Metallo-Supramolecular Self-Assembly with Reduced-Symmetry Ligands

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Metallo-supramolecular self-assembly tends to be performed with single metal ions and single, highly symmetrical, ligands. This simplifies the self-assembly process as without sufficient bias within the system a mixture of products may be formed. However, with various applications of metallo-supramolecular species having been demonstrated, the ability to generate more intricate architectures is keenly sought after. The use of reduced symmetry ligands is one route to this goal, and allows access to lower-symmetry assemblies. Multiple coordination pockets can also be introduced in this manner, giving rise to assemblies with metal ions in different coordination environments, which can be exploited for the controlled synthesis of mixed-metal species. Herein we discuss the different approaches that have been used to control self-assembly with low symmetry ligands, including the use of mixed-denticity ligands, the incorporation of geometric constraints, charge separation strategies and the use of repulsive or attractive non-covalent interactions between ligands.

Introduction

Metallo-supramolecular chemistry has advanced spectacularly over the last four decades.\(^1\) Emanating from the early work of Lehn,\(^2\) Fujita,\(^3\) Stang,\(^4\) Atwood\(^5\) and others, the beauty of these assemblies derives from their simplicity. By careful design, trivial ligands can be combined with judiciously chosen metal ions to give intricate self-assembled architectures. Manifold applications\(^6\) of these assemblies have now been developed: stabilization of reactive species,\(^7\) catalysis,\(^8\) gas storage,\(^9\) and biological activity\(^10\) have all been realized and continue to be built upon with extraordinary results.

In parallel with this application-driven research, fundamental interest in the construction of metallo-supramolecular architectures remains active. Given the preponderance of functions that these relatively simple architectures have been shown to display, the desire for more intricate assemblies, potentially capable of more elaborate tasks, is perhaps unsurprising. As such there have been reports of larger\(^11\) and larger\(^12\) (and larger still\(^13\)) assemblies, multi-cavity systems\(^14\) stellated cages\(^15\) interlocked and entangled species,\(^16\) functionalized architectures\(^17\) and heteroleptic assemblies\(^18\).

However, for the vast majority of these assemblies the ligand components used remain highly symmetrical to facilitate the self-assembly process and avoid formation of mixtures of products. Being able to control the assembly of unsymmetrical ligands would allow access to lower symmetry architectures, with implications for the segregation/relative positioning of functional groups and binding of low symmetry guests.

In this review we seek to highlight the different strategies that have been used to imbue reduced symmetry ligands with the ability to self-sort into single metallo-supramolecular assemblies out of a potential mixture. This is not intended to be comprehensive, but rather select examples will be used to illustrate different methodologies. We have divided the strategies for ligand design into the following headings: mixed-denticity ligands, geometric complementarity, charge separation and non-covalent influences. In this overview of the field a focus will be placed on discrete assemblies; the concept of ‘geometry mismatch’ in constructing metal-organic frameworks (MOFs) of unusual topologies has been the topic of a recent review.\(^19\)

Mixed-Denticity Ligands

Transition metal ions are commonly used for purposes of self-assembly due in large part to their predictable coordination geometries. This was exploited to great effect by Jean-Marie Lehn, whose idea of maximal site occupancy allows the likely empirical formula (metal:ligand ratio) of a metallo-supramolecular species to be determined from the overall denticity of the ligand and the preferred coordination geometry/number of the chosen metal ion.\(^20\) Although there are exceptions, this simple rule-of-thumb remains incredibly useful in the design of these systems.

Coordination geometries can usually be satisfied with multiples of a single ligand type, e.g. an octahedral geometry could be fulfilled by six monodentate ligands, three bidentate ligands or two tridentate ligands. It is also possible to form heteroleptic structures – complexes with more than one ligand – in which individual ligands have denticities multiples of which are not ideal for the chosen metal ion by themselves.

It is important to consider this when designing ligands incorporating more than one coordinating motif. For the controlled self-assembly of ligands of this sort there are two concepts that are more commonly associated with heteroleptic self-assembly from a mixture of ligands (Figure 1). The first is integrative self-sorting, in which a metal ion binds to two (or more) different ligating moieties to fulfill its coordination geometry. Generally this will give architectures in which all metal ions are in identical environments. The second is narcissistic self-sorting whereby metal ions bind to a single type of coordinating moiety; this results in an assembly in which metal ions are present in different coordination environments.
It is likely to result (statistical sorting).

