the yellow solid was dried overnight under vacuum in a desiccator with P₂O₅ to give compound **3.05** as a light yellow solid (0.45 g, 10.45 mmol, 95% yield). ¹H NMR (500 MHz, Chloroform-*d*) δ 9.24 (s, 1H), 7.62 (s, 2H), 4.19 (d, *J* = 6.4 Hz, 4H), 3.36 (s, 3H), 2.38 (m, 2H), 1.21 (d, *J* = 6.8 Hz, 12H). The characteristic data corresponded with reported literature values.^[3]

4,6-diisobutoxy-10-methyl-N2,N8-di(pyridin-3-yl)pyrido[3,2-g]quinoline-2,8-dicarboxamide (3.07, ligand L1)

A solution of compound **3.05** (213.2 mg, 0.5 mmol, 1.0 Equiv.) and HATU (570

mg, 1.5 mmol, 3.0 Equiv.) in DMF (15 mL) were stirred 0.5 hour at 0 °C under argon, then 3-aminopyridine **3.06** (112.9 mg, 1.2 mmol, 2.4 Equiv.) and Et₃N (202 mg, 2.0 mmol, 4 Equiv.) were added, the reaction mixture was allowed to stir for 24 hours at room temperature in dark. The DMF in the reaction mixture was removed under reduced pressure, the resulting oily substances was then diluted with H₂O (50 mL), and a fine powder progressively precipitated out. Then the solid was collected by filtration and the desired crude compound was isolated, and the crude material was purified by silica gel flash column (v/v, CH₂Cl₂:MeOH = 10:1) to give compound **3.07** as a yellow powder (ligand **L1**, 245.4 mg, 0.28 mmol, 56.0% yield). ¹H NMR (500 MHz, DMSO-*d*₆) δ 10.81 (s, 2H), 9.11 (d, *J* = 2.3 Hz, 2H), 9.02 (s, 1H), 8.40 (d, *J* = 4.7 Hz, 2H), 8.34 (d, *J* = 8.3 Hz, 2H), 7.59 (s, 2H), 7.49 (dd, *J* = 8.2, 4.7 Hz, 2H), 4.23 (d, *J* = 6.1 Hz, 4H), 3.54 (s, 3H), 2.27 (m, 2H), 1.16 (d, *J* = 6.7 Hz, 12H). ¹H NMR (500 MHz, Chloroform-*d*) δ 10.46 (s, 2H), 9.20 (s, 1H), 8.96 (s, 2H), 8.48 – 8.42 (m, 4H), 7.71 (s, 2H), 7.41 (dd, *J* = 8.2, 4.8 Hz, 2H), 4.19 (d, *J* = 6.4 Hz, 4H), 3.48 (s, 3H), 2.39 (dp, *J* = 13.2, 6.5 Hz, 2H), 1.22 (d, *J* = 6.7 Hz, 12H). ¹³C NMR (75 MHz, Chloroform-*d*) δ 164.35, 162.86, 151.40, 145.63, 144.76, 141.48, 135.78, 134.57, 126.67, 123.96, 121.52, 114.46, 96.39, 75.52, 28.41, 19.27, 13.03. HR-MS (ESI) *m/z* calculated. For C₃₃H₃₄N₆O₄ [M+H]¹⁺:579.2714, found 579.2722.

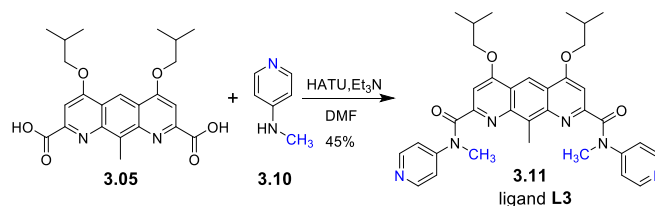
4,6-diisobutoxy-10-methyl-N2,N8-di(pyridin-4-yl)pyrido[3,2-*g*]quinoline-2,8-dicarboxamide (3.09, ligand L2)



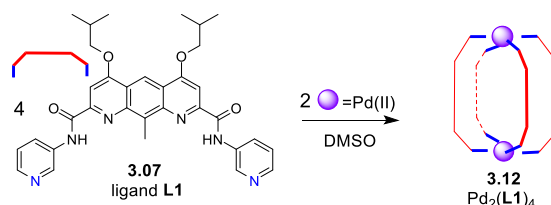
Compound **3.09** (ligand **L2**, 208 mg, 0.36 mmol, 71.9% yield) was obtained as a yellow powder following the same procedure used for compound **3.07**

(ligand **L1**), using 4-aminopyridine **3.08** (112.9 mg, 1.2 mmol, 2.4 Equiv.) as reagent. ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 10.91 (s, 2H), 9.03 (s, 1H), 8.58 (d, $J = 6.2$ Hz, 4H), 7.97 (d, $J = 6.3$ Hz, 4H), 7.59 (s, 2H), 4.24 (d, $J = 6.1$ Hz, 4H), 3.53 (s, 3H), 2.28 (m, 2H), 1.16 (d, $J = 6.7$ Hz, 12H). ^1H NMR (500 MHz, Chloroform- d) δ 10.47 (s, 2H), 9.14 (s, 1H), 8.64 (dd, $J = 4.7, 1.5$ Hz, 4H), 7.78 – 7.75 (m, 4H), 7.65 (s, 2H), 4.17 (d, $J = 6.4$ Hz, 4H), 3.40 (s, 3H), 2.38 (m, 2H), 1.21 (d, $J = 6.7$ Hz, 12H). ^{13}C NMR (75 MHz, Chloroform- d) δ 164.49, 163.08, 151.15, 144.75, 144.47, 135.90, 121.68, 114.63, 113.76, 96.46, 75.59, 28.42, 19.28, 13.02. HR-MS (ESI) m/z calculated. For $\text{C}_{33}\text{H}_{34}\text{N}_6\text{O}_4$ $[\text{M}+\text{H}]^{1+}$: 579.2714, found 579.2715.

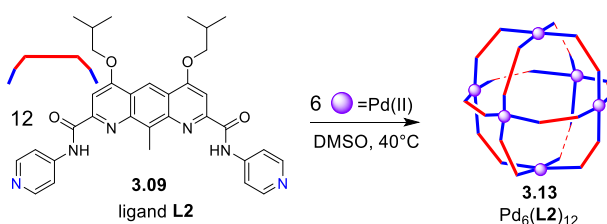
4,6-diisobutoxy-N2,N8,10-trimethyl-N2,N8-di(pyridin-4-yl)pyrido[3,2-g]quinoline-2,8-dicarboxamide (3.11, ligand L3)



Compound **3.11** (ligand **L3**, 138.4 mg, 0.22 mmol, 45.5% yield) was obtained as a yellow powder following the same procedure used for compound **3.07** (ligand **L1**), using 4-(Methylamino)pyridine **3.10** (129.8 mg, 1.2 mmol, 2.4 Equiv.) instead of 4-aminopyridine. ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 8.86 (s, 1H), 8.33 (d, $J = 6.1$ Hz, 4H), 7.27 (s, 2H), 7.22 (d, $J = 6.0$ Hz, 4H), 4.14 (d, $J = 6.2$ Hz, 4H), 3.49 (s, 6H), 2.22 (m, 2H), 2.17 (s, 3H), 1.10 (d, $J = 6.7$ Hz, 12H). ^{13}C NMR (75 MHz, $\text{DMSO}-d_6$) δ 168.20, 162.66, 155.03, 152.28, 150.55, 144.26, 135.99, 120.81, 120.12, 112.71, 99.97, 75.04, 37.37, 28.16, 19.25, 11.75. HR-MS (ESI) m/z calculated. For $\text{C}_{35}\text{H}_{38}\text{N}_6\text{O}_4$ $[\text{M}+\text{H}]^{1+}$: 607.3027, found 607.3024.

Complex 3.12, Pd₂(L1)₄

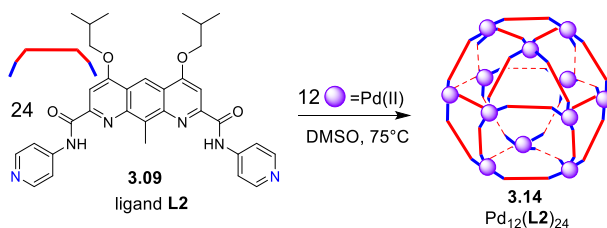
To a suspension of compound **3.07** (ligand **L1**, 5.79 mg, 0.01 mmol, 1.0 Equiv.) and Pd²⁺ (NO₃⁻, BF₄⁻, CF₃SO₃⁻ or PF₆⁻ salt, 0.005 mmol, 0.5 Equiv.) in 0.6 mL DMSO-*d*₆, the mixture was heated at 75°C for 2 hour. The turbid suspension of ligands gradually turned clear to give a yellow solution that was characterized by NMR to show formation of complex **3.12**, Pd₂(**L1**)₄(BF₄)₄. ¹H NMR (500 MHz, DMSO-*d*₆) δ 11.36 (s, 2H), 9.34 (d, *J* = 9.2 Hz, 2H), 9.09 (s, 1H), 8.96 (d, *J* = 2.0 Hz, 2H), 8.54 (d, *J* = 5.2 Hz, 2H), 7.81 (dd, *J* = 8.6, 5.8 Hz, 2H), 7.54 (s, 2H), 4.20 (d, *J* = 5.2 Hz, 4H), 3.65 (s, 3H), 2.23 (m, 2H), 1.10 (d, *J* = 6.7 Hz, 12H). ¹³C NMR (75 MHz, DMSO-*d*₆) δ 163.40, 161.35, 151.19, 144.91, 143.02, 141.24, 136.14, 128.48, 119.32, 111.67, 96.29, 73.17, 26.07, 20.86, 17.08, 11.80. ESI-TOF-MS for Pd₂(**L1**)₄(BF₄)₄·: The following picked signals are those at the high intensities. *m/z* Calcd for [M-2(BF₄⁻)]²⁺ 1350.4377, found 1350.4298; Calcd for [M-3(BF₄⁻)]³⁺ 871.2904, found 871.2852; Calcd for [M-4(BF₄⁻)]⁴⁺ 631.7167, found 631.7125.

Complex 3.13, Pd₆(L2)₁₂

To a suspension of compound **3.09** (ligand **L2**, 5.79 mg, 0.01 mmol, 1.0 Equiv.) and Pd²⁺ (NO₃⁻, BF₄⁻, CF₃SO₃⁻ or PF₆⁻ salt, 0.005 mmol, 0.5 Equiv.) in 0.6 mL

DMSO- d_6 , the mixture was heated at 40°C for 3 hours. The turbid suspension of ligands gradually turned clear to give a yellow solution that was characterized by NMR to show formation of complex **3.13**, $\text{Pd}_6(\text{L2})_{12}(\text{NO}_3)_{12}$. ^1H NMR (500 MHz, DMSO- d_6) δ 11.41 (s, 2H), 9.29 (s, 4H), 9.09 (s, 1H), 8.25 (s, 4H), 7.59 (s, 2H), 4.27 (s, 4H), 3.51 (s, 2H), 2.27 (s, 2H), 1.18 - 1.09 (m, 12H). CSI-TOF-MS for $\text{Pd}_6(\text{L2})_{12}(\text{BF}_4)_{12}$: The following picked signals are those at the high intensities. m/z Calcd for $[\text{M}-4(\text{BF}_4^-)]^{4+}$ 2069.1590, found 2069.1508; Calcd for $[\text{M}-5(\text{BF}_4^-)]^{5+}$ 1637.9263, found 1637.9187; Calcd for $[\text{M}-6(\text{BF}_4^-)]^{6+}$ 1350.1044, found 1350.0922; Calcd for $[\text{M}-7(\text{BF}_4^-)]^{7+}$ 1145.0890, found 1145.0785; Calcd for $[\text{M}-8(\text{BF}_4^-)]^{8+}$ 991.2024, found 991.1931; Calcd for $[\text{M}-9(\text{BF}_4^-)]^{9+}$ 871.4017, found 871.3994.

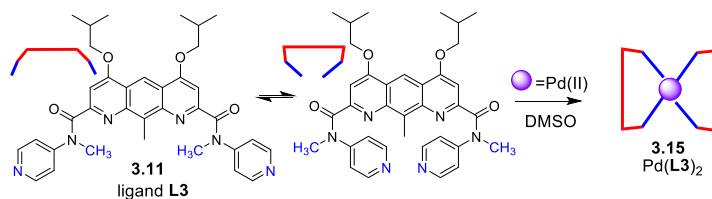
Complex 3.14, $\text{Pd}_{12}(\text{L2})_{24}$



To a suspension of compound **3.09** (ligand **L2**, 5.79 mg, 0.01 mmol, 1.0 Equiv.) and Pd^{2+} (NO_3^- , BF_4^- , CF_3SO_3^- or PF_6^- salt, 0.005 mmol, 0.5 Equiv.) in 0.6 mL DMSO- d_6 , the mixture was heated at 75°C for 5 hours under monitoring by NMR. The turbid suspension of ligands gradually turned clear to give a yellow solution that was characterized by NMR to show formation of complex **3.14**, $\text{Pd}_{12}(\text{L2})_{24}(\text{NO}_3)_{24}$. ^1H NMR (500 MHz, DMSO- d_6) δ 11.35 (s, 2H), 9.12 (s, 1H), 8.72 (s, 4H), 8.25 (s, 4H), 7.66 (s, 2H), 4.29 (s, 4H), 3.59 (s, 2H), 2.29 (s, 2H), 1.17 (d, $J = 6.0$ Hz, 12H). CSI-TOF-MS for $\text{Pd}_{12}(\text{L2})_{24}(\text{BF}_4)_{24}$: The following picked signals are those at the high intensities. m/z Calcd for $[\text{M}-8(\text{BF}_4^-)]^{8+}$ 2069.1590, found 2069.1558; Calcd for $[\text{M}-9(\text{BF}_4^-)]^{9+}$ 1829.5853, found 1829.5836; Calcd for $[\text{M}-10(\text{BF}_4^-)]^{10+}$ 1638.0264, found 1638.0257; Calcd for

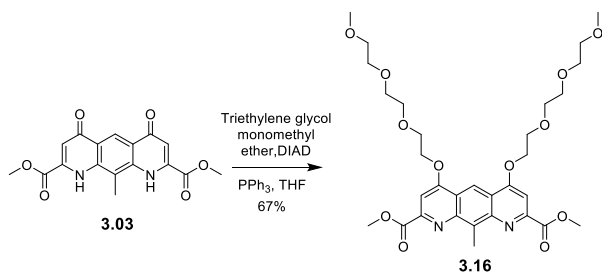
$[M-11(BF_4^-)]^{11+}$ 1481.2054, found 1481.2010; Calcd for $[M-12(BF_4^-)]^{12+}$ 1350.5213, found 1350.5218; Calcd for $[M-13(BF_4^-)]^{13+}$ 1239.9424, found 1239.9324.

Complex 3.15, $Pd(L3)_2$



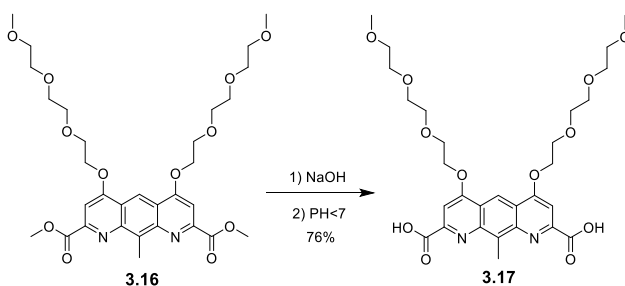
To a suspension of compound **3.11** (ligand **L3**, 6.06 mg, 0.01 mmol, 1.0 Equiv.) and Pd^{2+} (NO_3^- , BF_4^- , $CF_3SO_3^-$ or PF_6^- salt, 0.005 mmol, 0.5 Equiv.) in 0.6 mL $DMSO-d_6$ was heated at $75^\circ C$ for 2 hour. The turbid suspension of ligands gradually turned clear to give a yellow solution that was characterized by NMR to show formation of complex **3.15**, $Pd(L3)_2(BF_4)_2$. 1H NMR (500 MHz, $DMSO-d_6$) δ 8.83 (s, 1H), 8.77 (s, 4H), 7.34 (s, 2H), 7.26 (s, 4H), 4.18 (d, $J = 6.0$ Hz, 4H), 3.47 (s, 6H), 2.24 (m, 2H), 1.12 (d, $J = 6.7$ Hz, 12H). ^{13}C NMR (75 MHz, $DMSO-d_6$) δ 165.46, 161.10, 149.57, 148.42, 140.75, 121.42, 118.67, 116.44, 97.76, 73.16, 35.05, 26.06. HR-MS for $Pd(L3)_2(BF_4)_2$: The following picked signals are those at the high intensities. m/z Calcd for $[M-(BF_4^-)]^{1+}$ 1405.4997, found 1405.4993; Calcd for $[M-2(BF_4^-)]^{2+}$ 659.2478, found 659.2477.

Dimethyl 4,6-bis(2-(2-(2-methoxyethoxy)ethoxy)ethoxy)-10-methylpyrido[3,2-g]quinoline-2,8-dicarboxylate (3.16)

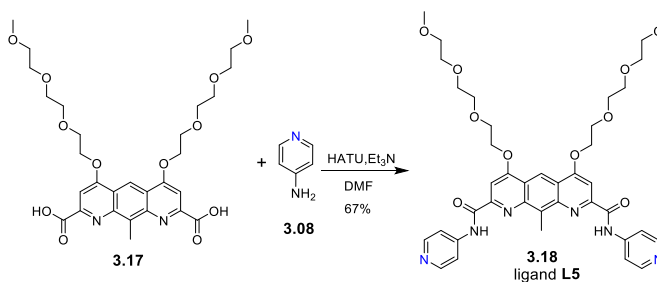


Compound **3.15** (4.26g, 6.7 mmol, 67% yield) was obtained as a yellow powder following the same procedure used for compound **3.04**, using triethylene glycol monomethyl ether (3.6 g, 22 mmol, 2.2 Equiv.) as reagent instead of iso-butyl alcohol. ^1H NMR (300 MHz, Chloroform- d) δ 9.08 (s, 1H), 7.55 (s, 2H), 4.58 – 4.51 (m, 4H), 4.09 (m, 10H), 3.84 (dd, J = 6.0, 3.4 Hz, 4H), 3.72 (dd, J = 6.0, 3.4 Hz, 4H), 3.68 – 3.63 (m, 4H), 3.54 – 3.49 (m, 7H), 3.34 (s, 6H). ^{13}C NMR (75 MHz, Chloroform- d) δ 166.31, 163.21, 149.69, 145.94, 139.32, 121.45, 113.70, 99.00, 71.92, 71.12, 70.77, 70.64, 69.27, 68.61, 59.00, 53.20, 13.14. HR-MS (ESI) m/z calculated. For $\text{C}_{31}\text{H}_{42}\text{N}_2\text{O}_{12}$ $[\text{M}+\text{H}]^{1+}$: 635.2811, found 635.2807.

4,6-bis(2-(2-(2-methoxyethoxy)ethoxy)ethoxy)-10-methylpyrido[3,2-g]quinoline-2,8-dicarboxylic acid (3.17)

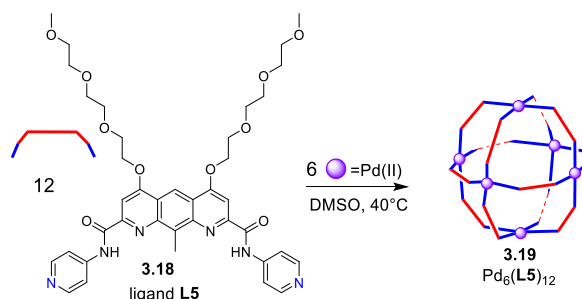


Compound **3.16** (3.21 g, 5 mmol, 1.0 Equiv.) was placed in a 250 mL round-bottomed flask and dissolved in 100 mL of 1,4-dioxane: H_2O (1:1). KOH (1.12



then diluted with H₂O (50 mL), and fine powder progressively precipitated out. Then the solid was collected by filtration and the desired crude compound was isolated, and the crude material was purified by silica gel flash column (v/v, CH₂Cl₂:MeOH = 10:1) to give compound **3.18** as a yellow powder (ligand **L5**, 263 mg, 0.34 mmol, 67% yield). ¹H NMR (300 MHz, DMSO-*d*₆) δ 11.06 (s, 2H), 8.89 (s, 1H), 8.64 (d, *J* = 6.5 Hz, 4H), 8.09 (d, *J* = 6.7 Hz, 4H), 7.59 (s, 2H), 4.65 – 4.55 (m, 4H), 4.04 – 3.99 (m, 4H), 3.74 (m, 4H), 3.61 (m, 4H), 3.52 (m, 4H), 3.41 – 3.38 (m, 7H), 3.17 (s, 6H). ¹³C NMR (75 MHz, DMSO-*d*₆) δ 163.98, 163.36, 151.14, 148.26, 147.22, 144.27, 137.68, 120.82, 115.14, 113.36, 97.30, 71.73, 70.76, 70.39, 70.12, 69.48, 69.06, 58.47, 13.39. HR-MS (ESI) *m/z* calculated. For C₃₉H₄₇O₁₀N₆ [M+H]¹⁺: 759.3348, found 759.3349.

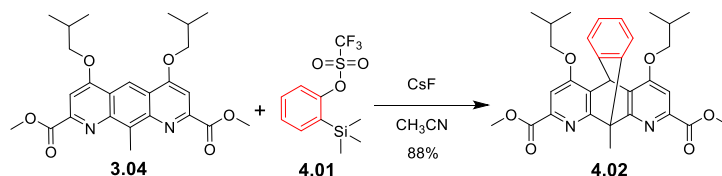
Complex **3.18**, Pd₆(**L5**)₁₂



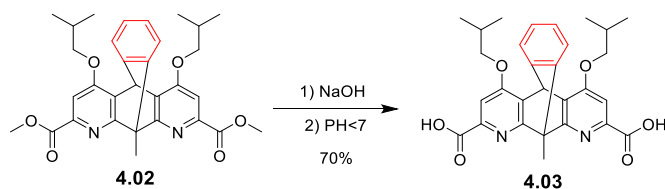
To a suspension of compound **3.18** (ligand **L5**, 7.58 mg, 0.01 mmol, 1.0 Equiv.) and Pd²⁺ (NO₃⁻, BF₄⁻, CF₃SO₃⁻ or PF₆⁻ salt, 0.005 mmol, 0.5 Equiv.) in 0.6 mL DMSO-*d*₆, the mixture was heated at 40°C for 3h. The turbid suspension of ligands gradually turned clear to give a yellow solution that was characterized by NMR to show formation of complex **3.19**, Pd₆(**L5**)₁₂(BF₄)₁₂. ¹H NMR (300 MHz, DMSO-*d*₆) δ 11.42 (s, 2H), 9.29 (s, 4H), 9.02 (s, 1H), 8.25 (s, 4H), 7.64 (s, 2H), 4.60 (s, 4H), 3.98 (s, 4H), 3.73 – 3.68 (m, 4H), 3.59 – 3.55 (m, 4H), 3.51 – 3.48 (m, 4H), 3.31-3.38 (m, 4H), 3.13 (s, 6H).