Integrative Self-Sorting

The concept of integrative self-sorting entails the precise assembly of heteromeric structures through orthogonal interactions between multiple, different, components. Through careful design of molecular recognition sites it has been shown possible to achieve mixed-ligand metallo-supramolecular architectures with high fidelity. By borrowing design principles for the construction of heteroleptic species, and incorporating multiple recognition sites into a single ligand, it should be possible to obtain a well-defined product upon self-assembly with metal ions, despite the potential for forming a mixture of homoleptic complexes.

Metalloporphyrin complexes are well known to bind axial ligands; this motif has been used for the self-assembly of porphyrin-based systems and the templated synthesis of multi-porphyrin arrays. If ligand units are appended off the periphery of the porphyrin macrocycle itself then these may be able to self-assemble into metallacyclic species. An early example of this was reported by Hunter and Sarson. Zinc complex 1 was prepared in which a 4-pyridyl ligand was attached to the porphyrin core via a 2,6-pyridinedicarboxamide linker. This was determined to exist in solution as the metallacyclic dimer (Figure 2a) which was capable of binding terephthalamide derivatives through hydrogen-bonding interactions with the pyridinedicarboxamide units. In a subsequent study, the connectivity between a zinc porphyrin and a phenylpyridinecarboxamide moiety was systematically varied to give a family of six ligands, five of which were observed to form dimeric assemblies (Figure 2b). The sixth (3, Figure 2c), incorporating a linear para-phenyl-4-pyridinedicarboxamide arm parallel to the plane of the porphyrin, yielded a square tetramer as shown by vapor pressure osmometry.

Ikeda and co-workers reported an interesting variant on this motif in which a zinc pyrazolyl porphyrin complex was found to assemble into a trimeric or tetrameric metallacycle depending on whether the pyrazole N-substituent was a proton or methyl group, respectively. This approach is not limited to zinc complexes, as demonstrated by Imamura and co-workers who prepared a ruthenium porphyrin complex incorporating a 4-pyridyl unit (4). The pyridine bound axially to Ru(II) (the other axial site occupied by either a CO or pyridine ligand) giving rise to a discrete tetramer (Figure 2d).

This behavior is not unique to porphyrin complexes, as demonstrated by Reek and co-workers. Sub-component self-assembly of 3,4-diaminopyridine (5) with 3-tert-butylsalicylaldehyde (6) and Zn(II) resulted in formation of the salphen-type complex 7 (Figure 3a) in which the exo-pyridyl unit was shown to bind axially to the Zn(II) ion, forming a tetrameric assembly (Figure 3b). Dis-assembly of this metallacycle could be induced upon addition of excess pyridine (Py) to displace the internal pyridyl ligand, resulting in the monomeric [7(Py)] complex.

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Metal ions that prefer to adopt a square planar coordination environment, such as palladium(II) and platinum(II), can be used to similar effect with a combination of tridentate and monodentate ligands, a design that has previously been used to prepare heteroleptic assemblies.\(^\text{[29]}\) Nabeshima and co-workers synthesized ligand \(8\) with parallel terpyridine and 3-pyridine fragments (Figure 4a). Self-assembly with Pt(II) resulted in quantitative formation of the dinuclear metallacycle, capable of binding a range of aromatic guests through π-stacking and hydrogen-bonding interactions (Figure 4b).\(^\text{[30]}\) Vilar and co-workers also exploited this motif in the synthesis of \(\text{M}_{11}L_1\) (\(\text{M}=\text{Pd(II)}\) or Pt(II)) metallacycles assembled from a terpyridine ligand with a tethered purine derivative (9, Figure 4c). In addition to solid state confirmation of the macrocyclic structure (Figure 4d), persistence of the dimeric complexes in DMSO solution was supported by DOSY NMR. These complexes were shown to preferentially interact with G-quadruplex DNA over duplex DNA, with docking studies indicating significant π-π interactions between the metallacycle and guanine quartet.\(^\text{[31]}\) An analogous metallacyclic dimer was also obtained upon reaction of 9 with Cu(II), with the square pyramidal geometry of the metal ions completed by axial water ligands.\(^\text{[32]}\) Coronado, Gaviña and co-workers were also able to achieve integrative self-sorting with Cu(II). Upon assembly with a rigid ligand incorporating both terpyridine and phenanthroline units, a hexanuclear metallacycle was obtained with each metal center occupying a \([3 + 2]\) heteroleptic coordination environment, giving rise to a square pyramidal geometry.\(^\text{[33]}\)