2.2 Synthesis in chapter 4

Dimethyl 4,16-diisobutoxy-10-methyl-5,10-dihydro-10,5-[2,3]pyridinobenzo[g]quinoline-2,14-dicarboxylate(4.02)

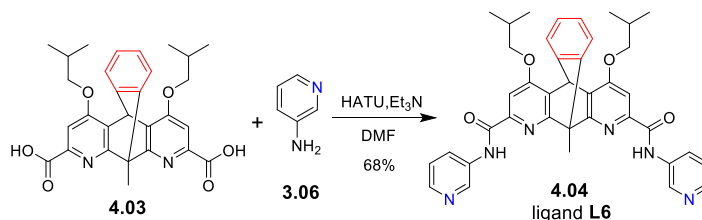


A mixture of compound **3.04** (2.3 g, 5 mmol, 1.0 Equiv.), 2-(Trimethylsilyl)phenyl trifluoromethanesulfonate (3.576g, 12 mmol, 2.4 Equiv.) and caesium fluoride (1.812g, 12 mmol, 2.4 Equiv.) in dry CH₃CN were heated at 55°C for 48 h. The CH₃CN was removed under reduced pressure, the residue was diluted with 200 mL of CH₂Cl₂ and washed with water. The organic layer was dried over NaSO₄, filtered, and then solvent was removed under reduced pressure. The crude material was purified by recrystallization (v/v, CH₂Cl₂:n-hexane = 1:1) to give compound **4.02** as a white powder (2.304g, 88.4% yield). ¹H NMR (500 MHz, Chloroform-*d*) δ 7.50 – 7.48 (m, 1H), 7.43 (s, 3H), 7.10 – 7.04 (m, 2H), 6.28 (s, 1H), 3.93 (s, 6H), 3.87 (d, *J* = 5.6 Hz, 4H), 2.57 (s, 3H), 2.20 (dp, *J* = 13.3, 6.7 Hz, 2H), 1.12 (d, *J* = 6.7 Hz, 12H). ¹³C NMR (75 MHz, Chloroform-*d*) δ 166.13, 159.39, 145.24, 143.37, 129.55, 125.71, 125.67, 123.83, 123.10, 107.42, 74.65, 55.99, 52.80, 37.58, 19.10. HR-MS (ESI) *m/z* calculated. For C₃₁H₃₄N₂O₆ [M+H]¹⁺:531.2490, found 531.2493.

4,16-diisobutoxy-10-methyl-5,10-dihydro-10,5-[2,3]pyridinobenzo[g]quinoline-2,14-dicarboxylic acid (4.03)

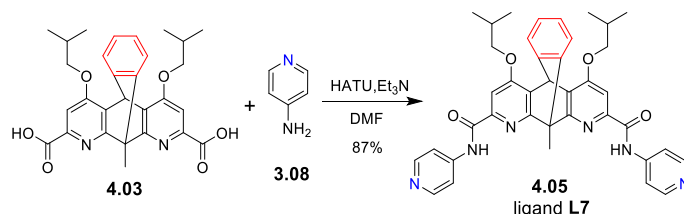
Compound **4.02** (1.0 g, 2.0 mmol, 1.0 Equiv.) and NaOH (320 mg, 8.0 mmol, 4.0 Equiv.) were dissolved in 100 mL of THF and MeOH (1:1), this mixture was then stirred at room temperature for 24 hours. The solvent was removed under reduced pressure, the crude product was redissolved in 100 mL H₂O and then acidified to ~pH=4 with aqueous citric acid. It was extracted with chloroform (3 × 50 mL) and dried with Na₂SO₄. Then, solvent was removed under reduced pressure, the crude product was purified by recrystallization (v/v, CH₂Cl₂: n-hexane = 1:1) to give compound **4.03** as a white powder (703.8 mg, 1.4 mmol, 70.1% yield). ¹H NMR (500 MHz, Chloroform-*d*) δ 7.55 (s, 2H), 7.51 – 7.46 (m, 2H), 7.11-7.17 (m, 2H), 6.32 (s, 1H), 3.92 (d, *J* = 6.5 Hz, 4H), 2.47 (s, 3H), 2.22 (m, 2H), 1.12 (d, *J* = 6.7 Hz, 12H). ¹³C NMR (75 MHz, Chloroform-*d*) δ 166.84, 164.12, 160.82, 144.99, 143.52, 143.05, 130.80, 126.41, 126.20, 124.34, 122.84, 105.85, 75.24, 54.84, 37.73, 28.15, 19.01, 10.64. HR-MS (ESI) *m/z* calculated. For C₂₉H₃₁N₂O₆ [M+H]¹⁺:503.2177, found 503.2177, [M+Na]¹⁺:525.1996, found 525.1998.

4,16-diisobutoxy-10-methyl-N2,N14-di(pyridin-3-yl)-5,10-dihydro-10,5-[2,3]pyridinobenzo[g]quinoline-2,14-dicarboxamide (4.04, ligand L6)



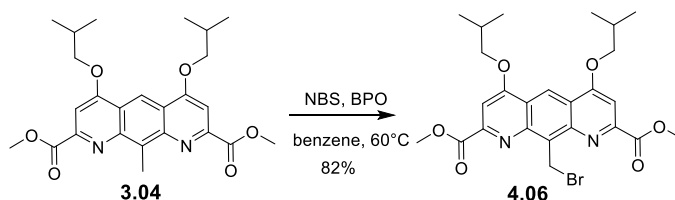
A solution of compound **4.03** (251.1 mg, 0.5 mmol, 1.0 Equiv.) and HATU (570 mg, 1.5 mmol, 3.0 Equiv.) in DMF (15 mL) were stirred 0.5 hour at 0°C under argon, then 3-aminopyridine **3.06** (112.9 mg, 1.2 mmol, 2.4 Equiv.) and Et₃N (202 mg, 2.0 mmol, 4 Equiv.) were added, and the reaction mixture was allowed to stir for 24 hours at room temperature in the dark. The DMF in the reaction mixture was removed under reduced pressure, the resulting oily substances were then diluted with H₂O (50 mL), and a fine powder progressively precipitated out. Then the solid was collected by filtration and the desired crude compound was isolated, and the crude material was purified by silica gel flash column (v/v, CH₂Cl₂: MeOH = 10:1) to give compound **4.04** as a white powder (ligand **L6**, 222.4 mg, 0.34 mmol, 68.0% yield). ¹H NMR (500 MHz, Chloroform-*d*) δ 10.18 (s, 2H), 8.86 (s, 2H), 8.40 (s, 2H), 8.35 (d, *J* = 8.3 Hz, 2H), 7.62 (s, 2H), 7.52 (dd, *J* = 20.0, 6.9 Hz, 2H), 7.36 (m, 2H), 7.18 – 7.11 (m, 2H), 6.33 (s, 1H), 3.95 (d, *J* = 6.5 Hz, 4H), 2.62 (s, 3H), 2.27 – 2.19 (m, 2H), 1.13 (d, *J* = 6.7 Hz, 12H). ¹H NMR (500 MHz, Acetonitrile-*d*₃) δ 10.11 (s, 2H), 8.90 (d, *J* = 2.4 Hz, 2H), 8.35 (dd, *J* = 4.7, 1.3 Hz, 2H), 8.24 (ddd, *J* = 8.3, 2.6, 1.5 Hz, 2H), 7.63 (s, 2H), 7.61 (d, *J* = 7.1 Hz, 1H), 7.55 (d, *J* = 6.7 Hz, 1H), 7.37 (dd, *J* = 8.3, 4.7 Hz, 2H), 7.19 – 7.13 (m, 2H), 6.41 (s, 1H), 4.02 (dd, *J* = 6.4, 1.7 Hz, 4H), 2.67 (s, 2H), 2.25 – 2.17 (m, 3H), 1.13 (dd, *J* = 6.7, 2.3 Hz, 12H). ¹³C NMR (75 MHz, Chloroform-*d*) δ 167.01, 162.56, 160.45, 146.60, 145.69, 145.39, 143.68, 141.37, 134.47, 129.67, 126.63, 126.16, 125.91, 124.19, 123.75, 122.67, 104.66, 74.98, 55.17, 37.66, 28.22, 19.09, 10.94. HR-MS (ESI) *m/z* calculated. For C₃₉H₃₈N₆O₄ [M+H]¹⁺: 655.3027, found 655.3025.

4,16-diisobutoxy-10-methyl-N2,N14-di(pyridin-4-yl)-5,10-dihydro-10,5-[2,3]pyridinobenzo[g]quinoline-2,14-dicarboxamide (4.05, ligand L7)



Compound **4.05** (ligand **L7**, 287 mg, 0.43 mmol, 87.7% yield) was obtained as a white powder following the same procedure used for compound **4.04** (ligand **L6**), 4-aminopyridine **3.08** (112.9 mg, 1.2 mmol, 2.4 Equiv.) was used as reagent. ^1H NMR (500 MHz, Chloroform-*d*) δ 10.27 (s, 2H), 8.57 (d, J = 6.2 Hz, 4H), 7.70 (d, J = 6.2 Hz, 4H), 7.62 (s, 2H), 7.49 – 7.53 (m, 2H), 7.18 – 7.11 (m, 2H), 6.33 (s, 1H), 3.95 (d, J = 6.5 Hz, 4H), 2.61 (s, 3H), 2.28 – 2.19 (m, 2H), 1.14 (d, J = 6.7 Hz, 12H). ^1H NMR (500 MHz, DMSO-*d*₆) δ 10.54 (s, 2H), 8.52 (s, 4H), 7.85 (d, J = 6.1 Hz, 4H), 7.61 – 7.54 (m, 4H), 7.16 (m, 2H), 6.31 (s, 1H), 4.05 (d, J = 6.3 Hz, 4H), 2.65 (s, 3H), 2.15 (m, 2H), 1.10 (d, J = 6.7 Hz, 12H). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 166.97, 162.69, 160.51, 150.92, 146.32, 145.54, 144.41, 129.88, 126.24, 125.96, 124.25, 122.63, 113.59, 104.85, 75.02, 55.12, 37.68, 28.22, 19.13, 10.85. HR-MS (ESI) m/z calculated. For $\text{C}_{39}\text{H}_{38}\text{N}_6\text{O}_4$ $[\text{M}+\text{H}]^{1+}$: 655.3027, found 655.3025.

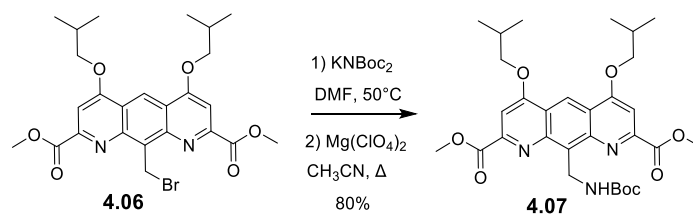
Dimethyl 10-(bromomethyl)-4,6-diisobutoxypyrido[3,2-*g*]quinoline-2,8-dicarboxylate (4.06)



In a 250 mL round-bottomed flask, methyl anthracene **3.04** (4.54 g, 10 mmol,

1.0 Equiv.), NBS (1.96 g, 11 mmol, 1.1 Equiv.), and benzoyl peroxide (1.21 g, 5 mmol, 0.5 Equiv.) were slurried in benzene (50 mL). The mixture was then heated to 65 °C and stirred overnight. The solvent was removed on the rotavap and the yellow residue was recrystallized from CH₂Cl₂/MeOH to yield the methyl bromo derivative **4.06** as dark yellow crystals. (4.4 g, 8.2 mmol, 82% yield). ¹H NMR (300 MHz, Chloroform-*d*) δ 9.28 (s, 1H), 7.51 (s, 2H), 6.16 (s, 2H), 4.14 (d, *J* = 6.4 Hz, 4H), 4.10 (s, 6H), 2.36 (dp, *J* = 13.3, 6.7 Hz, 2H), 1.20 (d, *J* = 6.7 Hz, 12H). The characteristic data corresponded with reported literature values.^[4]

Dimethyl 10-(((tert-butoxycarbonyl)amino)methyl)-4,6-diisobutoxypyrido[3,2-*g*]quinoline-2,8-dicarboxylate (4.07**)**

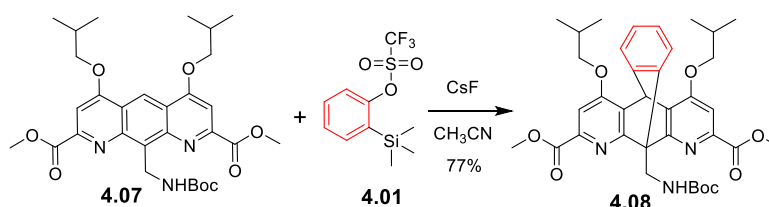


In a dry 25 mL round-bottomed flask, compound **4.06** (533.4 mg, 1 mmol, 1.0 Equiv.) and potassium di-tert-butyl pyrocarbonate (306.4 mg 1.2 mmol, 1.2 Equiv.) were slurried in 10 mL of anhydrous DMF under an inert gas atmosphere. The flask was then heated to 50°C for 12 hours. The solvent was removed from the vacuum line and then the crude residue was dissolved in 5 mL of MeCN. The mixture was heated to reflux and Mg(ClO₄)₂ (20 mg, 0.1 mmol, 0.1 Equiv.) was added. TLC carefully monitored the reaction and stopped when the intermediate product disappears (~30 min). The reaction was diluted with 30 mL of EtOAc and washed with the first H₂O, then brine solution. The organic layer was dried over MgSO₄, filtered, and then the solvent was removed via rotavap. The crude yellow solid was recrystallized with CH₂Cl₂/MeOH to give compound **4.07** as a yellow solid (455 mg, 0.8 mmol,

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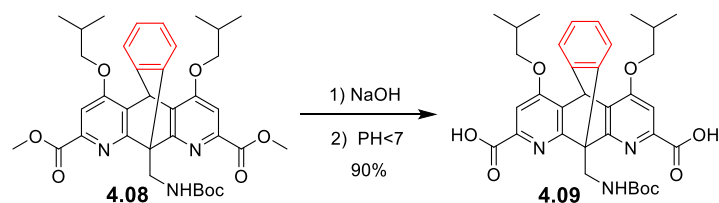
80% yield). ^1H NMR (300 MHz, Chloroform-*d*) δ 9.22 (s, 1H), 7.49 (s, 2H), 5.79 (d, J = 6.1 Hz, 2H), 4.13 (d, J = 6.4 Hz, 4H), 4.09 (s, 6H), 2.36 (m, 2H), 1.43 (s, 9H), 1.20 (d, J = 6.7 Hz, 12H). The characteristic data corresponded with reported literature values.^[4]

Dimethyl 10-(((tert-butoxycarbonyl)amino)methyl)-4,16-diisobutoxy-5,10-dihydro-10,5-[2,3]pyridinobenzo[g]quinoline-2,14-dicarboxylate(4.08)



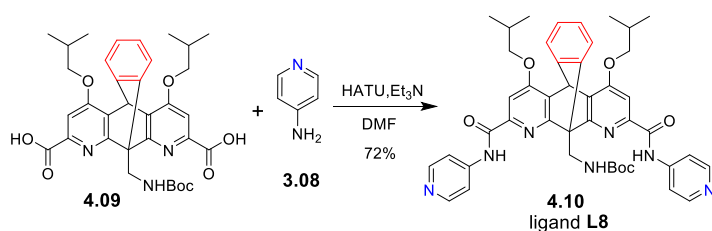
Compound **4.08** (2.511g, 3.8 mmol, 77.4% yield) was obtained as a pale yellow powder following the same procedure used for compound **4.02**, compound **4.07** (2.852 g, 5 mmol, 1.0 Equiv.) was used as reagent. ^1H NMR (500 MHz, Chloroform-*d*) δ 7.83 (d, J = 7.2 Hz, 1H), 7.41 (m, 3H), 7.14 (t, J = 6.4 Hz, 1H), 7.04 - 7.09 (m, 2H), 6.21 (s, 1H), 5.04 (d, J = 6.4 Hz, 2H), 3.92 (s, 6H), 3.86 (d, J = 6.5 Hz, 4H), 2.19 (m, 2H), 1.51 (s, 9H), 1.10 (d, J = 6.7 Hz, 12H). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 167.34, 165.90, 159.59, 156.57, 145.17, 143.67, 143.42, 130.02, 126.12, 125.83, 124.51, 123.94, 107.29, 78.63, 74.73, 58.67, 52.68, 37.82, 28.56, 28.20, 19.12, 19.06. HR-MS (ESI) calculated. For $\text{C}_{36}\text{H}_{43}\text{N}_3\text{O}_8$ $[\text{M}+\text{H}]^{1+}$: 646.3123, found 646.3120.

Dimethyl 10-(((tert-butoxycarbonyl)amino)methyl)-4,16-diisobutoxy-5,10-dihydro-10,5-[2,3]pyridinobenzo[g]quinoline-2,14-dicarboxylate(4.09)



Compound **4.09** (1.11g, 1.8 mmol, 90.0% yield) was obtained as a pale yellow powder following the same procedure used for compound **4.03**, compound **4.08** (1.29 g, 2 mmol, 1.0 Equiv.) was used as reagent. ^1H NMR (500 MHz, Chloroform-*d*) δ 7.58 (s, 2H), 7.45 – 7.42 (m, 1H), 7.38 (d, J = 6.9 Hz, 1H), 7.14 – 7.07 (m, 2H), 6.27 (s, 1H), 6.04 (t, J = 6.4 Hz, 1H), 4.98 (d, J = 6.5 Hz, 2H), 3.92 (d, J = 6.4 Hz, 4H), 2.21 (m, 2H), 1.47 (s, 9H), 1.11 (d, J = 6.7 Hz, 12H). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 165.35, 164.59, 160.99, 157.04, 144.28, 144.09, 130.62, 126.45, 126.32, 124.54, 122.81, 106.40, 80.44, 75.25, 58.42, 37.92, 28.63, 28.13, 19.00. HR-MS (ESI) calculated. For $\text{C}_{34}\text{H}_{39}\text{N}_3\text{O}_8$ $[\text{M}+\text{H}]^{1+}$: 618.2810, found 618.2810, $[\text{M}+\text{Na}]^{1+}$: 640.2629, found 640.2626.

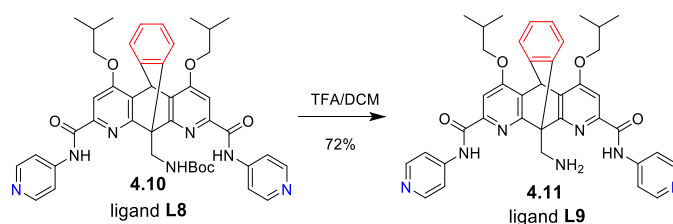
Tert-butyl((4,16-diisobutoxy-2,14-bis(pyridin-4-ylcarbamoyl)-10,5-[2,3]pyridinobenzo[g]quinolin-10(5H)-yl)methyl)carbamate(4.10, ligand L8)



Compound **4.10** (ligand **L8**, 276 mg, 0.36 mmol, 72.0% yield) was obtained as a pale yellow following the same procedure used for compound **4.04** (ligand

L6), compound **4.09** (308 mg, 0.5 mmol, 1.0 Equiv.) and 3-aminopyridine **3.08** (112.9 mg, 1.2 mmol, 2.4 Equiv.) was used as reagent. ^1H NMR (500 MHz, Chloroform-*d*) δ 10.30 (s, 2H), 8.58 (s, 4H), 7.84 (d, J = 5.2 Hz, 4H), 7.66 (s, 2H), 7.42-7.46 (m, 2H), 7.15 – 7.07 (m, 2H), 6.43 (s, 1H), 6.29 (s, 1H), 5.10 (d, J = 6.2 Hz, 2H), 3.96 (d, J = 6.5 Hz, 4H), 2.19-2.27 (m, 2H), 1.32 (s, 9H), 1.13 (d, J = 6.7 Hz, 12H). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 165.34, 162.75, 160.91, 156.33, 150.73, 146.96, 144.75, 143.54, 129.92, 126.36, 126.16, 124.47, 122.67, 105.22, 79.64, 75.11, 58.31, 37.84, 37.25, 28.43, 28.18, 19.10, 19.04. HR-MS (ESI) m/z calculated. For $\text{C}_{44}\text{H}_{47}\text{N}_7\text{O}_6$ $[\text{M}+\text{H}]^{1+}$: 3661, found 770.3654.

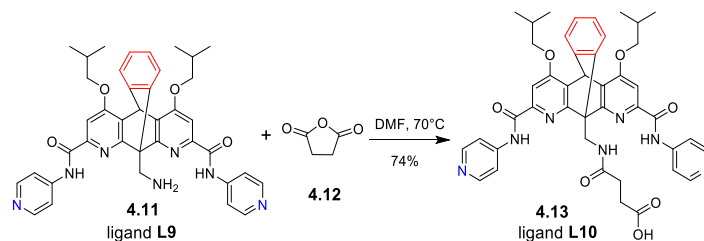
10-(aminomethyl)-4,16-diisobutoxy-N2,N14-di(pyridin-4-yl)-5,10-dihydro-10,5-[2,3]pyridinobenzo[g]quinoline-2,14-dicarboxamide (4.11, ligand L9)



Compound **4.10** (ligand **L8**, 769 mg, 1 mmol, 1.0 Equiv.) was dissolved in 20 mL mixture of CH_2Cl_2 and TFA (v/v=1:1) and the solution was stirred for 12 hours at room temperature, then the solvents were removed by rotary evaporation. The crude material was slurried in CHCl_3 and washed with NaHCO_3 aqueous solution. The organic phase was then washed with water and brine and then dried over Na_2SO_4 . The solution was filtered and the solvent was removed by rotary evaporation. The crude material was purified by silica gel flash column (v/v, CH_2Cl_2 : MeOH = 10:1) to give compound **4.11** as a pale yellow powder (ligand **L9**, 361 mg, 0.54 mmol, 54.0% yield). ^1H NMR (500 MHz, DMSO-*d*₆) δ 10.46 (s, 2H), 8.54 (d, J = 6.3 Hz, 4H), 7.83 (d, J =

4.8, 4H), 7.67 – 7.59 (m, 4H), 7.19 (m, 2H), 6.29 (s, 1H), 4.82 (s, 2H), 4.08 (d, $J = 6.3$ Hz, 4H), 2.18 – 2.08 (m, 2H), 1.07 (d, $J = 6.6$ Hz, 12H). ^{13}C NMR (75 MHz, $\text{DMSO-}d_6$) δ 165.93, 163.64, 160.43, 150.86, 148.00, 145.23, 144.35, 143.82, 129.83, 126.87, 126.32, 114.86, 106.03, 74.92, 58.25, 37.67, 28.15, 19.19. HR-MS (ESI) m/z calculated. For $\text{C}_{39}\text{H}_{39}\text{N}_7\text{O}_4$ $[\text{M}+\text{H}]^{1+}$: 670.3136, found 670.3120.

4-(((4,16-diisobutoxy-2,14-bis(pyridin-4-ylcarbamoyl)-10,5-[2,3]pyridinobenzo[g]quinolin-10(5H)-yl)methyl)amino)-4-oxobutanoic acid (4.13, ligand L10)

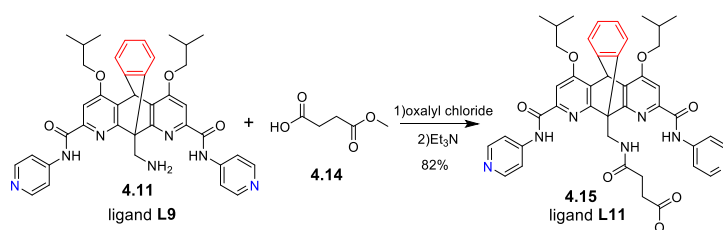


Compound **4.11** (ligand **L9**, 669 mg, 1 mmol, 1.0 Equiv.) and dihydro-2,5-furandione **4.12** (150 mg, 1.5 mmol, 1.5 Equiv.) was dissolved in DMF (15 mL) were stirred at 70°C for 24 hours under argon, then the solvents were removed by rotary evaporation, the resulting oily substance was then diluted with H_2O (50 mL), and the fine powder progressively precipitated out. Then the solid was collected by filtration and the desired crude compound was isolated, and the crude material was purified by recrystallization (v/v, CH_2Cl_2 :n-hexane = 1:1) to give compound **4.13** as a white powder (ligand **L10**, 569 mg, 0.74 mmol, 74.0% yield). ^1H NMR (500 MHz, $\text{DMSO-}d_6$) δ 11.98 (s, 1H), 11.05 (s, 2H), 8.65 (d, $J = 6.0$ Hz, 4H), 8.19 (d, $J = 5.3$ Hz, 4H), 8.07 (s, 1H), 7.60-7.64 (m, 3H), 7.56 (d, $J = 6.9$ Hz, 1H), 7.19 – 7.12 (m, 2H), 6.29 (s, 1H), 5.18 (d, $J = 5.9$ Hz, 2H), 4.09 (d, $J = 6.3$ Hz, 4H), 2.46-2.48 (m, 2H), 2.38-2.42 (m, 2H), 2.20 – 2.12 (m, 2H), 1.10 (d, $J = 6.7$ Hz, 12H). ^{13}C NMR (75 MHz, $\text{DMSO-}d_6$) δ 174.05, 173.56, 165.63, 163.98, 160.54, 148.52, 147.71, 147.39, 144.61, 126.91, 126.55, 124.79, 123.69, 115.00, 106.09, 74.97, 58.67, 37.75, 31.49,

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29.23, 28.17, 19.22. HR-MS (ESI) m/z calculated. For $C_{43}H_{43}N_7O_7$ $[M+H]^{1+}$: 770.3297, found 770.3296.

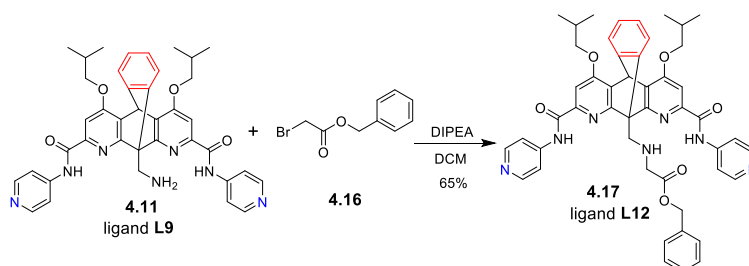
Methyl 4-(((4,16-diisobutoxy-2,14-bis(pyridin-4-ylcarbamoyl)-10,5-[2,3]pyridinobenzo[g]quinolin-10(5H)-yl)methyl)amino)-4-oxobutanoate (4.15, ligand L11)



In a dry round-bottomed flask was placed compound **4.14** (15.85 mg, 0.12 mmol, 1.2 Equiv.) in 10 mL dry DCM. To this were added oxalyl chloride (30.24 mg, 0.24 mmol, 2.4 Equiv.) and a catalytic amount of DMF (1 drop). The reaction mixture was stirred under an inert atmosphere at room temperature for 2 hours. The solvent/acid mixture was evaporated to dryness using a high vacuum pump, its chloride was obtained as a solid in quantitative yield and directly used in the next step. In the above flask, additional compound **4.11** (66.9 mg, 0.1 mmol, 1.0 Equiv.) was dissolved in dry 20 mL DCM and cooled down to 0 °C. Then Et₃N (20.2 mg, 0.2 mmol, 2.0 Equiv.) was added dropwise, the resulting mixture was stirred 1 hour at 0 °C and 24 hours at room temperature. the solvents were removed by rotary evaporation, The crude material was purified by silica gel flash column (v/v, CH₂Cl₂: MeOH = 40:1) to give compound **4.15** as a white powder (ligand **L11**, 64.2 mg, 0.082 mmol, 82% yield). ¹H NMR (300 MHz, Chloroform-*d*) δ 10.23 (s, 2H), 8.58 (d, *J* = 6.2 Hz, 4H), 7.97 (d, *J* = 6.3 Hz, 4H), 7.68 (s, 3H), 7.45 (td, *J* = 6.7, 1.9 Hz, 2H), 7.15 – 7.09 (m, 2H), 6.31 (s, 1H), 5.23 (d, *J* = 6.0 Hz, 2H), 3.97 (d, *J* = 6.5 Hz, 4H), 3.42 (s, 3H), 2.62 – 2.55 (m, 2H), 2.43 – 2.36 (m, 2H), 2.24 (m, 2H), 1.14 (d, *J* = 6.7 Hz, 12H). ¹³C NMR (75 MHz, Chloroform-*d*) δ 173.55, 172.66, 165.28,

162.90, 160.87, 150.19, 147.04, 145.47, 144.42, 143.42, 130.01, 126.46, 126.20, 124.47, 122.63, 114.19, 105.44, 75.13, 58.08, 37.08, 32.15, 29.28, 28.19, 19.02. HR-MS (ESI) m/z calculated. For $C_{44}H_{45}N_7O_7$ $[M+H]^{1+}$: 784.3453, found 784.3427.

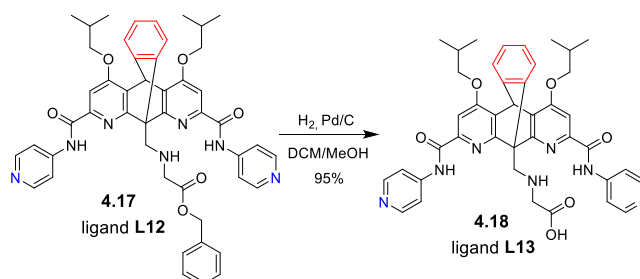
Benzyl 3-(((4,16-diisobutoxy-2,14-bis(pyridin-4-ylcarbamoyl)-10,5-[2,3]pyridinobenzo[g]quinolin-10(5H)-yl)methyl)amino)propanoate (4.17, ligand L12)



To a solution of compound **4.11** (ligand **L9**, 66.9 mg, 0.1 mmol, 1.0 Equiv.) and N,N-diisopropylethylamine (DIPEA, 19.4 mg, 0.15 mmol, 1.5 Equiv.) in dry DCM, which was slowly added benzyl bromoacetate **4.16** (27.5 mg, 0.12 mmol, 1.2 Equiv.) at 0 °C. The mixture was stirred for 12 hours at room temperature, then the solvents were removed by rotary evaporation. The crude material was purified by silica gel flash column (v/v, CH_2Cl_2 : MeOH = 10:1) to give compound **4.17** as a white powder (ligand **L12**, 53 mg, 0.065 mmol, 65.0% yield). 1H NMR (500 MHz, Chloroform- d) δ 10.26 (s, 2H), 8.52 (d, J = 6.3 Hz, 4H), 7.90 (d, J = 6.4 Hz, 1H), 7.76 – 7.72 (m, 4H), 7.65 (s, 2H), 7.50 – 7.37 (m, 6H), 7.17 – 7.09 (m, 2H), 6.30 (s, 1H), 5.42 (s, 2H), 4.40 (s, 2H), 3.98 – 3.93 (m, 6H), 3.77 (s, 1H), 2.23 (m, 2H), 1.13 (d, J = 6.7 Hz, 12H). 1H NMR (500 MHz, DMSO- d_6) δ 10.52 (s, 2H), 8.48 (d, J = 6.3 Hz, 4H), 8.08 (d, J = 7.4 Hz, 1H), 7.83 (d, J = 6.4 Hz, 4H), 7.58 (s, 2H), 7.52 (d, J = 6.1 Hz, 1H), 7.47 (d, J = 7.1 Hz, 2H), 7.37 (dt, J = 13.5, 7.0 Hz, 3H), 7.17 – 7.08 (m, 2H), 6.26 (s, 1H), 5.35 (s, 2H), 4.46 (d, J = 5.0 Hz, 2H), 4.05 (d, J = 6.3 Hz, 4H), 3.98 (d, J = 5.3 Hz, 2H), 3.66 – 3.57 (m, 1H), 2.14 (dp, J = 13.2, 6.5 Hz, 2H), 1.09 (d,

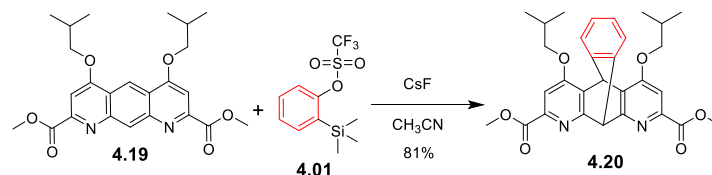
$J = 6.7$ Hz, 12H). ^{13}C NMR (75 MHz, Chloroform- d) δ 174.38, 166.25, 162.91, 150.70, 146.82, 144.77, 143.89, 135.33, 130.51, 128.93, 128.16, 125.84, 124.09, 114.26, 105.25, 75.00, 67.15, 57.71, 52.07, 46.74, 37.84, 28.19, 19.06. HR-MS (ESI) m/z calculated. For $\text{C}_{48}\text{H}_{47}\text{N}_7\text{O}_6$ $[\text{M}+\text{H}]^{1+}$: 818.3661, found 818.3626.

3-(((4,16-diisobutoxy-2,14-bis(pyridin-4-ylcarbamoyl)-10,5-[2,3]pyridinobenzo[g]quinolin-10(5H)-yl)methyl)amino)propanoic acid (4.18, ligand L13)



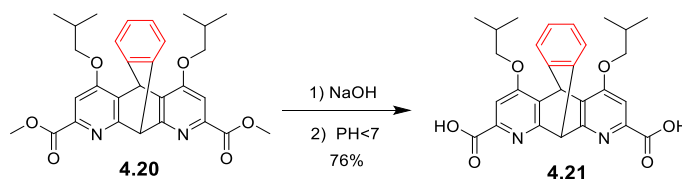
To a stirred solution of compound **4.17** (ligand **L12**, 81.7 mg, 0.1 mmol, 1.0 Equiv.) in 10 mL methanol/DCM (1:1) was added 50mg Pd/C (10%). The mixture was hydrogenated at atmospheric pressure overnight. The reaction mixture was filtered through a pad of celite and the filtrate was evaporated to dryness to give compound **4.18** as a grey powder (ligand **L13**, 69 mg, 0.095 mmol, 95% yield). ^1H NMR (500 MHz, DMSO- d_6) δ 11.06 (s, 2H), 9.08 (s, 1H), 8.54 (d, $J = 6.4$ Hz, 4H), 8.08 (d, $J = 6.5$ Hz, 4H), 7.69 (s, 2H), 7.63 – 7.58 (m, 2H), 7.20 – 7.14 (m, 2H), 6.30 (s, 1H), 5.03 (s, 2H), 4.14 (s, 2H), 4.10 (d, $J = 6.3$ Hz, 4H), 2.15 (dp, $J = 13.2, 6.6$ Hz, 2H), 1.09 (d, $J = 7.7$ Hz, 12H). ^{13}C NMR (75 MHz, DMSO- d_6) δ 168.25, 164.11, 163.41, 149.80, 148.20, 146.52, 143.68, 142.68, 129.32, 127.46, 126.69, 125.10, 123.25, 115.17, 107.19, 75.07, 55.73, 51.32, 37.62, 28.16, 19.19. HR-MS (ESI) m/z calculated. For $\text{C}_{41}\text{H}_{41}\text{N}_7\text{O}_6$ $[\text{M}+\text{H}]^{1+}$: 728.3191, found 728.3186, $[\text{M}+\text{H}]^{2+}$: 364.6632, found 364.6634.

Dimethyl 4,16-diisobutoxy-10-methyl-5,10-dihydro-10,5-[2,3]pyridinobenzo[g]quinoline-2,14-dicarboxylate (4.20)



Compound **4.20** (418 mg, 0.81 mmol, 81% yield) was obtained as a white powder following the same procedure used for compound **4.02**, compound **4.19** (440 mg, 1 mmol, 1.0 Equiv.) was used as reagent and was synthesized according to literature procedures.^[4] ^1H NMR (300 MHz, Chloroform- d) δ 7.54 (d, J = 3.0 Hz, 1H), 7.47 (s, 2H), 7.44 (d, J = 1.4 Hz, 1H), 7.09 – 7.04 (m, 2H), 6.28 (s, 1H), 6.00 (s, 1H), 3.96 (s, 6H), 3.88 (d, J = 6.5 Hz, 4H), 2.20 (dt, J = 13.3, 6.6 Hz, 2H), 1.12 (d, J = 6.7 Hz, 12H). ^{13}C NMR (75 MHz, Chloroform- d) δ 167.35, 165.83, 159.77, 145.60, 143.39, 129.01, 126.00, 124.05, 107.76, 74.72, 58.89, 52.97, 38.53, 28.21, 19.05. HR-MS (ESI) m/z calculated. For $\text{C}_{30}\text{H}_{32}\text{N}_2\text{O}_6$ $[\text{M}+\text{H}]^{1+}$: 517.2333, found 517.2332.

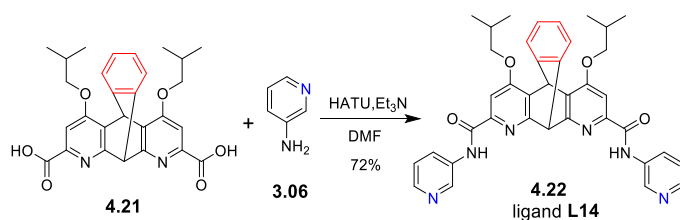
4,16-diisobutoxy-5,10-dihydro-10,5-[2,3]pyridinobenzo[g]quinoline-2,14-dicarboxylic acid (4.21)



Compound **4.21** (185 mg, 0.38 mmol, 76% yield) was obtained as a white powder following the same procedure used for compound **4.03**. Compound **4.20** (258 mg, 0.50 mmol, 1.0 Equiv.) was used as reagent. ^1H NMR (500 MHz, DMSO- d_6) δ 7.69 – 7.66 (m, 1H), 7.52 – 7.49 (m, 1H), 7.43 (s, 2H), 7.12 – 7.07 (m, 2H), 6.21 (s, 1H), 5.74 (s, 1H), 3.96 (d, J = 6.3 Hz, 4H), 2.09 (tt, J =

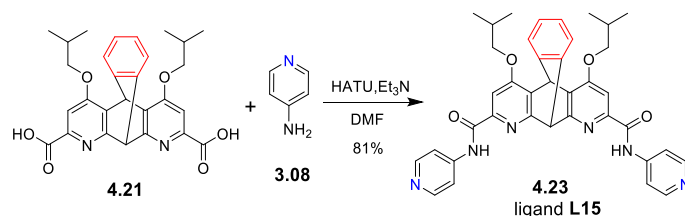
13.5, 6.6 Hz, 2H), 1.05 (d, J = 8.1 Hz, 12H).).

4,16-diisobutoxy-N2,N14-di(pyridin-4-yl)-5,10-dihydro-10,5-[2,3]pyridinobenzo[g]quinoline-2,14-dicarboxamide(4.22, ligand L14)



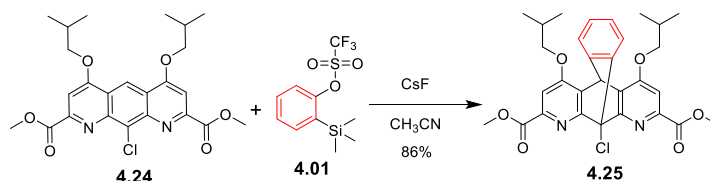
Compound **4.22** (ligand **L14**, 46.1 mg, 0.72 mmol, 72% yield) was obtained as a white powder following the same procedure used for compound **4.04** (ligand **L6**). Compound **4.21** (48.8 mg, 0.1 mmol, 1.0 Equiv.) and 3-aminopyridine **3.06** (22.6 mg, 0.24 mmol, 2.4 Equiv.) were used as reagent. ¹H NMR (300 MHz, Chloroform-*d*) δ 10.09 (s, 2H), 8.88 (s, 2H), 8.42 – 8.33 (m, 4H), 7.67 – 7.63 (m, 3H), 7.52 (dd, J = 3.2, 1.5 Hz, 1H), 7.14 (dd, J = 5.5, 3.1 Hz, 2H), 6.32 (s, 1H), 5.81 (s, 1H), 3.95 (d, J = 6.5 Hz, 4H), 2.26 – 2.20 (m, 2H), 1.13 (d, J = 6.8 Hz, 12H). HR-MS (ESI) m/z calculated. For C₃₈H₃₆N₆O₄ [M+H]¹⁺:641.2871, found 641.2867.

4,16-diisobutoxy-N2,N14-di(pyridin-4-yl)-5,10-dihydro-10,5-[2,3]pyridinobenzo[g]quinoline-2,14-dicarboxamide (4.23, ligand L15)



Compound **4.23** (ligand **L15**, 51.8 mg, 0.081 mmol, 81% yield) was obtained as a white powder following the same procedure used for compound **4.04** (ligand **L6**). Compound **4.21** (48.8 mg, 0.1 mmol, 1.0 Equiv.) and 4-aminopyridine **3.08** (22.6 mg, 0.24 mmol, 2.4 Equiv.) were used as reagent. ^1H NMR (300 MHz, Chloroform-*d*) δ 10.15 (s, 2H), 8.57 (s, 4H), 7.71 (s, 4H), 7.63 (d, J = 3.2 Hz, 3H), 7.53 – 7.50 (m, 1H), 7.15 – 7.12 (m, 2H), 6.32 (s, 1H), 5.79 (s, 1H), 3.95 (d, J = 6.5 Hz, 4H), 2.27 – 2.19 (m, 2H), 1.13 (d, J = 6.7 Hz, 12H). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 165.91, 162.59, 160.73, 150.76, 147.00, 142.90, 142.58, 129.11, 126.52, 126.23, 125.38, 124.47, 105.22, 75.02, 58.61, 38.59, 28.20, 19.06. HR-MS (ESI) m/z calculated. For $\text{C}_{38}\text{H}_{36}\text{N}_6\text{O}_4$ $[\text{M}+\text{H}]^{1+}$: 641.2871, found 641.2862.

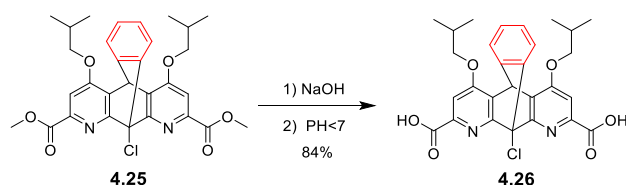
Dimethyl 10-chloro-4,16-diisobutoxy-5,10-dihydro-10,5-[2,3]pyridinobenzo[g]quinoline-2,14-dicarboxylate (4.25)



Compound **4.25** (474 mg, 0.86 mmol, 86% yield) was obtained as a white powder following the same procedure used for compound **4.02**, compound **4.24** (475 mg, 1 mmol, 1.0 Equiv.) was used as reagent and was synthesized

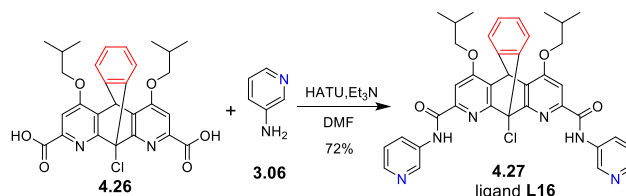
according to literature procedures.^[4] ^1H NMR (500 MHz, Chloroform-*d*) δ 7.91 – 7.89 (m, 1H), 7.53 (s, 2H), 7.48 – 7.45 (m, 1H), 7.16 – 7.13 (m, 2H), 6.29 (s, 1H), 3.94 (s, 6H), 3.90 (d, J = 6.5 Hz, 4H), 2.21 (dp, J = 12.6, 6.2 Hz, 2H), 1.12 (d, J = 6.7 Hz, 12H). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 165.76, 163.74, 159.87, 145.75, 142.74, 140.77, 127.71, 126.93, 126.06, 123.92, 123.66, 108.22, 76.08, 75.03, 52.98, 36.95, 28.21, 19.05. HR-MS (ESI) m/z calculated. For $\text{C}_{30}\text{H}_{31}\text{ClN}_2\text{O}_6$ $[\text{M}+\text{H}]^{1+}$: 551.1943, found 551.1946.