Preston and co-workers utilized a similar \([3 + 1]\) motif for square planar metal ions in ligands 10 and 11 incorporating a monodentate 4-pyridine and a tridentate binding pocket (Figure 5a). When combined with a stoichiometric amount of either a Pd(II) or Pt(II) source at a concentration of 5 mM, formation of dimeric metallacycles was observed in all cases. For the elongated ligand 11, however, increasing the concentration of both the Pd(II) and Pt(II) complexes led to formation of second species, determined to be the metallo-[2]-catenanes, arising from interlocking of two metallacycles (Figure 5b).\(^\text{[34]}\)

This approach has also been shown to be effective for the construction of three-dimensional structures. Eddaoudi and co-workers reported the self-assembly of In(III) with 2,5-pyridinedicarboxylic acid (H\(_2\)12) under solvothermal conditions. Crystals were obtained allowing structural analysis by SCXRD, and revealed the formation of a hexanuclear octahedral cage (Figure 6a). Each of the In(III) centers are coordinated to two 2-pyridinecarboxylate chelates and two 5-carboxylates with a total coordination number of 7 (Figure 6b). Although the cage could be effectively synthesized in good yield (73%), changes

Figure 2. a) Equilibrium between zinc-porphyrin 1 and self-assembled metal-lacyclic dimer 12; b) Single crystal X-ray diffraction (SCXRD) structure of dimer 2; c) ligand 3 was found to assemble into a tetrameric metallacycle, 3e d) Imamura’s ruthenium-porphyrin tetramer 4e.

Figure 3. a) Subcomponent self-assembly of pyridyldiamine 5 and salicylaldehyde 6 with Zn(OAc)\(_2\) yielded the Zn(ll)-salphen complex 7. b) SCXRD structure of tetrameric Zn(ll)-salphen complex, 7e. Hydrogen atoms and tert-butyl groups have been omitted for clarity.

Figure 4. a) Nabeshima’s terpyridine/pyridine ligand, 8, and b) SCXRD structure of the corresponding [Pt\(_2\)(B)\(_3\)]\(^{11+}\) metallacycle with encapsulated dihydroxynaphthalene guest. c) Vilar’s terpyridine/guanosine ligand, 9, and d) SCXRD structure of its dimeric Pd(ll) metallacycle, [Pd\(_6\)(9)\(_4\)]\(^{11+}\). Hydrogen atoms have been omitted for clarity.

Figure 5. a) Preston’s [3 + 1] ligand design and b) DFT calculated structure of metallo-[2]-catenane ([Pd\(_6\)(11)\(_3\)]\(_{11+}\)). Hydrogen atoms have been omitted for clarity.
in the reaction conditions led to formation primarily of a two-dimensional polymeric network, suggesting that this particular coordination mode is unlikely to be useful for reliable prediction of self-assembly outcomes.38

Narcissistic Self-Sorting

In contrast to the previous examples in which the formation of heteroleptic coordination environments was favored, if ligands display a propensity for self-association upon binding metal ions then homoleptic species will dominate. This phenomenon of narcissistic self-sorting can be used to assemble multiple ions then homoleptic species will dominate. This phenomenon display a propensity for self-association upon binding metal ions. In contrast to the previous examples in which the formation of heteroleptic coordination environments was favored, if ligands of different denticity that, unlike those employed for integrative self-sorting, are capable of satisfying the coordination geometry of the chosen metal ion with integer multiples of themselves.