10-chloro-4,16-diisobutoxy-5,10-dihydro-10,5-[2,3]pyridinobenzo[g]quinoline-2,14-dicarboxylic acid (4.26)



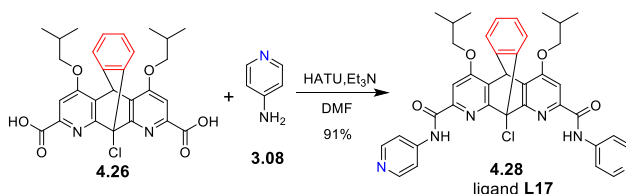
Compound **4.26** (219 mg, 0.42 mmol, 84% yield) was obtained as a white powder following the same procedure used for compound **4.03**. Compound **4.25** (276 mg, 0.50 mmol, 1.0 Equiv.) was used as reagent. ^1H NMR (500 MHz, Chloroform-*d*) δ 7.86 (d, J = 8.5 Hz, 1H), 7.61 (s, 2H), 7.50 (dd, J = 7.1, 1.2 Hz, 1H), 7.25 – 7.19 (m, 2H), 6.33 (s, 1H), 3.95 (d, J = 6.5 Hz, 4H), 2.23 (dt, J = 13.3, 6.7 Hz, 2H), 1.13 (d, J = 6.7 Hz, 12H). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 163.75, 162.30, 161.18, 144.01, 141.88, 140.55, 128.83, 127.52, 126.58, 124.14, 123.47, 106.65, 75.59, 74.92, 37.12, 28.13, 18.97. HR-MS (ESI) m/z calculated. For $\text{C}_{28}\text{H}_{27}\text{ClN}_2\text{O}_6$ $[\text{M}+\text{H}]^{1+}$: 523.1630, found 523.1633.

10-chloro-4,16-diisobutoxy-N2,N14-di(pyridin-3-yl)-5,10-dihydro-10,5-[2,3]pyridinobenzo[g]quinoline-2,14-dicarboxamide (4.27, ligand L16)



Compound **4.27** (ligand **L16**, 46.1 mg, 0.89 mmol, 89% yield) was obtained as a white powder following the same procedure used for compound **4.04** (ligand **L6**). Compound **4.26** (52.3 mg, 0.1 mmol, 1.0 Equiv.) and 3-aminopyridine **3.06** (22.6 mg, 0.24 mmol, 2.4 Equiv.) were used as reagents. ¹H NMR (300 MHz, Chloroform-*d*) δ 10.22 (s, 2H), 8.90 (d, *J* = 2.2 Hz, 2H), 8.41 (dd, *J* = 4.7, 1.4 Hz, 2H), 8.29 (ddd, *J* = 8.3, 2.6, 1.5 Hz, 2H), 7.94 – 7.90 (m, 1H), 7.69 (s, 2H), 7.55 – 7.51 (m, 1H), 7.33 (dd, *J* = 8.3, 4.7 Hz, 2H), 7.24 – 7.19 (m, 2H), 6.34 (s, 1H), 3.98 (d, *J* = 6.5 Hz, 4H), 2.24 (dt, *J* = 13.2, 6.6 Hz, 2H), 1.14 (d, *J* = 6.7 Hz, 12H). ¹³C NMR (75 MHz, Chloroform-*d*) δ 162.27, 162.07, 160.85, 147.09, 145.48, 142.40, 141.52, 141.13, 134.38, 127.69, 127.32, 126.69, 126.34, 124.03, 123.71, 123.28, 105.47, 75.90, 75.33, 37.03, 28.20, 19.06. HR-MS (ESI) *m/z* calculated. For C₃₈H₃₅ClN₆O₄ [M+H]¹⁺: 675.2481, found 675.2481.

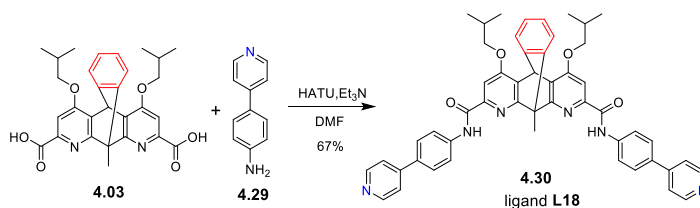
10-chloro-4,16-diisobutoxy-N2,N14-di(pyridin-4-yl)-5,10-dihydro-10,5-[2,3]pyridinobenzo[g]quinoline-2,14-dicarboxamide (4.28, ligand L17)



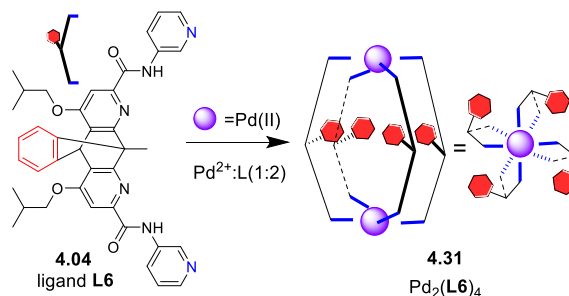
Compound **4.28** (ligand **L17**, 61.4 mg, 0.091 mmol, 91% yield) was obtained as a white powder following the same procedure used for compound **4.04**

(ligand **L6**). Compound **4.26** (52.3 mg, 0.1 mmol, 1.0 Equiv.) and 4-aminopyridine **3.08** (22.6 mg, 0.24 mmol, 2.4 Equiv.) were used as reagent. ^1H NMR (300 MHz, Chloroform-*d*) δ 10.30 (s, 2H), 8.58 (d, J = 5.4 Hz, 4H), 7.92 – 7.89 (m, 1H), 7.70 (d, J = 6.2 Hz, 6H), 7.55 – 7.51 (m, 1H), 7.24 – 7.20 (m, 2H), 6.34 (s, 1H), 3.98 (d, J = 6.5 Hz, 4H), 2.24 (dp, J = 13.5, 7.0 Hz, 2H), 1.14 (d, J = 6.7 Hz, 12H). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 162.25, 160.91, 150.89, 146.78, 144.34, 142.27, 141.00, 127.90, 127.40, 126.39, 124.11, 123.24, 113.70, 105.64, 75.88, 75.37, 37.05, 28.20, 19.05. HR-MS (ESI) m/z calculated. For $\text{C}_{38}\text{H}_{35}\text{ClN}_6\text{O}_4$ $[\text{M}+\text{H}]^{1+}$: 675.2481, found 675.2523.

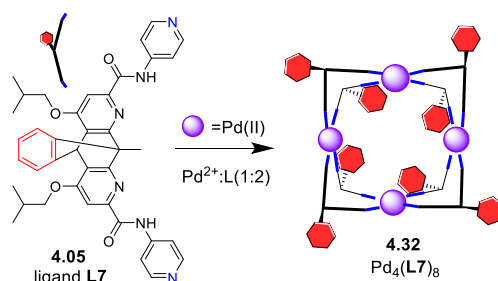
4,16-diisobutoxy-10-methyl-N2,N14-bis(4-(pyridin-4-yl)phenyl)-5,10-dihydro-10,5-[2,3]pyridinobenzo[*g*]quinoline-2,14-dicarboxamide(4.30, ligand **L18)**



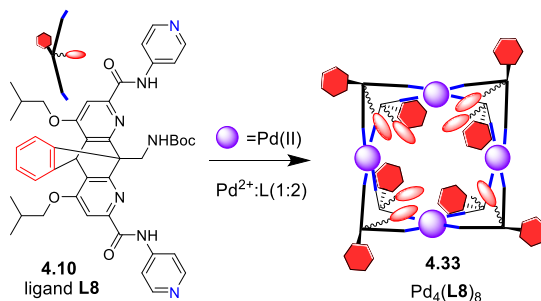
Compound **4.30** (ligand **L17**, 273 mg, 0.34 mmol, 67 % yield) was obtained as a white powder following the same procedure used for compound **4.04** (ligand **L6**), 4-(pyridin-4-yl)aniline **4.29** (112.9 mg, 1.2 mmol, 2.4 Equiv.) was used as reagent and was synthesized according to literature procedures.^[5] ^1H NMR (500 MHz, Chloroform-*d*) δ 10.24 (s, 2H), 8.66 (d, J = 6.1 Hz, 4H), 7.89 (d, J = 8.7 Hz, 4H), 7.70 (d, J = 8.7 Hz, 4H), 7.65 (s, 2H), 7.56 – 7.50 (m, 6H), 7.18 – 7.12 (m, 2H), 6.34 (s, 1H), 3.96 (d, J = 6.5 Hz, 4H), 2.65 (s, 3H), 2.24 (m, 2H), 1.14 (d, J = 6.7 Hz, 12H). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 166.94, 162.18, 160.47, 150.27, 147.58, 146.94, 145.77, 143.79, 138.68, 133.70, 129.54, 127.73, 126.16, 125.87, 124.20, 122.60, 121.22, 120.09, 104.63, 74.96, 55.18, 37.67, 28.23, 19.10, 10.94. HR-MS (ESI) m/z calculated. For $\text{C}_{51}\text{H}_{46}\text{N}_6\text{O}_4$ $[\text{M}+\text{H}]^{1+}$: 807.3653, found 807.3682.

Complex 4.31, Pd₂(L6)₄

To a suspension of compound **4.04** (ligand **L6**, 6.54 mg, 0.01 mmol, 1.0 Equiv.) and Pd(CH₃CN)₄(BF₄)₂ (1.15 mg, 0.005 mmol, 0.5 Equiv.) in 0.6 mL CH₃CN or DMF, the mixture was heated at 40°C for 4 hours. The turbid suspension of ligands gradually turned clear to give a yellow solution that was characterized by NMR to show formation of complex **4.31**, Pd₂(L6)₄(BF₄)₄. Diethyl ether was added to precipitate the isolated product Pd₂(L6)₄(BF₄)₄. ¹H NMR (500 MHz, Acetonitrile-*d*₃) δ 10.15 (s, 2H), 9.26 (ddd, *J* = 8.8, 2.2, 1.1 Hz, 2H), 8.57 (d, *J* = 2.3 Hz, 2H), 7.94 (d, *J* = 5.0 Hz, 2H), 7.64 (s, 2H), 7.50 – 7.44 (m, 4H), 7.05 – 7.01 (m, 1H), 6.90 (t, *J* = 8.1 Hz, 1H), 6.41 (s, 1H), 4.01 (dd, *J* = 21.3, 6.4 Hz, 4H), 2.76 (s, 3H), 2.22 – 2.19 (m, 2H), 1.12 (dd, *J* = 6.7, 2.2 Hz, 12H). ESI-TOF-MS for Pd₂(L6)₄(BF₄)₄: The following picked signals are those at the high intensities. *m/z* Calcd for [M-2(BF₄⁻)]²⁺ 1502.5008, found 1502.5026; Calcd for [M-3(BF₄⁻)]³⁺ 972.6657, found 972.6660; Calcd for [M-4(BF₄⁻)]⁴⁺ 707.7482, found 707.7484.

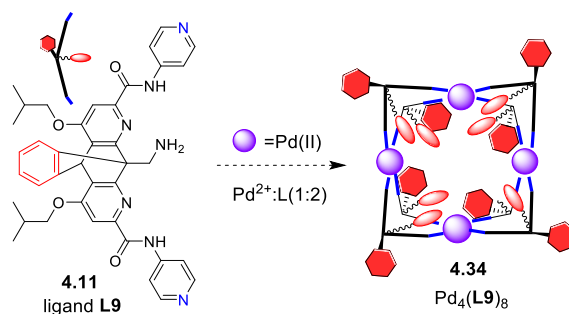
Complex 4.32, Pd₄(L7)₈

To a solution of compound **4.05** (ligand **L7**, 6.54 mg, 0.01 mmol, 1.0 Equiv.) and Pd(CH₃CN)₄(BF₄)₂ (1.15 mg, 0.005 mmol, 0.5 Equiv.) in 0.6 mL DMSO or DMF, the mixture was heated at 40°C for 4 hours to give a yellow solution that was characterized by NMR to show formation of complex **4.32**, Pd₄(**L7**)₈(BF₄)₈. Diethyl ether was added to precipitate the isolated product Pd₄(**L7**)₈(BF₄)₈. ¹H NMR (500MHz, DMSO-*d*₆) δ 10.83 (s, 2H), 9.10 (s, 4H), 8.12 (s, 4H), 7.50-7.58 (m, 4H), 7.15 (s, 2H), 6.28 (s, 1H), 4.02 (s, 4H), 2.65 (s, 3H), 2.10 (m, 2H), 1.05 (d, *J* = 6.5 Hz, 12H). ESI-TOF-MS for Pd₄(**L7**)₈(BF₄)₈: The following picked signals are those at the high intensities. *m/z* Calcd for [M-3(BF₄⁻)]³⁺ 2033.0028, found 2032.6786, Calcd for [M-4(BF₄⁻)]⁴⁺ 1502.5008, found 1502.5018, Calcd for [M-5(BF₄⁻)]⁵⁺ 1184.7998, found 1184.7991, Calcd for [M-6(BF₄⁻)]⁶⁺ 972.8326, found 972.8315, Calcd for [M-7(BF₄⁻)]⁷⁺ 821.4273, found 821.4265.

Complex 4.33, Pd₄(L8)₈

To a solution of compound **4.10** (ligand **L8**, 7.70 mg, 0.01 mmol, 1.0 Equiv.) and $\text{Pd}(\text{CH}_3\text{CN})_4(\text{BF}_4)_2$ (1.15 mg, 0.005 mmol, 0.5 Equiv.) in 0.6 mL DMSO or DMF, the mixture was heated at 40°C for 4 hours to give a yellow solution that was characterized by NMR to show formation of complex **4.33**, $\text{Pd}_4(\text{L8})_8(\text{BF}_4)_8$. Diethyl ether was added to precipitate the isolated product $\text{Pd}_4(\text{L8})_8(\text{BF}_4)_8$. ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 11.09 (s, 2H), 9.11 (s, 4H), 8.15 (s, 4H), 7.55 (s, 4H), 7.15 (s, 2H), 6.24 (s, 1H), 5.11 (s, 2H), 4.04 (s, 4H), 2.14 (s, 2H), 1.06 (s, 12H). ESI-TOF-MS for $\text{Pd}_4(\text{L8})_8(\text{BF}_4)_8$: The following picked signals are those at the high intensities. m/z Calcd for $[\text{M}-3(\text{BF}_4^-)]^{3+}$ 2339.5053, found 2339.4903, m/z Calcd for $[\text{M}-4(\text{BF}_4^-)]^{4+}$ 1732.8779, found 1732.8614, m/z Calcd for $[\text{M}-5(\text{BF}_4^-)]^{5+}$ 1368.9015, found 1368.8919, m/z Calcd for $[\text{M}-6(\text{BF}_4^-)]^{6+}$ 1126.2505, found 1126.2430, m/z Calcd for $[\text{M}-7(\text{BF}_4^-)]^{7+}$ 953.0713, found 953.0664. ESI-TOF-MS for $\text{Pd}_5(\text{L8})_{10}(\text{BF}_4)_{10}$: m/z Calcd for $[\text{M}-7(\text{BF}_4^-)]^{7+}$ 1213.0188, found 1213.0115.

Complex 4.34, $\text{Pd}_4(\text{L9})_8$

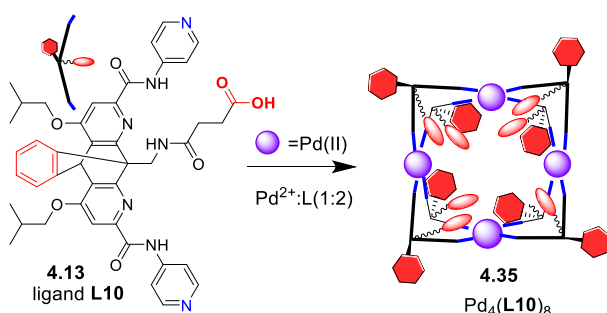


To a solution of compound **4.11** (ligand **L9**, 7.70 mg, 0.01 mmol, 1.0 Equiv.) and $\text{Pd}(\text{CH}_3\text{CN})_4(\text{BF}_4)_2$ (1.15 mg, 0.005 mmol, 0.5 Equiv.) in 0.6 mL DMSO or DMF, the mixture was heated at 40°C for 4 hours to give a yellow solution that was characterized by NMR to show the formation of two sets of signals overlapping that is difficult for integration, a set of broad peaks assign to complex **4.33**, $\text{Pd}_4(\text{L8})_8(\text{BF}_4)_8$ and another set of signals should be by-products with lower nuclear. Diethyl ether was added to precipitate the isolated

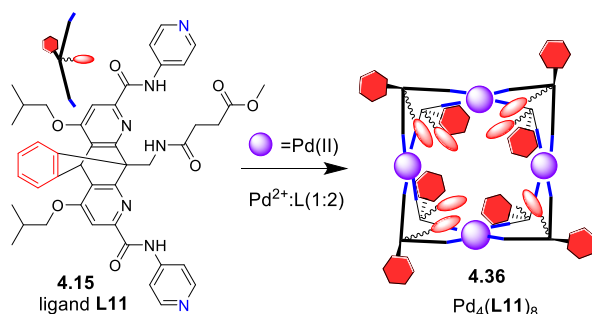
Chapter VIII

product. ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ broad peaks at δ 10.78, 9.26, 8.45, 8.21, 7.62, 7.19, 6.28, 4.06, 2.16, 1.06. Another set of signals at δ 10.93, 8.77, 8.19, 7.69, 7.24, 6.35, 4.11, 2.16, 1.11. ESI-TOF-MS for $\text{Pd}_4(\text{L9})_8(\text{BF}_4)_8$: Signals not detected for M_4L_8 and only unknown oligomeric species observed.

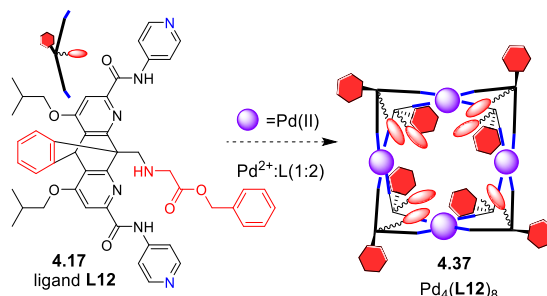
Complex 4.35, $\text{Pd}_4(\text{L10})_8$



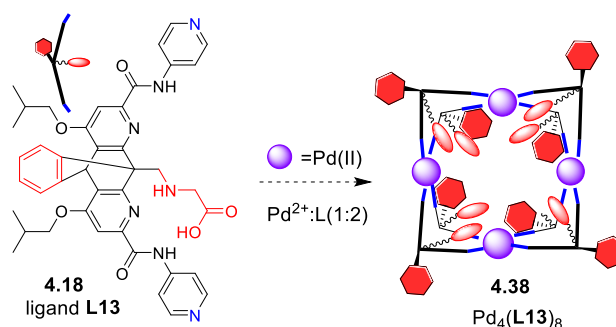
To a solution of compound **4.13** (ligand **L10**, 7.69 mg, 0.01 mmol, 1.0 Equiv.) and $\text{Pd}(\text{CH}_3\text{CN})_4(\text{BF}_4)_2$ (1.15 mg, 0.005 mmol, 0.5 Equiv.) in 0.6 mL DMSO or DMF, the mixture was heated at 40°C for 4 hours to give a yellow solution that was characterized by NMR to show formation of complex **4.35**, $\text{Pd}_4(\text{L10})_8(\text{BF}_4)_8$. Diethyl ether was added to precipitate the isolated product $\text{Pd}_4(\text{L10})_8(\text{BF}_4)_8$. ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 10.99 (s, 2H), 9.17 (s, 4H), 8.26 (s, 4H), 7.91-7.99 (m, 1H), 7.55 (m, 4H), 7.14 (s, 2H), 6.24 (s, 1H), 5.16 (s, 2H), 4.03 (s, 4H), 2.36 (s, 2H), 2.24 (s, 2H), 2.11 (s, 2H), 1.04 (d, $J = 6.4$ Hz, 12H). ESI-TOF-MS for $\text{Pd}_4(\text{L10})_8(\text{BF}_4)_8$: The following picked signals are those at the high intensities. m/z Calcd for $[\text{M}-4(\text{BF}_4^-)]^{4+}$ 1732.5550, found 1732.5381, m/z Calcd for $[\text{M}-5(\text{BF}_4^-)]^{5+}$ 1368.8432, found 1368.8322, m/z Calcd for $[\text{M}-6(\text{BF}_4^-)]^{6+}$ 1126.2020, found 1126.1941, m/z Calcd for $[\text{M}-7(\text{BF}_4^-)]^{7+}$ 953.0297, found 953.0235. Of note, ESI-TOF-MS for $\text{Pd}_5(\text{L10})_{10}(\text{BF}_4)_{10}$: m/z Calcd for $[\text{M}-7(\text{BF}_4^-)]^{7+}$ 1212.9668, found 1212.9580.

Complex 4.36, Pd₄(L11)₈

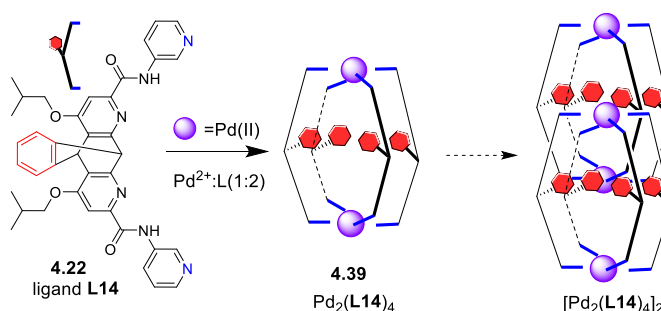
To a solution of compound **4.15** (ligand **L11**, 3.92 mg, 0.005 mmol, 1.0 Equiv.) and Pd(CH₃CN)₄(BF₄)₂ (0.6 mg, 0.0025 mmol, 0.5 Equiv.) in 0.6 mL DMSO or DMF, the mixture was heated at 40°C for 4 hours to give a yellow solution that was characterized by NMR to show formation of complex **4.36**, Pd₄(**L11**)₈(BF₄)₈. Diethyl ether was added to precipitate the isolated product Pd₄(**L11**)₈(BF₄)₈. ¹H NMR (300 MHz, DMSO-*d*₆) δ 11.01 (s, 2H), 9.26 – 8.79 (m, 4H), 8.24 (s, 4H), 7.60 (d, *J* = 23.9 Hz, 5H), 7.14 (s, 2H), 6.24 (s, 1H), 5.15 (s, 2H), 4.03 (s, 10H), 2.43 (s, 2H), 2.14 (s, 2H), 1.76 (s, 2H), 1.07 (s, 12H). ESI-TOF-MS for Pd₄(**L11**)₈(BF₄)₈: The following picked signals are those at the high intensities. *m/z* Calcd for [M-3(BF₄⁻)]³⁺ 2377.1166, found 2377.1146, *m/z* Calcd for [M-4(BF₄⁻)]⁴⁺ 1760.8365, found 1760.7814, *m/z* Calcd for [M-5(BF₄⁻)]⁵⁺ 1391.2683, found 1391.2647, *m/z* Calcd for [M-6(BF₄⁻)]⁶⁺ 1144.8896, found 1144.8874, *m/z* Calcd for [M-7(BF₄⁻)]⁷⁺ 969.0477, found 969.0462, *m/z* Calcd for [M-8(BF₄⁻)]⁸⁺ 837.0412, found 837.0398. ESI-TOF-MS for Pd₅(**L10**)₁₀(BF₄)₁₀: *m/z* Calcd for [M-7(BF₄⁻)]⁷⁺ 1232.9892, found 1232.9875.

Complex 4.37, $\text{Pd}_4(\text{L12})_8$ 

To a solution of compound **4.17** (ligand **L12**, 4.09 mg, 0.005 mmol, 1.0 Equiv.) and $\text{Pd}(\text{CH}_3\text{CN})_4(\text{BF}_4)_2$ (0.6 mg, 0.0025 mmol, 0.5 Equiv.) in 0.6 mL DMSO or DMF, the mixture was heated at 40°C for 4 hours to give a yellow solution that was characterized by NMR to show the formation of Pd(II) complex. However, after trying different mass spectrometry conditions, the composition was still unsuccessfully confirmed. Based on similar ligands and the 1D and 2D NMR results are more complex but still similar to the other M_4L_8 species, we postulate that ligand **L12** could self-assemble into $\text{Pd}_4(\text{L12})_8(\text{BF}_4)_8$ as main products. Of note, this needs further confirmation and determination. ^1H NMR (500 MHz, $\text{DMSO}-d_6$): the following picks are obvious but broad or overlap with impurity peaks. The accurate integration is impossible, δ 10.70, 9.01, 8.48, 8.08, 7.52, 7.31, 7.07, 6.20, 5.22, 4.39, 3.98, 2.11, 1.03. ESI-TOF-MS for $\text{Pd}_4(\text{L12})_8(\text{BF}_4)_8$: Signals not detected for M_4L_8 and only unknown oligomeric species observed.

Complex 4.38, Pd₄(L13)₈

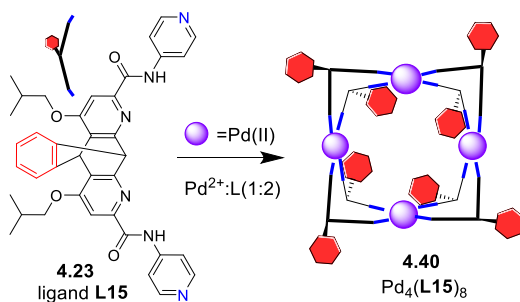
To a solution of compound **4.18** (ligand **L13**, 3.6 mg, 0.005 mmol, 1.0 Equiv.) and Pd(CH₃CN)₄(BF₄)₂ (0.6 mg, 0.0025 mmol, 0.5 Equiv.) in 0.6 mL DMSO or DMF, the mixture was heated at 40°C for 4 hours to give a yellow solution that was characterized by NMR to show formation of complex **4.38** Pd₄(**L13**)₈(BF₄)₈. Diethyl ether was added to precipitate the isolated product Pd₄(**L13**)₈(BF₄)₈. ¹H NMR (300 MHz, DMSO-*d*₆) δ 11.09 (s, 2H), 8.70 (s, 4H), 8.20 (s, 4H), 7.69 (d, *J* = 24.4 Hz, 4H), 7.22 (s, 2H), 6.32 (d, *J* = 14.0 Hz, 1H), 5.11 (s, 2H), 4.12 (s, 4H), 2.23 – 2.10 (m, 2H), 1.11 (d, *J* = 6.6 Hz, 12H). ESI-TOF-MS for Pd₄(**L13**)₈(BF₄)₈: Signals not detected for M₄L₈ and only unknown oligomeric species observed.

Complex 4.39, Pd₂(L14)₄

To a suspension of compound **4.22** (ligand **L6**, 3.2 mg, 0.005 mmol, 1.0 Equiv.) and Pd(CH₃CN)₄(BF₄)₂ (0.6 mg, 0.0025 mmol, 0.5 Equiv.) in 0.6 mL CH₃CN or

DMF, the mixture was heated at 40°C for 4 hours, the turbid suspension of ligands gradually turned clear to give a yellow solution and characterized by NMR, complicated NMR. HR-MS for $\text{Pd}_2(\text{L14})_4(\text{BF}_4)_4$: The following picked signals are those at high intensities. m/z Calcd for $[\text{M}-2(\text{BF}_4^-)]^{2+}$ 1474.4693, found 1474.4708, m/z Calcd for $[\text{M}-3(\text{BF}_4^-)]^{3+}$ 953.9781, found 953.9785, m/z Calcd for $[\text{M}-4(\text{BF}_4^-)]^{4+}$ 693.7325, found 693.7224. Another set of HR-MS for Interlocked dimer $[\text{Pd}_2(\text{L14})_4(\text{BF}_4)_4]_2$: The following picked signals are those at the high intensities. m/z Calcd for $[\text{M}-3(\text{BF}_4^-)]^{3+}$ 1995.2942, found 1995.299, m/z Calcd for $[\text{M}-4(\text{BF}_4^-)]^{4+}$ 1474.7196, found 1474.7210, m/z Calcd for $[\text{M}-5(\text{BF}_4^-)]^{5+}$ 1162.3748, found 1162.3760.

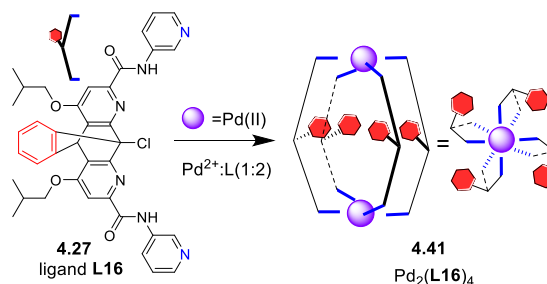
Complex 4.40, $\text{Pd}_4(\text{L15})_8$



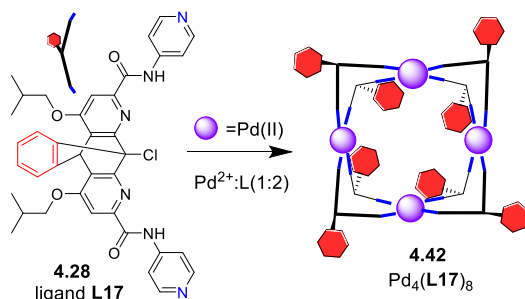
To a solution of compound **4.23** (ligand **L15**, 3.2 mg, 0.005 mmol, 1.0 Equiv.) and $\text{Pd}(\text{CH}_3\text{CN})_4(\text{BF}_4)_2$ (0.6 mg, 0.0025 mmol, 0.5 Equiv.) in 0.6 mL DMSO or DMF, the mixture was heated at 40°C for 4 hours to give a yellow solution that was characterized by NMR to show formation of complex **4.40**, $\text{Pd}_4(\text{L15})_8(\text{BF}_4)_8$. ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 11.24 (s, 2H), 9.12 (s, 4H), 8.21 (s, 4H), 7.56 (s, 4H), 7.10 (s, 2H), 6.25 (s, 1H), 5.98 (s, 1H), 4.00 (s, 4H), 2.11 (s, 2H), 1.04 (s, 13H). HR-MS for $\text{Pd}_4(\text{L15})_8(\text{BF}_4)_8$: The following picked signals are those at the high intensities. m/z Calcd for $[\text{M}-3(\text{BF}_4^-)]^{3+}$ 1994.9607, found 1994.9449, m/z Calcd for $[\text{M}-4(\text{BF}_4^-)]^{4+}$ 1474.4695, found 1474.4595, m/z Calcd for $[\text{M}-5(\text{BF}_4^-)]^{5+}$ 1162.3748, found 1164.3684, m/z Calcd for $[\text{M}-6(\text{BF}_4^-)]^{6+}$ 954.1450, found 954.1401, m/z Calcd for $[\text{M}-7(\text{BF}_4^-)]^{7+}$ 805.4094,

found 805.4054.

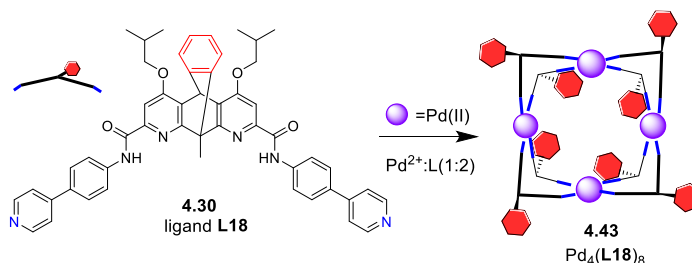
Complex 4.41, Pd₂(L16)₄



To a suspension of compound **4.27** (ligand **L16**, 3.2 mg, 0.005 mmol, 1.0 Equiv.) and Pd(CH₃CN)₄(BF₄)₂ (0.6 mg, 0.0025 mmol, 0.5 Equiv.) in 0.6 mL CH₃CN or DMF, the mixture was heated at 40°C for 4 hours, the turbid suspension of ligands gradually turned clear to give a yellow solution that was characterized by NMR to show formation of complex **4.41**, Pd₂(**L16**)₄(BF₄)₄. Diethyl ether was added to precipitate the isolated product Pd₂(**L16**)₄(BF₄)₄. ¹H NMR (500 MHz, Acetonitrile-*d*₃) δ 10.16 (s, 2H), 9.25 (d, *J* = 8.7 Hz, 2H), 8.62 (d, *J* = 2.3 Hz, 2H), 7.95 (d, *J* = 4.9 Hz, 2H), 7.72 (d, *J* = 9.8 Hz, 3H), 7.56 (d, *J* = 7.0 Hz, 1H), 7.46 (dd, *J* = 8.7, 5.6 Hz, 2H), 7.13 (td, *J* = 7.5, 1.1 Hz, 1H), 7.00 (td, *J* = 7.6, 1.0 Hz, 1H), 6.44 (s, 1H), 4.07 – 4.00 (m, 4H), 2.24 – 2.19 (m, 2H), 1.12 (dd, *J* = 6.7, 2.2 Hz, 12H). ESI-TOF-MS for Pd₂(**L16**)₄(BF₄)₄: The following picked signals are those at the high intensities. *m/z* Calcd for [M-2(BF₄⁻)]²⁺ 1543.3901, found 1543.3909, *m/z* Calcd for [M-3(BF₄⁻)]³⁺ 999.9254, found 999.9254, *m/z* Calcd for [M-4(BF₄⁻)]⁴⁺ 728.1930, found 728.1929.

Complex 4.42, $\text{Pd}_4(\text{L17})_8$ 

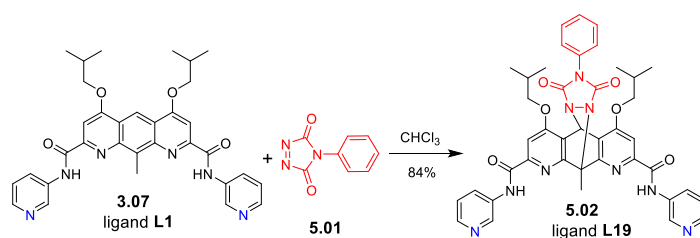
To a solution of compound **4.28** (ligand **L17**, 3.4 mg, 0.005 mmol, 1.0 Equiv.) and $\text{Pd}(\text{CH}_3\text{CN})_4(\text{BF}_4)_2$ (0.6 mg, 0.0025 mmol, 0.5 Equiv.) in 0.6 mL DMSO or DMF, the mixture was heated at 40°C for 4 hours to give a yellow solution that was characterized by NMR to show formation of complex **4.42**, $\text{Pd}_4(\text{L17})_8(\text{BF}_4)_8$. ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 10.78 (s, 2H), 9.09 (s, 4H), 8.11 (s, 4H), 7.81 (s, 1H), 7.67 (s, 1H), 7.60 (s, 2H), 7.23 (s, 2H), 6.31 (s, 1H), 4.05 (s, 4H), 2.11 (s, 2H), 1.05 (d, $J = 5.7$ Hz, 12H). HR-MS for $\text{Pd}_4(\text{L17})_8(\text{BF}_4)_8$: The following picked signals are those at the high intensities. m/z Calcd for $[\text{M}-3(\text{BF}_4^-)]^{3+}$ 2086.8550, found 2086.8529, m/z Calcd for $[\text{M}-4(\text{BF}_4^-)]^{4+}$ 1543.3902, found 1543.3869, m/z Calcd for $[\text{M}-5(\text{BF}_4^-)]^{5+}$ 1217.3313, found 1217.3082, m/z Calcd for $[\text{M}-6(\text{BF}_4^-)]^{6+}$ 1000.2588, found 1000.2558, m/z Calcd for $[\text{M}-7(\text{BF}_4^-)]^{7+}$ 844.7926, found 844.7914, m/z Calcd for $[\text{M}-8(\text{BF}_4^-)]^{8+}$ 728.3180, found 728.3208.

Complex 4.43, $\text{Pd}_4(\text{L18})_8$ 

To a solution of compound **4.30** (ligand **L18**, 4.0 mg, 0.005 mmol, 1.0 Equiv.) and $\text{Pd}(\text{CH}_3\text{CN})_4(\text{BF}_4)_2$ (0.6 mg, 0.0025 mmol, 0.5 Equiv.) in 0.6 mL DMSO or DMF, the mixture was heated at 40°C for 4 hours to give a yellow solution that was characterized by NMR to show formation of complex **4.43** $\text{Pd}_4(\text{L18})_8(\text{BF}_4)_8$. Diethyl ether was added to precipitate the isolated product $\text{Pd}_4(\text{L18})_8(\text{BF}_4)_8$. ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 10.49 (s, 2H), 9.19 (d, J = 24.9 Hz, 4H), 8.03 (s, 12H), 7.56 (s, 4H), 7.15 (s, 2H), 6.29 (s, 1H), 4.04 (s, 4H), 2.64 (s, 3H), 2.14 (d, J = 6.3 Hz, 2H), 1.09 (s, 12H). HR-MS for $\text{Pd}_4(\text{L18})_8(\text{BF}_4)_8$: The following picked signals are those at the high intensities. m/z Calcd for $[\text{M}-3(\text{BF}_4^-)]^{3+}$ 2438.1707, found 2438.2027, m/z Calcd for $[\text{M}-4(\text{BF}_4^-)]^{4+}$ 1806.8767, found 1806.8917, m/z Calcd for $[\text{M}-5(\text{BF}_4^-)]^{5+}$ 1428.3008, found 1428.3101, m/z Calcd for $[\text{M}-6(\text{BF}_4^-)]^{6+}$ 1175.7499, found 1175.7568, m/z Calcd for $[\text{M}-7(\text{BF}_4^-)]^{7+}$ 995.3565, found 995.3624, m/z Calcd for $[\text{M}-8(\text{BF}_4^-)]^{8+}$ 860.0614, found 860.0667.

2.3 Synthesis in chapter 5

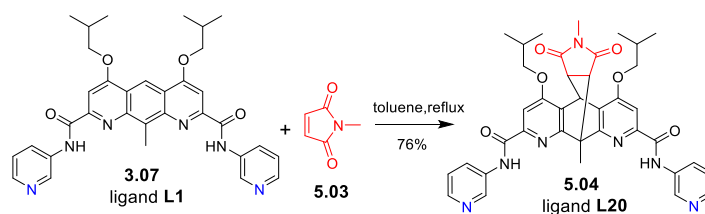
4,6-diisobutoxy-10-methyl-13,15-dioxo-14-phenyl-N2,N8-di(pyridin-3-yl)-5,10-dihydro-5,10-[1,2]epitriazolopyrido[3,2-g]quinoline-2,8-dicarboxamide(**5.02**, ligand **L19**)



To a 25 mL flask was added compound **3.07** (ligand **L1**, 57.8 mg, 0.1 mmol, 1.0 Equiv.) and 4-phenyl-1,2,4-triazoline-3,5-dione **5.01** (26.2 mg, 0.15 mmol, 1.5 Equiv.), and 5 mL dry DCM. The solution was stirred for 12 hours at room temperature in dark, and was concentrated in vacuum. The resulting solid was purified by recrystallization with EtOAc and petroleum ether to yield compound

5.02 (ligand **L13**, 63.2 mg, 0.084 mmol, 84% yield). ^1H NMR (300 MHz, Chloroform-*d*) δ 9.99 (s, 2H), 8.90 (d, J = 2.3 Hz, 2H), 8.46 (d, J = 3.4 Hz, 2H), 8.33 (d, J = 8.4 Hz, 2H), 7.89 (s, 2H), 7.42 – 7.36 (m, 4H), 7.33 (d, J = 8.1 Hz, 3H), 4.14 – 3.97 (m, 4H), 2.93 (s, 3H), 2.35 – 2.21 (m, 2H), 1.14 (d, J = 6.7 Hz, 12H). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 161.60, 160.64, 158.38, 153.87, 149.78, 145.79, 141.48, 134.09, 131.02, 129.09, 126.92, 125.40, 123.82, 122.37, 106.89, 75.79, 68.24, 46.42, 28.08, 18.95, 12.36. HR-MS (ESI) m/z calculated. For $\text{C}_{41}\text{H}_{39}\text{N}_9\text{O}_6$ $[\text{M}+\text{H}]^{1+}$: 754.3096, found 754.3091.

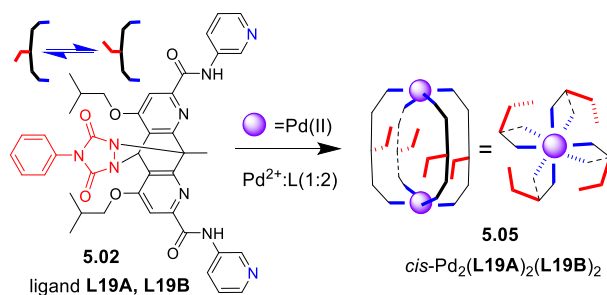
4,6-diisobutoxy-10,13-dimethyl-12,14-dioxo-N2,N8-di(pyridin-3-yl)-5,10-dihydro-5,10-[3,4]epipyrrolopyrido[3,2-g]quinoline-2,8-dicarboxamide(5.04, ligand L20)



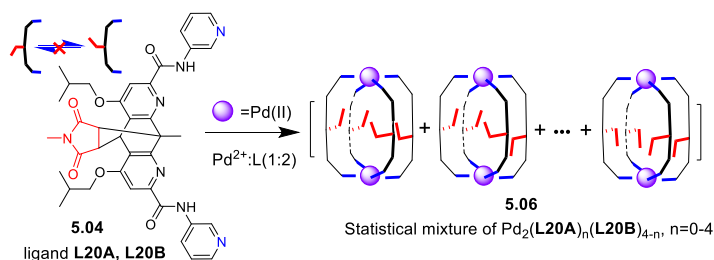
To a 25 mL flask was added compound **3.07** (ligand **L1**, 57.8 mg, 0.1 mmol, 1.0 Equiv.) and N-Methylmaleimide **5.03** (18.7 mg, 0.15 mmol, 1.5 Equiv.), and 10 mL toluene. The solution was refluxed for 12 hours and then was concentrated in vacuum. The crude material was purified by silica gel flash column (v/v, CH_2Cl_2 : MeOH = 10:1) to yield compound **5.04** (ligand **L20**, 52.4 mg, 0.076 mmol, 76% yield). ^1H NMR (300 MHz, Chloroform-*d*) δ 10.11 (s, 1H), 10.05 (s, 1H), 8.86 (d, J = 2.5 Hz, 2H), 8.44 – 8.39 (m, 2H), 8.33 – 8.25 (m, 2H), 7.75 (s, 1H), 7.69 (s, 1H), 7.35 (dt, J = 8.3, 4.1 Hz, 2H), 5.87 (d, J = 3.5 Hz, 1H), 4.09 – 3.85 (m, 4H), 3.39 (dd, J = 8.5, 3.5 Hz, 1H), 3.10 (d, J = 8.5 Hz, 1H), 2.65 (s, 3H), 2.51 (s, 3H), 2.24 (m, 2H), 1.12 (m, 12H). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 174.87, 174.48, 163.55, 162.29, 162.23, 161.64, 161.05, 149.01, 148.49, 145.55, 141.43, 134.26, 126.68, 126.02, 123.75, 105.23,

105.04, 75.28, 75.27, 50.26, 49.39, 47.10, 30.31, 28.14, 24.84, 19.03, 13.13.
HR-MS (ESI) m/z calculated. For $C_{38}H_{39}N_7O_6$ $[M+H]^{1+}$: 690.3035, found 690.3031.

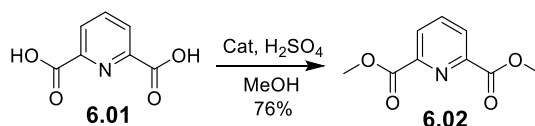
Complex 5.05, $cis\text{-Pd}_2(\text{L19A})_2(\text{L19B})_2$



To a suspension of compound **5.02** (ligand **L19A**, **L19B**, 3.76 mg, 0.005 mmol, 1.0 Equiv.) and $\text{Pd}(\text{CH}_3\text{CN})_4(\text{BF}_4)_2$ (0.6 mg, 0.0025 mmol, 0.5 Equiv.) in 0.6 mL CH_3CN or DMF, the mixture was heated at 40°C for 4 hours, the turbid suspension of ligands gradually turned clear to give a yellow solution that was characterized by NMR to show formation of complex **5.05** $cis\text{-Pd}_2(\text{L19A})_2(\text{L19B})_2(\text{BF}_4)_4$. Diethyl ether was added to precipitate the isolated product $cis\text{-Pd}_2(\text{L19A})_2(\text{L19B})_2(\text{BF}_4)_4$. ^1H NMR (300 MHz, Acetonitrile- d_3) δ 10.10 (s, 2H), 9.28 (d, J = 9.9 Hz, 2H), 8.61 (d, J = 2.2 Hz, 2H), 8.03 (d, J = 5.6 Hz, 2H), 7.83 (s, 2H), 7.54 (dd, J = 8.7, 5.7 Hz, 3H), 7.31 (dd, J = 5.2, 1.8 Hz, 4H), 7.13 – 7.04 (m, 4H), 4.08 (d, J = 6.4 Hz, 4H), 2.90 (s, 3H), 2.13 (d, J = 3.7 Hz, 2H), 1.10 (d, J = 6.7 Hz, 12H). ESI-TOF-MS for $cis\text{-Pd}_2(\text{L19A})_2(\text{L19B})_2(\text{BF}_4)_4$: The following picked signals are those at the high intensities. m/z Calcd for $[\text{M}-2(\text{BF}_4^-)]^{2+}$ 1700.5146, found 1700.5019; Calcd for $[\text{M}-3(\text{BF}_4^-)]^{3+}$ 1104.6749, found 1104.6683; Calcd for $[\text{M}-4(\text{BF}_4^-)]^{4+}$ 806.7551, found 806.7509.