Li and co-workers synthesized cage [Ni₄(H₃)₂]⁺ from the solvothermal reaction of ligand H₁₃ (obtained from the condensation of 4-formylimidazole and methylamine) with Ni(NO₃)₂·6H₂O (Figure 7a). The ligand possesses two binding sites, namely the bidentate chelate provided by the imidazole and imine (Figure 7b), and the monodentate imidazolate (Figure 7c). The Ni₄L₂ structure contains Ni(II) ions in two coordination environments: octahedral, provided by three bidentate ligands, and square planar, from coordination to four imidazolate units (Figure 7b and c). Recognizing that the presence of different coordination environments could be potentially exploited to construct heteronuclear architectures, the assembly reaction of a similar ligand with a mixture of Ni(II) and Cu(II) resulted in the isoreticular mixed-metal Ni₄CuL₂ complex, in which the Ni(II) ions exist in an octahedral geometry, whilst the Cu(II) ions are square planar.39 Using similar approaches other groups have generated related mixed-metal Fe(II)-Pt(II), Fe(II)-Pd(II), and Cu(II)-Fe(II)41 cube-shaped cages.

Raymond and co-workers were able to achieve narcissistic self-sorting within a heteronuclear system based on hard-soft-acid-base (HSAB) theory. Ligand H₁₄ incorporating a hard catechol moiety and soft phosphine donor, formed the complex [Ti(14)²⁺ with coordination to the Ti(IV) ions exclusively through the catecholate fragment. This left the phosphines free such that upon addition of [Pd(PhCN)₂Br₂] to the sufficiently inert Ti(IV) metallo-ligand, the mixed-metal pentanuclear cage [Pd₂Ti₁₄(14)Br₁₆] was formed (Figure 8a).42

Drawing inspiration from this, Hiraoka, Sakata and Shionoya reported a similar system with the pyridin-3-ylcatechol ligand H₁₅ which, through sequential coordination to Ti(IV) and Pd(II) ions, formed the cage complex [Pd₂Ti₁₄(15)Cl₁₆]⁺. Interconversion between this cage and a neutral tetranuclear metallocycle, [Pd₂Ti₁₄(H₁₅)₂(acac)₄Cl₄], could be achieved through addition of TiO(acac)₂ under acidic conditions, and the reverse effected through addition of H₂₁₅ and [Pd(CH₃CN)₂Cl₂] under basic conditions (acac = acetylacetonate).43 Alternatively the acac ligands of [Pd₂Ti₁₄(H₁₅)₂(acac)₄Cl₄] could be displaced by addition of a bis-tropolone ligand (16 or 17), resulting in heteroleptic mixed-metal assemblies. The rigidity of the tropolone ligand effectively controlled whether a tetranuclear ([Pd₂Ti₁₄(16)Cl₁₆]²⁺) or octanuclear ([Pd₂Ti₁₄(17)Cl₁₆]⁴⁺) cage was formed (Figure 8b).44 Using a similar approach Brechin, Lusby and co-workers have generated a series of magnetically interesting heterometallic cages.45

Exploiting differences in coordination preferences between metal ions has been successfully used to generate a variety of metallo-ligands capable of self-assembly to give mixed-metal architectures. For further examples and an in-depth account of this work the reader is directed to several recent reviews on the topic.46

To induce narcissistic self-assembly it is not essential to generate binding pockets of different coordination numbers/geometries, as demonstrated by Preston and co-workers. Addition of 0.5 eq. of Pd(II) to ligand 18 (Figure 9a) resulted in formation of the mononuclear complex, [Pd(18)₂⁺], without coordination of the 4-pyridyl triazole substituent (Figure 9b). An additional 0.5 eq. of Pd(II) gave the dinuclear metallocycle [Pd₂(18)₂S₂]⁴⁺ (S = DMSO/CH₃CN; Figure 9c); in DMSO this species was formed independent of the concentration. In acetonitrile, however, the discrete dinuclear complex was only formed exclusively at ligand concentrations below 3.5 mM, with oligo-/
bidentate triazolopyridine units, whilst the other three bind to four monodentate pyridines (Figure 9d). 

Exploitation of the different coordinating propensities of the bidentate and monodentate fragments of 18 enabled precision synthesis of a mixed-metal architecture. Initial coordination of the ligand with Pt(II) gave the homologous mononuclear complex [Pt(18)]^{18+}; subsequent addition of Pd(II) to this kinetically inert complex yielded the heteronuclear cage [Pt_Pd(18)]^{18+}, isostructural with its homonuclear analogue. This architecture was found to act as a photosensitizer for the light-induced reaction of anthracene with singlet oxygen to give the endoperoxide cycloaddition product. 