Complex 5.06, Pd₂(L20A)_n(L20B)_{4-n}, n=0-4

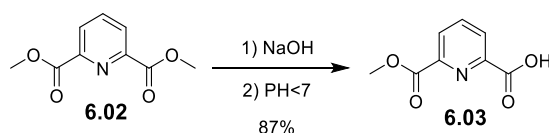
To a suspension of compound **5.04** (ligand **L20A**, **L20B**, 3.44 mg, 0.005 mmol, 1.0 Equiv.) and Pd(CH₃CN)₄(BF₄)₂ (0.6 mg, 0.0025 mmol, 0.5 Equiv.) in 0.6 mL CH₃CN or DMF, the mixture was heated at 40°C for 4 hours, the turbid suspension of ligands gradually turned clear to give a yellow solution. Furthermore, the complicated NMR with MS results showed the formation of the M₂L₄ cage as a statistical mixture of Pd₂(L20A)_n(L20B)_{4-n}, n=0-4. Diethyl ether was added to precipitate the isolated product. ESI-TOF-MS for Pd₂(L20A)_n(L20B)_{4-n}, n=0-4. The following picked signals are those at high intensities. *m/z* Calcd for [M-2(BF₄⁻)]²⁺ 1572.5021, found 1572.4913; Calcd for [M-3(BF₄⁻)]³⁺ 1019.3333, found 1019.3279; Calcd for [M-4(BF₄⁻)]⁴⁺ 742.7489, found 742.7469.

2.4 Synthesis in chapter 6**Dimethyl pyridine-2,6-dicarboxylate (6.02)**

Concentrated sulphuric acid (1 mL) was added dropwise to a solution of pyridine-2,6-dicarboxylic acid **6.01** (1.67 g, 10 mmol, 1.0 Equiv.) in methanol (100 mL). Then, the solution was refluxed for 48 hours and the solvent was removed in a vacuum. 100 mL CH₂Cl₂ was added and the product was washed

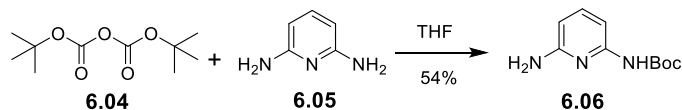
with water and sodium hydroxide aqueous solution. Removal of dichloromethane to yield the compound **6.02** as a white solid (1.48 g, 7.6 mmol, 76% yield). ^1H NMR (300 MHz, Chloroform-*d*) δ 8.33 (d, J = 7.8 Hz, 2H), 8.08 – 8.01 (m, 1H), 4.04 (s, 6H). The characteristic data corresponded with reported literature values.^[6]

6-(methoxycarbonyl)picolinic acid (**6.03**)



Compound **6.02** (3.90 g, 20 mmol, 1.0 Equiv.) was dissolved in 200 mL methanol and sodium hydroxide (800 mg, 20 mmol, 1.0 Equiv.) in a minimal amount of water was added to the above solution. The mixture was stirred at room temperature for 12 hours and then the solvent was removed in a vacuum. The crude product was then dissolved in 200 mL water and extracted with dichloromethane (2×50 mL) to remove any starting material. The aqueous layer was acidified with 1M HCl aqueous solution to pH=~5 and extracted with ethyl acetate (5 ×100 mL). Removal of the solvent in vacuum to yield the pure compound **6.03** as a white solid (3.17 g, 17.5 mmol, 87% yield). ^1H NMR (300 MHz, Chloroform-*d*) δ 8.43 (dd, J = 7.7, 1.1 Hz, 1H), 8.37 (dd, J = 7.8, 1.1 Hz, 1H), 8.13 (t, J = 7.8 Hz, 1H), 4.04 (s, 3H). The characteristic data corresponded with reported literature values.^[6]

Tert-butyl (6-aminopyridin-2-yl)carbamate (**6.06**)

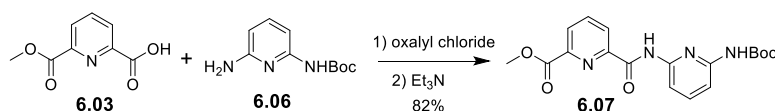


Di-tert-butylcarbonate **6.04** (10.0 g, 45.8 mmol, 1.0 Equiv.) was added to a

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solution of 2,6-diaminopyridine **6.05** (5.0 g, 45.8 mmol, 1.0 Equiv.) in 150 mL THF. The resulting solution was stirred at 60 °C overnight. After removing the solvent under vacuum, the crude product was purified by flash column chromatography to give compound **6.06** as a white solid (9.8 g, 45.8 mmol, 54% yield). ¹H NMR (300 MHz, Chloroform-*d*) δ 7.45-7.40 (m, 1H), 7.24-7.23(d, J=8.1Hz, 1H), 7.17(s, 1H), 6.18-6.16(d, J=8.4 Hz, 1H), 4.35 (s, 2H), 1.51 (s, 9H). The characteristic data corresponded with reported literature values.^[7]

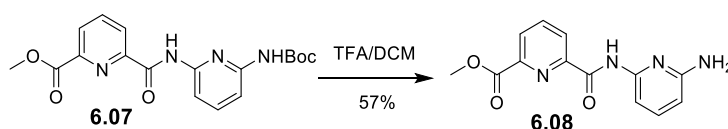
Methyl 6-((6-((tert-butoxycarbonyl)amino)pyridin-2-yl)carbamoyl)picolinate(**6.07**)



In a dry round-bottomed flask was placed 6-(methoxycarbonyl)picolinic acid **6.03** (1 g, 5.52 mmol, 1 Equiv.) in freshly distilled CHCl₃ (3.5 mL). Oxalyl chloride (3.5 mL, 7.5 Equiv.) and a catalytic amount of DMF (1 drop) were added to the above solution. The reaction mixture was stirred under an inert atmosphere at room temperature for 3 hours. The solvent/acid mixture was evaporated to dryness by means of a high vacuum pump. Methyl 6-(chlorocarbonyl)picolinate was obtained as a white solid in quantitative yield. In a dry round-bottomed flask, tert-butyl 6-aminopyridin-2-ylcarbamate **6.06** (1.27 g, 6.07 mmol, 1.1 Equiv.) and *N,N*-diisopropylethylamine (2.9 mL, 16.6 mmol, 3 Equiv.) were dissolved in freshly distilled CHCl₃ (11.5 mL). The flask was hermetically closed and remained under protecting gas during the reaction. In a second dry flask, acid chloride was dissolved in freshly distilled CHCl₃ (11.5 mL) under an inert atmosphere and added dropwise to the amine solution. The reaction mixture was stirred overnight at room temperature. The solution was then washed with a saturated NH₄Cl aqueous solution (3 x 30 mL) and the organic layer was dried over Na₂SO₄, filtered and rotary evaporated to afford a brown solid. The crude residue was purified by flash column chromatography (100% DCM to DCM/EtOAc 95:5, v/v) to give compound **6.07** as a white solid (1.95 g, 5.24 mmol, 95% yield). ¹H NMR (500

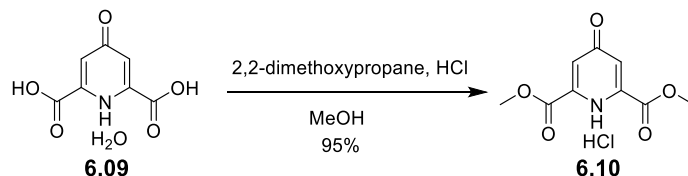
MHz, Chloroform-*d*) δ 10.23 (s, 1H), 8.47 (dd, J = 7.8, 1.1 Hz, 1H), 8.29 (d, J = 7.8, 1H), 8.07 (t, J = 7.8 Hz, 1H), 8.03 (dd, J = 7.7, 1.0 Hz, 1H), 7.77 – 7.69 (m, 2H), 7.14 (s, 1H), 4.06 (s, 3H), 1.53 (s, 9H). The characteristic data corresponded with reported literature values.^[8]

Methyl 6-((6-aminopyridin-2-yl)carbamoyl)picolinate(**6.08**)



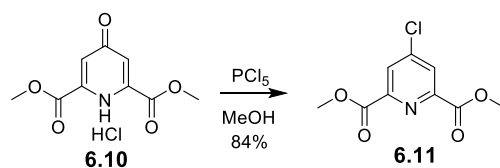
Compound **6.07** (744 mg, 2 mmol, 1.0 Equiv.) was dissolved in a 10mL mixture of DCM and TFA (v/v, 1:1) and the solution was stirred for 2 hours at room temperature, then the solvents were removed by rotary evaporation. The crude material was slurried in DCM and washed with NaHCO₃ aqueous solution. The organic phase was then washed with water and brine and then dried over Na₂SO₄. The solution was filtered and the solvent was removed by rotary evaporation to give compound **6.08** as a grey powder (310 mg, 1.4 mmol, 56.9% yield). ¹H NMR (300 MHz, Chloroform-*d*) δ 10.17 (s, 1H), 8.47 (d, J = 8.9 Hz, 1H), 8.28 (d, J = 8.8 Hz, 1H), 8.06 (t, J = 7.8 Hz, 1H), 7.74 (d, J = 7.7 Hz, 1H), 7.53 (t, J = 7.9 Hz, 1H), 6.35 (d, J = 7.9 Hz, 1H), 4.70 (s, 2H), 4.06 (s, 3H). ¹³C NMR (75 MHz, Chloroform-*d*) δ 164.91, 161.47, 157.60, 149.58, 146.74, 140.07, 138.78, 127.64, 125.55, 110.31, 104.86, 103.48, 53.00. HR-MS (ESI) m/z calculated. For C₁₃H₁₂N₄O₃ [M+H]¹⁺: 273.0982, found 273.0981.

Dimethyl 4-oxo-1,4-dihydropyridine-2,6-dicarboxylate, hydrogen chloride(6.10)



A suspension of chelidamic acid mono hydrate **6.09** (2 g, 9.94 mmol, 1.0 Equiv.) in MeOH (50 mL) was placed in a round-bottomed flask. To this, were added 2,2-dimethoxypropane (14.7 mL, 119 mmol) and concentrated HCl (1.5 mL, 17.9 mmol). The reaction mixture was refluxed for 4 hours under a CaCl₂ tube and then at room temperature overnight. After removing the solvent, the solid was triturated with Et₂O (30 mL x3), and the solution was separated from the solid by decantation. After drying the solid under vacuum, dimethyl chelidamate hydrochloride **6.10** was obtained as a white solid (2.35, 9.44 mmol, 95% yield). ¹H NMR (300 MHz, Chloroform-*d*) δ 7.38 (s, 2H), 4.02 (s, 6H). The characteristic data corresponded with reported literature values.^[9]

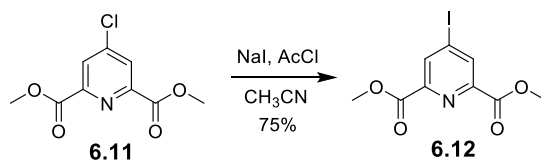
Dimethyl 4-chloropyridine-2,6-dicarboxylate(6.11)



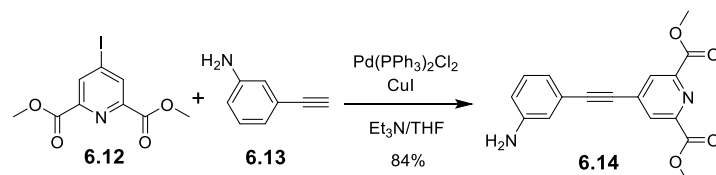
A mixture of 4-hydroxypyridine-2,6-dicarboxylic acid **6.10** (5 g, 24.9 mmol, 1.0 Equiv.) and PCl₅ (31.1 g, 149 mmol, 6.0 Equiv.) in CCl₄ (25 mL) was heated under reflux for one night. Then dry methanol (25 mL) was added dropwise over 40 min, and the resulting mixture was heated under reflux for 1 h. The solvent was evaporated to afford a yellow solid, which was dissolved in water (40 mL) and neutralized with Na₂CO₃ (80 mL). The resulting solid was

collected by filtration, washed with water and dissolved in CHCl_3 (120 mL). The organic solution was washed with saturated Na_2CO_3 aqueous solution (2x80 mL), brine (1x80 mL), and dried over Na_2SO_4 . Removing the solvent under reduced pressure and recrystallization of the residue from methanol gave compound **6.11** as a white crystal (4.84 g, 20.9 mmol, 84%). ^1H NMR (300 MHz, Chloroform-*d*) δ 8.31 (s, 2H), 4.04 (s, 6H). The characteristic data corresponded with reported literature values.^[10]

Dimethyl 4-iodopyridine-2,6-dicarboxylate(**6.12**)

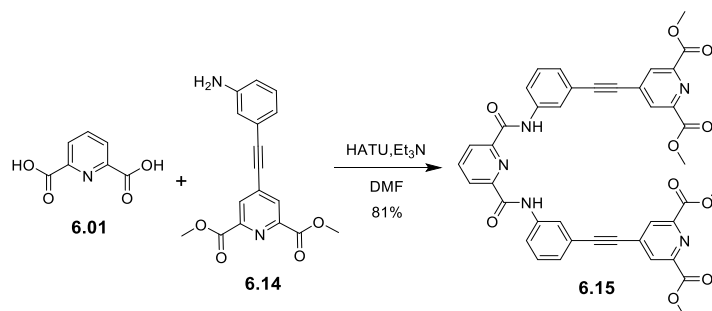


Acetyl chloride (2.05 g, 26.13 mmol, 1.9 mL, 3.0 Equiv.) was added to a mixture of dimethyl 4-chloropyridine-2,6-dicarboxylate **6.11** (2.00 g, 8.71 mmol, 1.0 Equiv.) and NaI (3.92 g, 26.13 mmol, 3.0 Equiv.) in dry CH_3CN (60 mL) at 0°C . The reaction mixture was sonicated for 4 hours under an argon atmosphere maintaining the bath temperature below 50°C . Then the reaction mixture was stirred at room temperature overnight. After cooling to 0°C saturated aqueous Na_2CO_3 (30 mL) and CH_2Cl_2 (100 mL) were added. The organic layer was washed with saturated aqueous $\text{Na}_2\text{S}_2\text{O}_3$ (1x100 mL), water (2x100 mL), and dried over Na_2SO_4 . Removing the solvent under reduced pressure and recrystallization of the residue from methanol gave compound **6.12** as a white solid (2.1 g, 6.53 mmol, 75% yield). ^1H NMR (300 MHz, Chloroform-*d*) δ 8.67 (s, 2H), 4.03 (s, 6H). The characteristic data corresponded with reported literature values.^[10]

Dimethyl 4-((3-aminophenyl)ethynyl)pyridine-2,6-dicarboxylate (**6.14**)

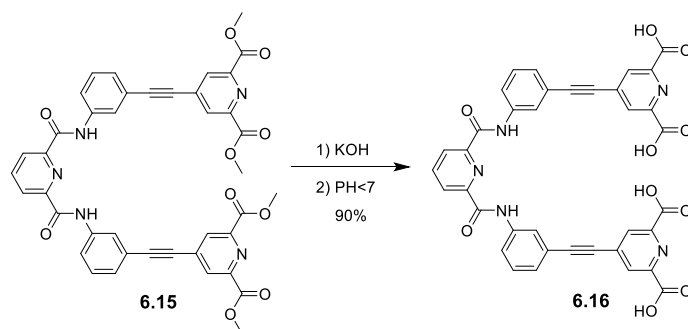
In a 50 mL flask, dimethyl-4-iodopyridine-2,6-dicarboxylate **6.12** (321 mg, 1 mmol, 1 Equiv.) was dissolved in a 30 mL mixture of THF and triethylamine (v/v, 1:1). The solution was thoroughly degassed by argon bubbling for 20 min and an 3-ethynylaniline **6.13** (140 mg, 1.2 mmol, 1.2 Equiv.), copper iodide (0.2 mmol, 38 mg, 0.2 Equiv.), and Pd(PPh₃)₂Cl₂ (69 mg, 0.1 mmol, 0.1 Equiv.) were added. The reaction was stirred at 40 °C for 12 h. The solution was evaporated under a vacuum, and the crude was purified by column chromatography on silica(ethyl acetate/petroleum ether, v/v=1:1) to yellow solid (260 mg, 0.84 mmol, 83.7%). ¹H NMR (300 MHz, Chloroform-*d*) δ 8.35 (s, 2H), 7.18 (t, *J* = 7.9 Hz, 1H), 6.98 (dt, *J* = 7.6, 1.1 Hz, 1H), 6.90 – 6.87 (m, 1H), 6.75 (m, 1H), 4.04 (s, 6H), 3.77 (s, 2H). ¹³C NMR (75 MHz, Chloroform-*d*) δ 164.78, 148.44, 146.49, 134.65, 129.66, 122.46, 122.04, 117.96, 116.76, 97.36, 84.76, 53.29. HR-MS (ESI) *m/z* calculated. For C₁₇H₁₄N₂O₄ [M+H]¹⁺: 311.1026, found 311.1026, [M+Na]¹⁺: 333.0846, found 333.0844, [M+K]¹⁺: 349.0585, found 349.0585.

Tetramethyl 4,4'-((((pyridine-2,6-dicarbonyl)bis(azanediyl))bis(3,1-phenylene))bis(ethyne-2,1-diyl))bis(pyridine-2,6-dicarboxylate) (6.15)



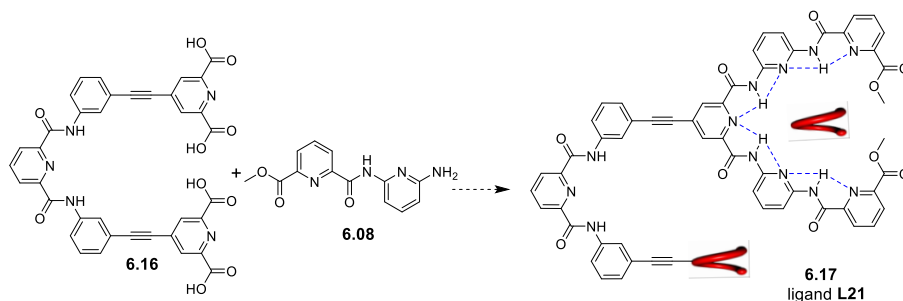
A solution of compound **6.01** (50.1 mg, 0.3 mmol, 1.0 Equiv.) and HATU (342 mg, 0.9 mmol, 3.0 Equiv.) in DMF (20 mL) were stirred 0.5h at 0°C under argon, then compound **6.14** (223.2 mg, 0.72 mmol, 2.4 Equiv.) and Et₃N (121 mg, 1.2 mmol, 4 Equiv.) were added, the reaction mixture was allowed to stir for 24 hours at room temperature in the dark. The DMF in the reaction mixture was removed under reduced pressure, the result of oily substances was then diluted with H₂O (100 mL), and lead to fine powder was progressively precipitated out. Then the solid was collected by filtration and the desired crude compound was isolated, and the crude material was purified by silica gel flash column (v/v, CH₂Cl₂:MeOH = 10:1) to give compound **6.15** as a yellow powder (180.2 mg, 0.24 mmol, 81.0% yield). ¹H NMR (300 MHz, Chloroform-*d*) δ 9.61 (s, 2H), 8.55 (d, *J* = 7.8 Hz, 2H), 8.35 (s, 4H), 8.24 – 8.17 (m, 1H), 8.14 – 8.11 (m, 2H), 7.77 (dt, *J* = 7.8, 1.6 Hz, 2H), 7.50 – 7.39 (m, 4H), 4.03 (s, 12H). HR-MS (ESI) *m/z* calculated. For C₄₁H₂₉N₅O₁₀ [M+H]¹⁺: 752.1987, found 752.1985, [M+Na]¹⁺: 774.1807, found 774.1804.

4,4'-((((pyridine-2,6-dicarbonyl)bis(azanediy))bis(3,1-phenylene))bis(ethyne-2,1-diyl))bis(pyridine-2,6-dicarboxylic acid) (6.16)

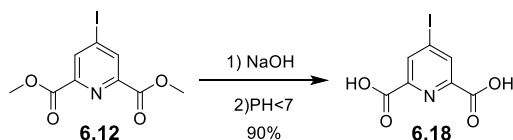


Compound **6.15** (112 mg, 0.15 mmol, 1.0 Equiv.) was placed in a 100 mL round-bottomed flask and dissolved in 50 mL of DCM: MeOH (1:1). KOH (168 mg, 3.0 mmol, 20 Equiv.) dissolved in MeOH (10 mL) was slowly added to this mixture. The reaction was then refluxed at 60°C for 24 h, 50 mL of water was added after the solvent was removed on the rotavap. The solution was acidified to ~pH 3 with 1M HCl aqueous solution leading to a yellow precipitate suspended in water. The yellow solid is collected by filtration and washed with H₂O. After partially drying on the filter, the solid was suspended in toluene and azeotroped three times with toluene. Afterward, the yellow solid was dried overnight under vacuum in a desiccator with P₂O₅ to give compound **6.16** as a light yellow solid (93.8 mg, 0.135 mmol, 90% yield). ¹H NMR (300 MHz, DMSO-*d*₆) δ 11.16 (s, 2H), 8.48 – 8.44 (m, 2H), 8.39 – 8.35 (m, 1H), 8.31 (s, 2H), 8.26 (s, 4H), 8.04 (d, *J* = 8.0 Hz, 2H), 7.57 (dt, *J* = 15.0, 7.7 Hz, 4H).

Compound 6.17, ligand L21

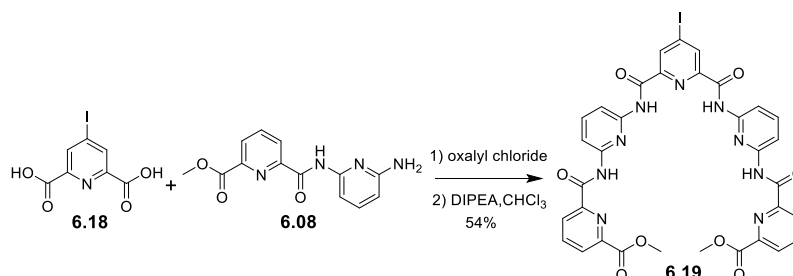


A solution of compound **6.16** (34.7 mg, 0.05 mmol, 1.0 Equiv.) and HATU (114 mg, 0.3 mmol, 6.0 Equiv.) in DMF (20 mL) were stirred 0.5h at 0°C under argon, then compound **6.08** (223.2 mg, 0.24 mmol, 4.8 Equiv.) and Et₃N (40 mg, 8 mmol, 8 Equiv.) was added, the reaction mixture was allowed to stir for 24 hours at room temperature in the dark. The DMF in the reaction mixture was removed under reduced pressure, the result of oily substances was then diluted with H₂O (100 mL), and the fine powder was progressively precipitated out. Then the solid was collected by filtration and the desired crude compound was isolated. However, the crude product was found to be insoluble in common organic solvents, thus limited for purification and characterization. Some other amide condensation methods (cat, PyBOP, acid chloride, etc.) were also tried that found to form similar insoluble products. Thus, this product is not the starting material but was limited by characterization to confirm its target product **6.17**. Moreover, for self-assembly, a ligand is expected to be dissolved at least in common organic solvents. We optimized the design and synthesis of new ligands next.

4-iodopyridine-2,6-dicarboxylic acid(6.18)

Dimethyl 4-iodopyridine-2,6-dicarboxylate **6.12** (1.5 g, 4.67 mmol, 1.0 Equiv.) was dissolved in 200 mL MeOH and sodium hydroxide (560 mg, 14.01 mmol, 3.0 Equiv.) in a minimal amount of water was added to the above solution. The resulting solution was stirred at room temperature for 24 hours and then the solvent was removed in a vacuum. The crude product was then dissolved in 100 mL water and extracted with 30 mL dichloromethane to remove any starting material. The aqueous layer was acidified with 1M HCl aqueous solution to pH $\approx$ 5. The resulting precipitate was filtered off, washed with water (3 x 20 mL), and dried under vacuum. The compound **6.18** was obtained as a white solid (1.23 g, 4.20 mmol, 90% yield). ^1H NMR (300 MHz, DMSO- d_6) δ 8.51 (s, 2H;), 13.57 (br). The characteristic data corresponded with reported literature values.^[10]

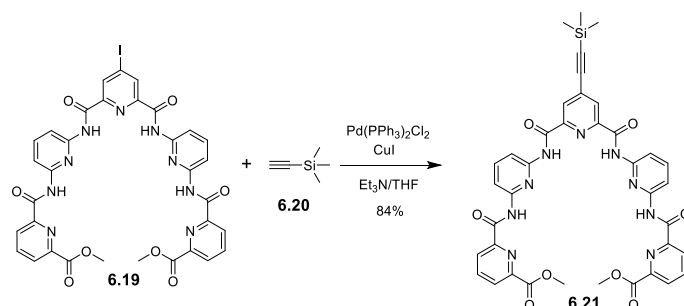
Dimethyl 6,6'-((((4-iodopyridine-2,6-dicarbonyl)bis(azanediyl))bis(pyridine-6,2-diyl))bis(azanediyl))bis(carbonyl)dipicolinate(6.19)



In a dry round-bottomed flask was placed 4-iodopyridine-2,6-dicarboxylic acid **6.18** (0.360 g, 1.228 mmol, 1.0 Equiv.) in freshly distilled CHCl_3 (15 mL). To this were added oxalyl chloride (0.42 mL, 4.0 Equiv.) and a catalytic amount

of DMF (1 drop). The reaction mixture was stirred under an inert atmosphere at room temperature for 3 hours. The solvent/acid mixture was evaporated to dryness using a high vacuum pump. 4-iodopyridine-2,6-dicarbonyl dichloride was obtained as a solid in quantitative yield and directly used in the next step. In a dry round-bottomed flask, compound **6.08** (0.702 g, 2.58 mmol, 2.1 eq.) and *N,N*-diisopropylethylamine (1.3 mL, 7.37 mmol, 6 Equiv.) were dissolved in freshly distilled CHCl_3 (8 mL). The flask was hermetically closed and remained under protecting gas during the reaction. In a second dry flask, the acid chloride was dissolved in freshly distilled CHCl_3 (10 mL) under inert atmosphere and added dropwise to the amine solution. The reaction mixture was stirred overnight at room temperature. The formed precipitate was filtered and recrystallized in MeOH to afford compound **6.19** as a white solid (530 mg, 0.66 mmol, 54% yield). ^1H NMR (300 MHz, Chloroform-*d*) δ 10.72 (s, 2H), 10.47 (s, 2H), 8.77 (s, 2H), 8.34 (dd, J = 6.3, 2.7 Hz, 2H), 8.14 (dd, J = 8.1, 4.3 Hz, 4H), 7.90 – 7.84 (m, 6H), 3.66 (s, 6H). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 163.93, 161.43, 160.39, 157.08, 149.37, 148.58, 145.92, 140.87, 138.46, 134.76, 129.82, 127.36, 125.49, 110.56, 110.30, 52.85. HR-MS (ESI) m/z calculated. For $\text{C}_{33}\text{H}_{24}\text{IN}_9\text{O}_8$ $[\text{M}+\text{H}]^{1+}$: 802.0865, found 802.0865, $[\text{M}+\text{Na}]^{1+}$: 824.0685, found 824.0682.

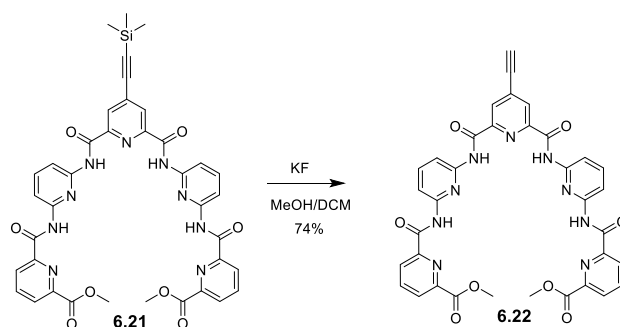
Dimethyl 6,6'-((((4-((trimethylsilyl)ethynyl)pyridine-2,6-dicarbonyl))bis(azanediyl))bis(pyridine-6,2-diyl))bis(azanediyl))bis(carbonyl))dipicolinate(6.21)



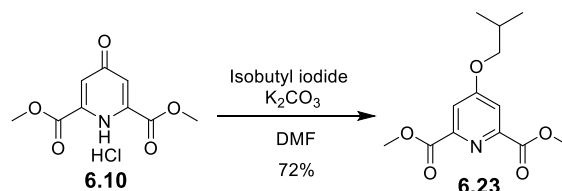
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In a 100 mL flask, compound **6.19** (400.5 mg, 0.5 mmol, 1 Equiv.) was dissolved in a mixture a 50 mL THF and triethylamine (v/v,1:2). The solution was thoroughly degassed by argon bubbling for 20 min and copper iodide (19 mg, 0.1 mmol, 0.2 Equiv.), and Pd(PPh₃)₂Cl₂ (35 mg, 0.05 mmol, 0.1 Equiv.) were added following the addition of trimethylsilylacetylene **6.20** (392 mg, 4 mmol, 8 Equiv.). The reaction was stirred at 40 °C for 24 h. The solution was evaporated under a vacuum, and the crude product was purified by silica gel flash column (v/v, CH₂Cl₂:MeOH = 10:1) to give as compound **6.21** a white powder(323 mg, 0.42 mmol, 84% yield) ¹H NMR (300 MHz, Chloroform-*d*) δ 10.78 (s, 2H), 10.53 (s, 2H), 8.43 (s, 2H), 8.32 (dd, *J* = 6.1, 2.9 Hz, 2H), 8.15 – 8.08 (m, 4H), 7.87 – 7.80 (m, 6H), 3.64 (s, 6H), 0.33 (s, 9H).

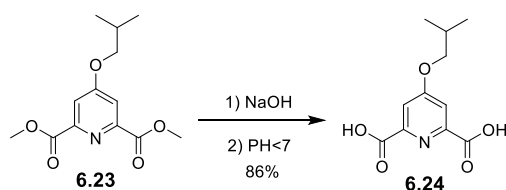
Dimethyl 6,6'-((((4-ethynylpyridine-2,6-dicarbonyl)bis(azanediyl))bis(pyridine-6,2-diyl))bis(azanediyl))bis(carbonyl))dipicolinate(6.22)



To a solution of compound **6.21** (385.5 mg, 0.5 mmol, 1.0 Equiv.) in MeOH/CH₂Cl₂ (v/v = 1:5) was added potassium fluoride (87.15 mg, 1.5 mmol, 3.0 Equiv.), the mixture was stirred at room temperature for 4 h. The solution was evaporated under a vacuum and the crude product was purified by silica gel flash column (v/v, CH₂Cl₂: MeOH = 20:1) to give compound **6.22** as a white powder (258 mg, 0.37 mmol, 74% yield). ¹H NMR (300 MHz, Chloroform-*d*) δ 10.61 (s, 2H), 10.44 (s, 2H), 8.49 (s, 2H), 8.35 (dd, *J* = 6.5, 2.5 Hz, 2H), 8.18 (dd, *J* = 7.7, 4.3 Hz, 4H), 7.91 – 7.84 (m, 6H), 3.67 (s, 6H), 3.55 (s, 1H).

Dimethyl 4-isobutoxypyridine-2,6-dicarboxylate(**6.23**)

Dimethyl-4-oxo-1,4-dihydropyridine-2,6-dicarboxylate **6.10** (2.11 g, 10 mmol, 1.0 Equiv.) and potassium carbonate (4.14 mg, 5.0 mmol, 3.0 Equiv.) were dissolved in 50 mL of anhydrous DMF and heated and stirred at 120 °C for 1.5 h. After, the system was cooled down to 70 °C, followed by adding Isobutyl iodide (2.76g, 3.75 mmol, 1.5 Equiv.) and stirred for another 3 hours. The solution was cooled down to room temperature. 50 mL of water were added, and the mixture was extracted with toluene(3 x 50 mL). The combined organic phase was dried with sodium sulfonate and evaporated under a vacuum to obtain compound **6.23** as a white solid (1.92 g, 7.2 mmol, 72% yield). 1H NMR (300 MHz, Chloroform-*d*) δ 7.81 (s, 2H), 4.01 (s, 6H), 3.90 (d, J = 6.5 Hz, 2H), 2.16 (dp, J = 13.3, 6.6 Hz, 1H), 1.06 (d, J = 6.7 Hz, 6H). The characteristic data corresponded with reported literature values.^[11]

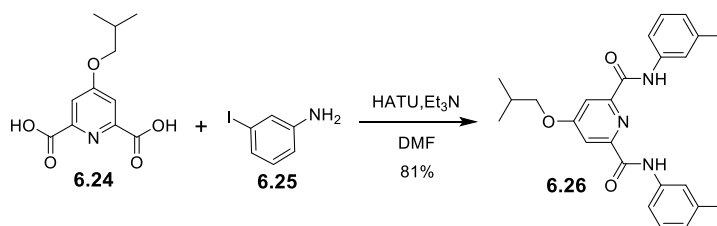
4-isobutoxypyridine-2,6-dicarboxylic acid(**6.24**)

Compound **6.23** (1.33 g, 5 mmol, 1.0 Equiv.) was dissolved in 200 mL MeOH and sodium hydroxide (600 mg, 15 mmol, 3.0 Equiv.) in a minimal amount of water was added to the above solution. The resulting solution was stirred at room temperature for 24 hours and then the solvent was removed in a vacuum.

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The crude product was then dissolved in 100 mL water and extracted with 30 mL dichloromethane to remove any starting material. The aqueous layer was acidified with 1M HCl aqueous solution to pH $\approx$ 5. The resulting precipitate was filtered off, washed with water (3 x 20 mL), and dried under vacuum. The compound **6.24** was obtained as a white solid (1.03 g, 4.3 mmol, 86% yield). ^1H NMR (300 MHz, Chloroform-*d*) δ 7.92 (s, 2H), 3.98 (d, J = 6.5 Hz, 2H), 2.19 (dp, J = 13.2, 6.4 Hz, 1H), 1.07 (d, J = 6.7 Hz, 6H). The characteristic data corresponded with reported literature values.^[11]

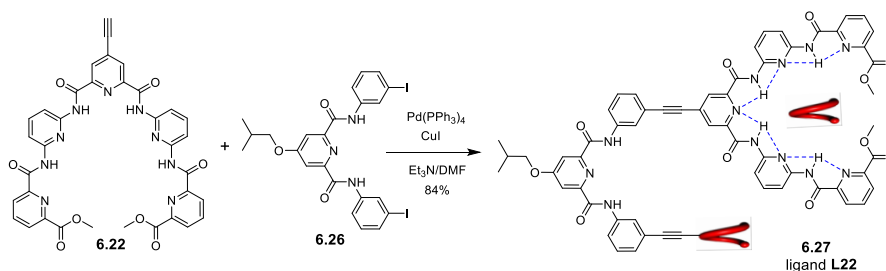
N2,N6-bis(3-iodophenyl)-4-isobutoxypyridine-2,6-dicarboxamide (**6.26**)



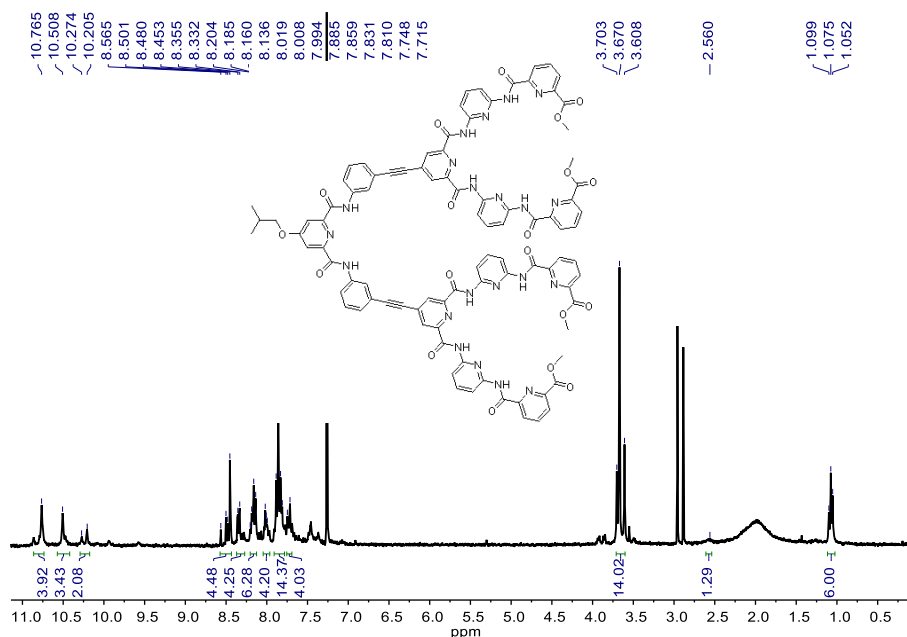
A solution of compound **6.24** (239.2 mg, 1 mmol, 1.0 Equiv.) and HATU (1.14 g, 3 mmol, 3.0 Equiv.) in DMF (30 mL) were stirred 0.5h at 0°C under argon, then compound **6.25** (525 mg, 2.4 mmol, 2.4 Equiv.) and Et₃N (404 mg, 4 mmol, 4 Equiv.) was added, the reaction mixture was allowed to stir for 24 hours at room temperature in dark. The DMF in the reaction mixture was removed under reduced pressure, the result of oily substances was then diluted with H₂O (100 mL), and the fine powder was progressively precipitated out. Then the solid was collected by filtration and the desired crude compound was isolated, and the crude material was purified by silica gel flash column (v/v, CH₂Cl₂:MeOH = 10:1) to give compound **6.26** as a white powder (518.4 mg, 0.81 mmol, 81.0% yield). ^1H NMR (300 MHz, Chloroform-*d*) δ 9.47 (s, 2H), 8.16 (t, J = 1.8 Hz, 2H), 7.93 (s, 2H), 7.72 (ddd, J = 8.2, 2.1, 0.8 Hz, 2H), 7.53 (ddd, J = 7.9, 1.5, 0.9 Hz, 2H), 7.13 (t, J = 8.0 Hz, 2H), 3.95 (d, J = 6.5 Hz, 2H), 2.18 (dp, J = 13.3, 6.7 Hz, 1H), 1.07 (d, J = 6.7 Hz, 6H). ^{13}C NMR (75

MHz, Chloroform-*d*) δ 161.26, 150.59, 138.24, 134.01, 130.65, 128.96, 119.51, 112.15, 94.32, 75.48, 28.01, 19.05. HR-MS (ESI) m/z calculated. For $C_{23}H_{21}I_2N_3O_3$ $[M+H]^+$: 641.9745, found 641.9745.

Compound 6.27, ligand L22

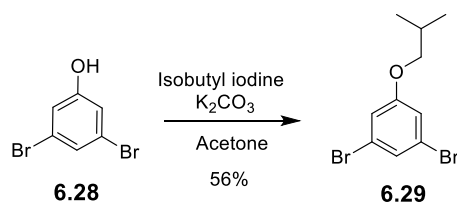


In a 25 mL flask, compound **6.26** (64 mg, 0.1 mmol, 1 Equiv.) was dissolved in 10 mL DMF. The solution was thoroughly degassed by argon bubbling for 20 min and compound **6.22** (167 mg, 0.24 mmol, 2.4 Equiv.), copper iodide (3.8 mg, 0.02 mmol, 0.2 Equiv.), Et₃N (40.4 mg, 0.4 mmol, 4 Equiv.) and Pd(PPh₃)₄ (11.55 mg, 0.01 mmol, 0.1 Equiv.) were added. The reaction was stirred at 70 °C for 24 h. The solution was evaporated under a vacuum, and the crude was purified by column chromatography on silica(DCM/MeOH, v/v=20:1) to yield compound **6.27** as a yellow solid (ligand **L22**, 149.9 mg, 0.084 mmol, 84% yield). HR-MS (ESI) m/z calculated. For $C_{93}H_{69}O_{19}N_{21}$ $[M+H]^+$: 1785.5181, found 1785.5194, $[M+Na]^+$: 1806.4971, found 1806.4954. Another set of HR-MS (ESI) m/z calculated. For dimer $[C_{93}H_{69}O_{19}N_{21}]_2$ $[M+2H]^{2+}$: 1785.0166, found 1785.0162. ¹H NMR (300 MHz, Chloroform-*d*), as characterized by mass spectrometry, is a mixture of monomers and dimers and may contain by-products. We are currently unable to separate and purify, so clean NMR is impossible. Crude NMR shows the characteristic peaks of the product and preliminary analysis found that the integration was close to the theoretical value. Refer to the attached ¹H NMR spectrum for details.



^1H NMR spectrum of Compound 6.27 (ligand L22) in CDCl_3

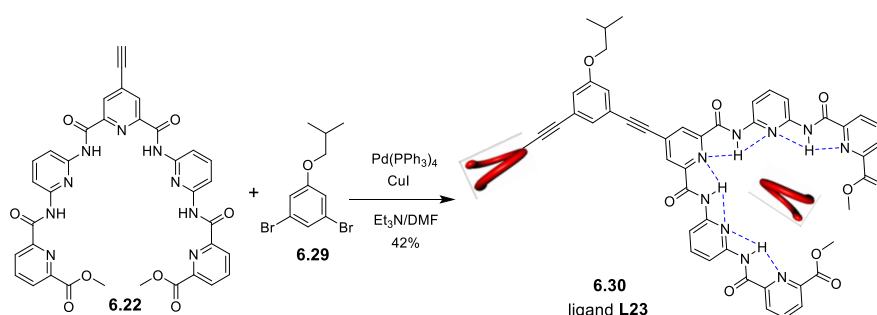
1,3-dibromo-5-isobutoxybenzene (6.29)



3,5-dibromophenol **6.28** (1.25 g, 5 mmol, 1.0 Equiv.) was dissolved in 50 mL acetone. To the solution, 1-iodo-2-methylpropane (1.38 g, 7.5 mmol, 1.5 Equiv.) and K_2CO_3 (1.38 g, 10 mmol, 2.0 Equiv.) were added. The suspension mixture was stirred at 85°C for 24 hours. The solution was concentrated in a vacuum, then poured into water, extracted with dichloromethane. The dichloromethane was dried over sodium sulfate and concentrated in a vacuum to yield a crude product. The residue was purified on silica gel flash column chromatography (petroleum ether) to give the product **6.29** (862 mg, 2.8 mmol 56 % yield) as

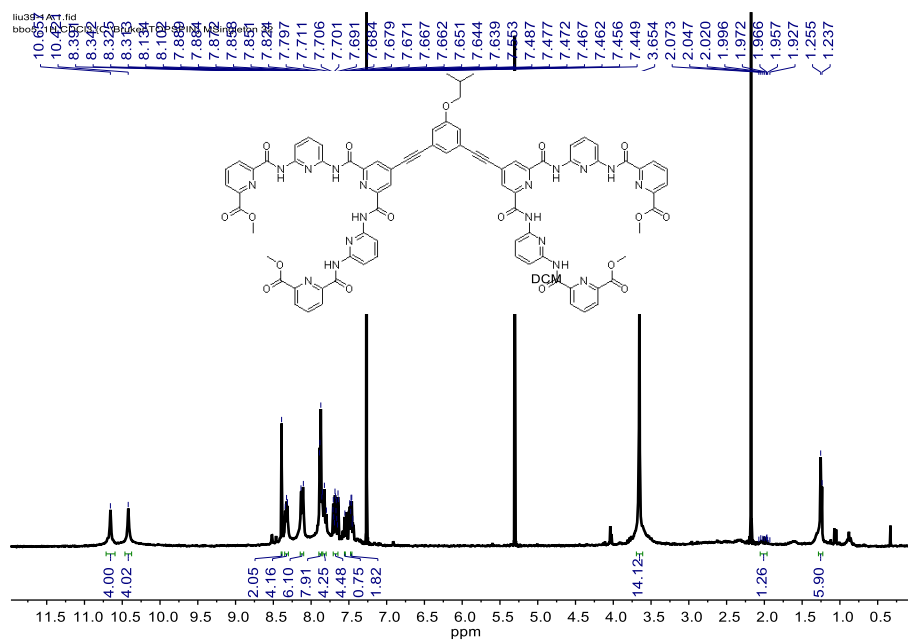
a colorless oil. ^1H NMR (300 MHz, Chloroform-*d*) δ 7.23 (t, J = 1.6 Hz, 1H), 6.99 (d, J = 1.6 Hz, 2H), 3.68 (d, J = 6.5 Hz, 2H), 2.06 (dp, J = 13.3, 6.7 Hz, 1H), 1.01 (d, J = 6.7 Hz, 6H). The characteristic data corresponded with reported literature values.^[12]

Compound 6.30, ligand L23



In a 25 mL flask, compound **6.29** (30.8 mg, 0.1 mmol, 1 Equiv.) was dissolved in 10 mL DMF. The solution was thoroughly degassed by argon bubbling for 20 min and compound **6.22** (167 mg, 0.24 mmol, 2.4 Equiv.), copper iodide (3.8 mg, 0.02 mmol, 0.2 Equiv.), Et_3N (40.4 mg, 0.4 mmol, 4 Equiv.) and $\text{Pd}(\text{PPh}_3)_4$ (11.55 mg, 0.01 mmol, 0.1 Equiv.) were added. The reaction was stirred at 70 °C for 24 h. The solution was evaporated under a vacuum, and the crude was purified by column chromatography on silica (DCM/MeOH, v/v=20:1) to yellow solid (64.8 mg, 0.042 mmol, 42% yield). ^1H NMR (300 MHz, Chloroform-*d*) δ 10.66 (s, 4H), 10.42 (s, 4H), 8.39 (s, 2H), 8.35 – 8.30 (m, 4H), 8.12 (d, J = 9.5 Hz, 6H), 7.90 – 7.86 (m, 8H), 7.82 (s, 4H), 7.71 – 7.64 (m, 4H), 7.55 (s, 1H), 7.47 (m, 2H), 3.65 (s, 14H), 2.06 – 1.96 (m, 1H), 1.25 (d, J = 5.4 Hz, 6H). Of note, Signals are overlapped in 7.4-8.8 ppm, the integration for each peaks may be inaccurate. Refer to the attached ^1H NMR spectrum for details.