Mondal and co-workers reported an interesting study in which a single ligand was shown to be capable of both integrative and narcissistic self-sorting. When ligand H_{19} (Figure 10a) was combined with Co(BF_{4})_2 an unusual pentahedral cage, [Co(H_{19})(BF_{4})]_2, was obtained. The SCXRD structure of this complex (Figure 10b) revealed two different octahedral Co(II) coordination environments. Three of the metal ions are coordinated to two tridentate pyridylhyrazide units (Figure 10c); the remaining two Co(II) ions are bound to three bidentate pyrazolopyridine moieties (Figure 10d), demonstrating effective narcissistic sorting of the ligand fragments. Conversely when H_{19} was reacted with Cu(ClO_{4})_2, a [2 × 2] grid complex was obtained with each Cu(II) ion occupying a five coordinate environment supplied by the integrative heteroleptic coordination of tridentate and bidentate ligand units (Figure 10e). 

Geometric Complementarity

If a low symmetry ligand does not contain coordinating units of different denticities, then an alternative mode for controlling the self-assembly process must be incorporated into the structure. Given the inherent directionality of lone pair orbitals and the predictable coordination geometry of transition metal ions, geometric constraints can be built into ligand frameworks to avoid formation of isomeric mixtures upon self-assembly.

This principle of geometric complementarity was demonstrated by Stang and co-workers through the self-assembly of ditopic ligands 20 and 21, incorporating one 3-pyridyl and one 4-pyridyl donor, with 60° or 120° diplatinum(II) clips 22 and 23, respectively (Figure 11a). In all cases the entropically favored polymeric species formed above this. Combining 18 and Pd(II) in a 4:3 ratio gave a mixture of different assemblies at low concentrations. Above 14 mM a single structure emerged, identified as the nona-nuclear cage [Pd_{9}(18)]^{18+}. In this structure each Pd(II) ion possesses a square planar coordination geometry; however, six of the ions are coordinated by two
there are four potential Pd₄L₄ cage isomers that could arise. Each of the ligands 25, 26 and 27 (Figure 13a) was shown to assemble into a single cage isomer in solution, and the ligand arrangement confirmed in two cases in the solid state by SCXRD (Figure 13b and c) to be the expected cis structures. The self-assemble of ligand 28 (Figure 13d) with Pd(II), however, resulted in a mixture of Pd₄L₄ cage isomers. As the cantilevering effect is smallest with this ligand, minimal ligand distortion is required to form other cage isomers, as supported by insignificant energy differences between two of the potential isomers as determined by DFT calculations. Replacing one of the pyridine donors with a picolyl unit gave ligand 29; this was shown to form a single cage isomer upon self-assembly with Pd(II) (suggested by DFT calculations to be the cis isomer), demonstrating that directing effects may be used in concert to control assembly with unsymmetrical ligands – in this case a combination of geometric complementarity and steric repulsion (vide infra).²⁶

A higher nuclearity system was reported by Cheng and co-workers: self-assembly of CuSO₄ with 4-(pyridin-3-yl)-1,2,4-triazole, 30, gave an octahedral cage, [Cu₃(30)]⁺⁺ (Figure 14a). Each Cu(II) center is bound to four ligands in a square planar arrangement through two pyridine and two triazole compo-

![Figure 11](image1.png)

Figure 11. a) Ditopic ligands 20 and 21 combined with diplatinum clips 22 and 23 to form [2 + 2] and [3 + 3] metallacycles, respectively, with exclusively head-to-tail arrangement of 20/21. b) SCXRD structure of [2 + 2] metallacycle assembled from 20 and 22. Hydrogen atoms have been omitted and PEt₃ ligands shown as stick models for clarity.

discrete metallacycles ([2 + 2] for 22 and [3 + 3] for 23) were formed, and exclusive formation of the head-to-tail ligand arrangement of 20/21, giving the least amount of distortion and bond strain in the ligand backbone, observed (Figure 11b).³¹

This geometric approach has been extended to the preparation of three-dimensional systems. Ogata and Yuasa synthesized ligand 24 incorporating parallel pyridine and imidazole ligands on a carbazole backbone (Figure 12). The use of coordinating moieties with different affinities for Pd(II) allowed switching between a mononuclear complex, with coordination solely through the imidazole units, and a dinuclear cage by varying the metalligand ratio. This “opening” and “closing” of the cage allowed capture and release of anionic guests. For the dinuclear cage, despite the potential for forming a mixture of Pd₄L₄ species, NMR spectroscopy indicated formation of a single architecture. DFT calculations suggested that the cis isomer (Figure 12) was significantly lower in energy than other possible structures.³²