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¹H NMR spectrum of Compound 6.30 (ligand L23) in CDCl₃

3. X-ray crystallography

The X-ray diffraction studies for compound **3.07** (ligands **L1**), compound **3.09** (ligand **L2**), complex **3.12** Pd₂(**L1**)₄, complex **4.35** Pd₄(**L10**)₁₀ and complex **5.05** Pd₂(**L19**)₄ were carried out at a MAR345 image plate using Mo-K α radiation generated by a Rigaku UltraX 18S rotating anode (Xenocs Fox3d mirrors) at UCLouvain. Prior to data collection, the crystals were flash-frozen to 150 K. Data integration and reduction was performed by CrysAlisPRO^[13] and the implemented absorption correction was applied. The structures were solved by SHELXT^[14] and refined against F^2 by SHELXL-2014/7.^[15] All non-hydrogen bonds were refined anisotropically, hydrogen atoms were added in calculated positions and refined in riding mode, with temperature factors 1.2 times higher than their parent atoms. Crystal data and structure refinement details are shown in Table **6.01**, Table **6.03** and Table **6.04**. The X-ray diffraction studies for complex **4.31** Pd₂(**L6**)₄, complex **4.32** Pd₄(**L7**)₁₀ and complex **4.33** Pd₄(**L8**)₁₀ were carried out on a Rigaku FRX rotating anode (2.9 kW) diffractometer at the IECB x-ray facility. Cu-K α radiation monochromated with high flux Osmic Varimax mirrors were used for data collection. The x-ray source is equipped with a Dectris Pilatus 200K detector and partial chi goniometer. All crystals were kept at 130 K during data collection. The Rigaku CrystalClear suite^[16] was used to index and integrate data with a multi-scan absorption correction. Structures were solved with the ShelXT^[14] structure solution program using Intrinsic Phasing, while structures were solved by direct methods with SIR2014.^[17] With Olex2,^[18] the structures were refined with the ShelXL^[14] refinement package using Least Squares minimization

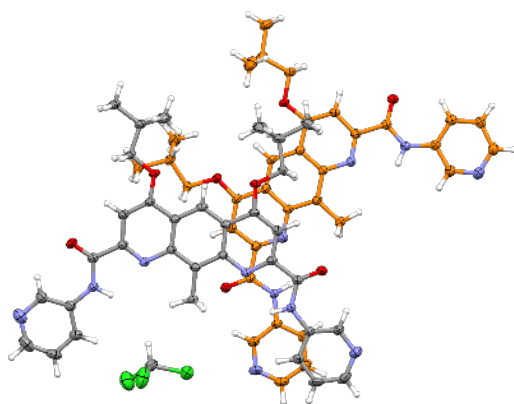


Figure 8.01 Crystal structure of compound **3.07** (ligands **L1**).

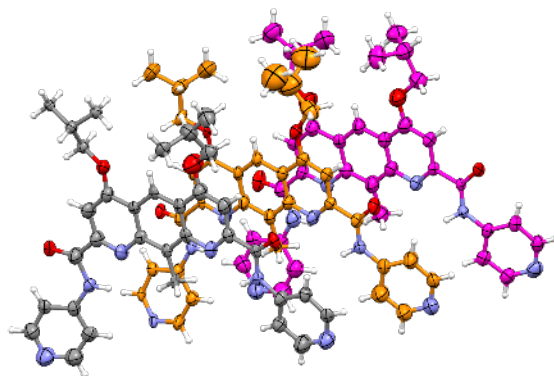


Figure 8.02 Crystal structure of compound **3.09** (ligand **L2**). The disorder was omitted for clarity.

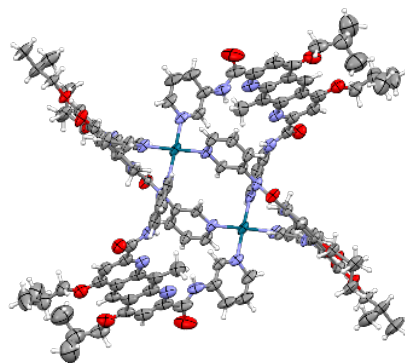


Figure 8.03 Crystal structure of complex **3.12**, Pd₂(**L1**)₄(BF₄)₄.

Table 8.01. Crystal data and refinement of compounds **3.07**, **3.09** and self-assembled complex **3.12**.

Parameter	3.07 (L1)	3.09 (L2)	3.12, Pd₂(L1)₄
Empirical formula	2(C ₃₃ H ₃₄ N ₆ O ₄)·CHCl ₃	C ₃₃ H ₃₄ N ₆ O ₄	C ₁₃₂ H ₁₃₆ N ₂₄ O ₁₆ Pd ₂ ·4(BF ₄)·2(C ₂ H ₆ OS) 5.528(C ₃ N O)· [+solvent]
Formula weight	1276.69	578.66	3435.02
Temperature (K)	150	150(2)	150
Wavelength (Å)	0.71073	0.71073	0.71073
Crystal system	Monoclinic	Triclinic	Triclinic
Space group	<i>P</i> 2 ₁ / <i>c</i>	<i>P</i> -1	<i>P</i> -1
<i>a</i> (Å)	13.7659 (4)	16.680(3)	17.1364 (8)
<i>b</i> (Å)	17.0380 (4)	20.168(4)	18.0479 (17)
<i>c</i> (Å)	27.1194 (5)	20.272(4)	18.1621 (18)
α (°)	90.00	62.77(2)	66.145 (9)
β (°)	97.269 (2)	65.752(18)	66.802 (7)
γ (°)	90.00	68.329(17)	78.332 (6)
Volume (Å ³)	6309.5 (3)	5389(2)	4715.7 (8)
<i>Z</i>	4	6	1
Calculated density (g/cm ³)	1.344	1.070	1.210
Absorption coefficient (mm ⁻¹)	0.21	0.072	0.29
<i>F</i> (000)	2680	1836	1785
Crystal size (mm)	0.45 × 0.06 × 0.02	0.45 × 0.14 × 0.07	0.18 × 0.12 × 0.09
θ range (deg)	2.818 to 25.252	2.959 to 19.209	2.848 to 23.375

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Refl. collected / unique	40825/11407	14024/14024	37937/13505
	[$R_{\text{int}} = 0.0560$]	[$R_{\text{int}} = \text{I}^*$]	[$R_{\text{int}} = 0.0760$]
Compl. to (θ)	0.996($\theta = 25.252$)	99.6 % ($\theta = 19.209^\circ$)	0.986 ($\theta = 23.375$)
Max. and min. transm.	1.00000, 0.43613	1.00000, 0.89690	1.00000, 0.76995
Data / restraints / parameters	11407/0/821	14024 / 1915 / 947	13505/343/1184
Goodness of fit on F^2	1.026	1.244	1.155
R_1^a [$I > 2\sigma(I)$]	0.0550	0.1708	0.0924
wR_2^b	0.1489	0.3082	0.2216
R_1^a (all data)	0.0861	0.3039	0.1222
wR_2^b	0.1489	0.3429	0.2368
$\Delta\rho_{\text{max/min}}$ (e. $\text{\AA}^{-3}$)	0.403, -0.484	0.494, -0.565	2.415, -0.603

* twinned data, refined against HKLF5 formatted data, imposing MERG 0

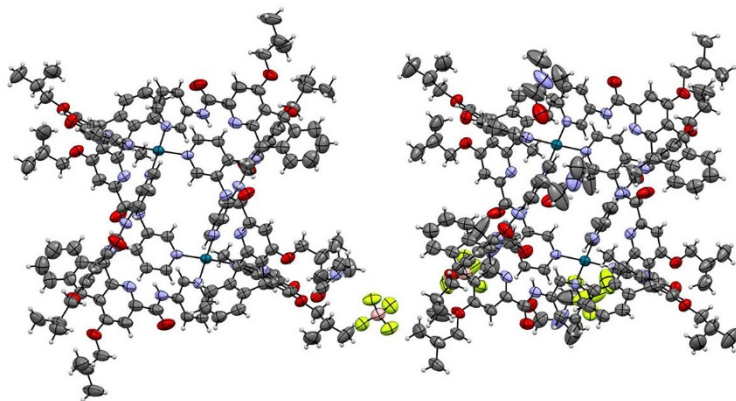


Figure 8.04 Crystal structure of complex **4.31**, $\text{Pd}_2(\text{L6})_4(\text{BF}_4)_4$.

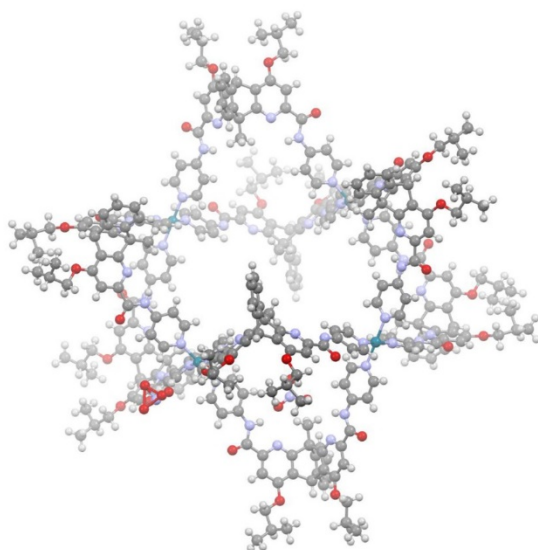


Figure 8.05 Crystal structure of complex **4.32**, $\text{Pd}_4(\text{L7})_8(\text{BF}_4)_8$.

Table 8.02. Crystal data and refinement of self-assembled complex **4.31** and **4.32**.

Parameter	4.31 , Pd ₂ (L6) ₄	4.32 , Pd ₄ (L7) ₈
Empirical formula	C ₁₅₆ H ₁₅₂ N ₂₄ O ₁₆ Pd ₂ , C ₁₅₆ H ₁₅₀ N ₂₄ O ₁₆ Pd ₂ , 10(C ₃ H ₇ NO), 6(BF ₄)	C ₃₁₂ H ₃₀₀ N ₄₈ O ₃₂ Pd ₄ , 3(N ₂ O ₆)
Formula weight	6913.41	6031.64
Temperature (K)	130	130
Wavelength (Å)	1.54178	1.54178
Crystal system	triclinic	orthorhombic
Space group	P-1	-P 2 2n
<i>a</i> (Å)	19.2769(6)	23.9081(6)
<i>b</i> (Å)	25.1261(8)	33.3421(12)
<i>c</i> (Å)	27.1224(11)	45.4165(9)
α (°)	72.208(3)	90
β (°)	69.826(3)	90
γ (°)	76.109(3)	90
Volume (Å ³)	11607.0(8)	36203.6(17)
<i>Z</i>	1	2
Calculated density (g/cm ³)	0.989	0.553
Absorption coefficient (mm ⁻¹)	1.782	1.069
<i>F</i> (000)	3596	6268
Crystal size (mm)	0.03 × 0.03 × 0.03	0.03 × 0.03 × 0.03
θ range (deg)	3.315 to 68.245	2.993 to 44.396
Refl. collected / unique	122240/41650	191359/14335

	[$R_{\text{int}} = 0.0484$]	[$R_{\text{int}} = 0.0951$]
Compl. to (θ)	0.979	0.993
Max. and min. transm.	1.00000, 0.66067	1.00000, 0.69850
Data / restraints / parameters	41650/78/2183	14335/1977/967
Goodness of fit on F^2	1.029	1.311
R_1^a [$I > 2\sigma(I)$]	0.0824	0.1168
wR_2^b	0.2332	0.3406
R_1^a (all data)	0.0940	0.1535
wR_2^b	0.2466	0.3848
$\Delta\rho_{\text{max/min}}$ (e. $\text{\AA}^{-3}$)	2.332 and -0.664	0.740 to -0.531

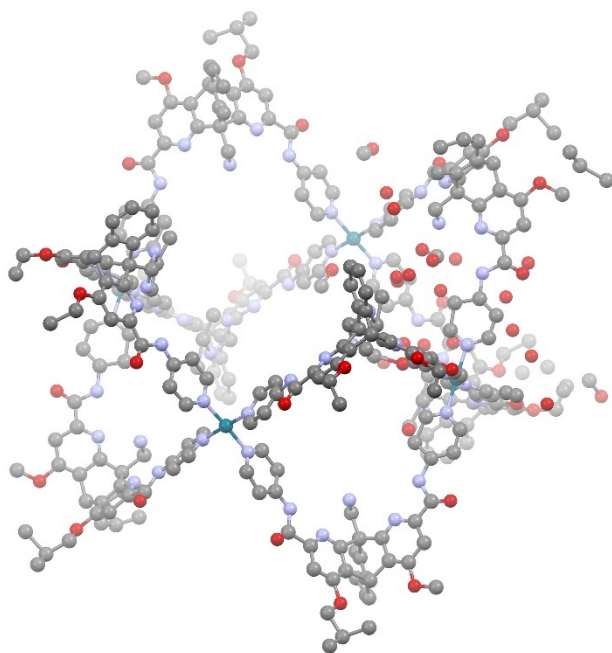


Figure 8.06 The preliminary crystal structure of complex **4.33**, $\text{Pd}_4(\text{L8})_8(\text{BF}_4)_8$.

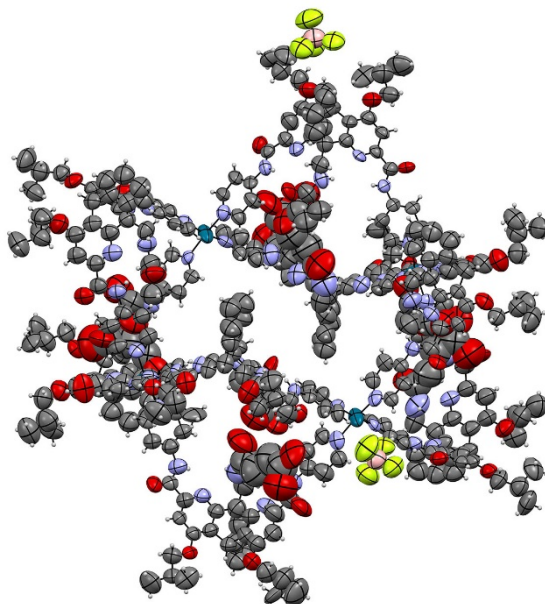


Figure 8.07 Crystal structure of complex **4.35**, $\text{Pd}_4(\text{L10})_8(\text{BF}_4)_8$.

Table 8.03. Crystal data and refinement of self-assembled complex **4.35**.

Parameter	4.35 , Pd ₄ (L 10) ₈
Empirical formula	C ₃₄₄ H ₃₃₆ B ₄ F ₁₆ N ₅₆ O ₅₆ Pd ₄
Formula weight	6923.51
Temperature (K)	120(2) K
Wavelength (Å)	0.71073 Å
Crystal system	Monoclinic
Space group	<i>I</i> 2
<i>a</i> (Å)	<i>a</i> = 36.244(3) Å
<i>b</i> (Å)	<i>b</i> = 27.1208(14) Å
<i>c</i> (Å)	<i>c</i> = 36.145(3) Å
α (°)	90°.
β (°)	90.202(8)°.
γ (°)	90°.
Volume (Å ³)	35529(5) Å ³
<i>Z</i>	2
Calculated density (g/cm ³)	0.647 g/cm ³
Absorption coefficient (mm ⁻¹)	0.143 mm ⁻¹
<i>F</i> (000)	7176
Crystal size (mm)	0.30 x 0.30 x 0.25 mm ³
θ range (deg)	2.817 to 17.225°.
Refl. collected / unique	54626
	21299 [R(int) = 0.1094]
Compl. to (θ)	99.4 %
Max. and min. transm.	1.00000 and 0.92622
Data / restraints / parameters	21299 / 2950 / 2165
Goodness of fit on F^2	1.103
R_1^a [$I > 2\sigma(I)$]	$R_1 = 0.0699$,
wR_2^b	$wR_2 = 0.1515$
R_1^a (all data)	$R_1 = 0.1437$,
wR_2^b	$wR_2 = 0.1820$
$\Delta\rho_{\text{max/min}}$ (e. Å ⁻³)	0.270 and -0.180 e.Å ⁻³

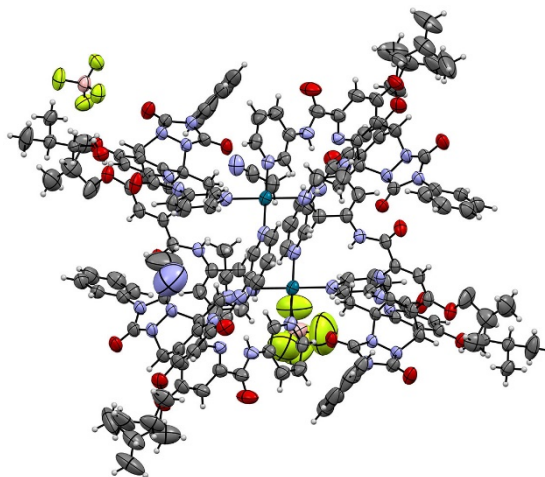


Figure 8.08 Crystal structure of complex **5.05**, *cis*-Pd₂(**L19A**)₂(**L19B**)₂(BF₄)₄. Solvent molecules, anions and disorders were omitted for clarity.

Table 8.04. Crystal data and refinement of self-assembled complex **5.05**.

Parameter	5.05 , <i>cis</i> -Pd ₂ (L19A) ₂ (L19B) ₂
Empirical formula	C176 H174 B4 F16 N42 O26 Pd2
Formula weight	3853.60
Temperature (K)	150(2) K
Wavelength (Å)	0.71073 Å
Crystal system	Trigonal
Space group	R-3
<i>a</i> (Å)	<i>a</i> = 43.6366(8) Å
<i>b</i> (Å)	<i>b</i> = 43.6366(8) Å
<i>c</i> (Å)	<i>c</i> = 30.7516(4) Å
α (°)	$\alpha = 90^\circ$.
β (°)	$\beta = 90^\circ$.
γ (°)	$\gamma = 120^\circ$.
Volume (Å ³)	50711(2) Å ³
<i>Z</i>	9
Calculated density (g/cm ³)	1.136 g/cm ³
Absorption coefficient (mm ⁻¹)	0.237 mm ⁻¹
<i>F</i> (000)	17892
Crystal size (mm)	0.30 x 0.30 x 0.25 mm ³
θ range (deg)	2.928 to 25.252°.
Refl. collected / unique	110151
	20376 [R(int) = 0.0524]
Compl. to (θ)	99.8 %
Max. and min. transm.	1.00000 and 0.68289
Data / restraints / parameters	20376 / 446 / 1381
Goodness of fit on F^2	1.090
R_1^a [$I > 2\sigma(I)$]	$R_1 = 0.0602$,
wR_2^b	$wR_2 = 0.1600$
R_1^a (all data)	$R_1 = 0.0797$,
wR_2^b	$wR_2 = 0.1720$
$\Delta\rho_{\max/\min}$ (e. Å ⁻³)	1.048 and -0.706 e.Å ⁻³

4. Computational modeling

4.1 Molecular dynamics analysis of endohedral hydrogen bonding

The tight-binding molecular dynamics simulations used to study the compound **3.09** (ligand **L2**) with endohedral hydrogen bonding and ligand **L4** without endohedral hydrogen bonding were performed by Dr. David A. Poole III at the University of Amsterdam. The angle of ligands is determined from the vectors along each pyridine ($C4 \rightarrow N1$). Each trajectory was approximately 4000 frames starting at the optimized geometry. A simple histogram of the frames found at each angle (rounded to 5 deg) shows that each ligand has apparent preferences in line with the observed cage formation (less populated states are less energetically favored). From this, the **L2** ligand prefers narrow angles forming the M_3L_6 and M_6L_{12} structures quickly, but the wider angle for the M_6L_{12} is less populated. The **L4** ligand is wildly flexible and seems likely to form more extensive networks or cage structures. The visualization of the **L4** simulation shows a free dihedral rotation between anthracene and amide planes, and intuitively it seems more likely to form networks than well-defined cages. Still, the simulation data clearly shows the importance of hydrogen bonding for maintaining the overall ligand shape and allowing for cage formation.

4.2 PM6 model structure of complexes M_6L_{12} and $M_{12}L_{24}$

The geometry-optimized structure of ligands **L1**, **L2**, complexes $Pd_2(L1)_4$, $Pd_6(L2)_{12}$ and $Pd_{12}(L2)_{24}$ were performed at the semi-empirical PM6 level using Gaussian 09 package.^[19] The size, bend angle(θ), twisted pattern and overall configurations of PM6 model structures are comparative to the crystal structure of ligands **L1**, **L2**, and complex $Pd_2(L1)_4$. The geometry-optimized structure for $Pd_6(L2)_{12}$, $Pd_{12}(L2)_{24}$ and $Pd(L3)_2$ were performed using the same semi-empirical PM6 level of theory.

4.3 Density functional theory calculations

All models were constructed using Avogadro and the semi-empirical PM6 level was used to optimize the geometry of all structures before optimization using density functional theory (DFT). The resulting geometries were optimized at DFT calculations with B3LYP/6-31G(d) level of theory for organic ligands and B3LYP/def2-SVP level of theory for metal-organic cages using Gaussian 09 package^[19] The geometry of complex Pd₂(**L6**)₄ and complex *cis*-Pd₂(**L19A**)₂(**L19B**)₂ optimized with DFT matches well with their crystal structures.

5. DOSY spectra

Stokes-Einstein equation,

$$D = \frac{k_B T}{6\pi\eta r},$$

was applied to estimate the dynamic radius for compounds used as ligands and the species resulting from ligands self-assembly with Pd(II) ions. **D** is diffusion coefficient obtained from the DOSY spectrum, **k_B** is Boltzmann constant, **T** is the absolute temperature, viscosity (**η**) tested to be 0.362 mPa•s for CD₃CN, 2.17 mPa•s for DMSO-d₆ and 0.802 mPa•s for DMF-d₇, and **r** is the estimated dynamic radius.

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