Lewis and co-workers utilized a similar principle for the self-assembly of low symmetry ditopic ligands, incorporating parallel pyridine/isoquinoline donors, with ‘naked’ palladium(II) ions. The ligands were designed to exhibit a ‘cantilever’ effect, such that ligands arranged trans to each other would adopt an anti arrangement in order to best effect an idealized N₄ coordination solely through the imidazole units, and a dinuclear allowed switching between a mononuclear complex, with

![Figure 12](image2.png)

Figure 12. Self-assembly of unsymmetrical ligand 24 with Pd(III) ions to form cage cis-[Pd₄L₄][Cl]⁺⁺.

![Figure 13](image3.png)

Figure 13. a) Unsymmetrical ligands 25–27 selectively formed single Pd₄L₄ cage isomers upon complexation with Pd(II). SCXRD structures of b) cis-[Pd₄(25)][Cl]⁺⁺ and c) cis-[Pd₄(27)][Cl]⁺⁺. Hydrogen atoms have been omitted for clarity; blue and green colours denote relative ligand orientation. d) The ‘cantilever’ effect of ligand 28 was insufficient to induce formation of a single assembly; ligand 29, incorporating an additional steric directing methyl group, was observed to form a single Pd₄L₄ isomer.

![Figure 14](image4.png)

Figure 14. a) Self-assembly of CuSO₄ with 30 yielded coordination cage [Cu₃(30)]⁺⁺ with b) coordination of each Cu(II) ion to two pyridine and two triazole donors. Hydrogen atoms and axial ethanol ligands have been omitted for clarity.
nents in a cis arrangement (Figure 14b). Six ethanol molecules occupy the cavity of the cage, coordinated to the axial position of the Cu(II) ions.\(^{[34]}\)

Shionoya and co-workers were able to show that non-degenerate metal coordination environments could be formed in assemblies even when the ligand contained identical coordination motifs. Ligand 31, a reduced symmetry version of a tetrakis-bipyridine porphyrin that was shown to form an unusual undecanuclear assembly with Zn(II) ions,\(^{[35]}\) formed an \(\text{M}_{111}\) bowl structure upon addition of Co(OTf)\(_3\) in which three of the Co(II) ions were bound to two bipyridine units and two water molecules, and the fourth coordinated to three bipyridine moieties (Figure 15). As a result of the different coordination environments of the metal ions it was possible to selectively oxidize the tris-bipyridine Co(II) to the more inert Co(III) (Figure 15a), allowing selective transmetallation of the remaining Co(II) centres with Ni(II) (Figure 15b). Subsequent reduction of the Co(III) ion (Figure 15c) allowed access to the mixed-metal Ni(II),Co(II),L\(_2\) system that could not be prepared directly from the ligand and a mixture of Co(II) and Ni(II) precursors.\(^{[36]}\) Interestingly, reaction of 31 with Zn(II) resulted in two different complexes depending on the metal:ligand stoichiometry – when an equimolar ratio was used, a \(\text{Zn}_{14}\) capsule was obtained, with all four Zn(II) ions coordinated to three bipyridine units; conversely when an excess (1.4 eq.) of Zn(II) was used a \(\text{Zn}_{14}\) bowl formed, homologous to the previously reported Co(II) assembly.\(^{[37]}\)

**Charge Separation**

In 2003, Hor and co-workers reported the serendipitous isolation of a tetranuclear molecular square. Assembled from four cis-protected \([\text{Pt(dppf)}]^{2+}\) centers (dppf = 1,1’-bis(diphenylphosphino)ferrocene) and four isonicotinate ligands (32), the metallacycle was found to exist as a single isomer, in both solution and the solid state, with all ligands arranged in a head-to-tail fashion (Figure 16a).\(^{[38]}\) This was subsequently rationalized by Stang and co-workers as resulting from ‘charge-separation’, with the formal positive charge on the pyridine donors providing a repulsive interaction to drive formation of the ‘heteroleptic’ metal center, in which each Pt(II) binds to one pyridine and one carboxylate (Figure 16b). This principle has since been shown to be useful for the preparation of mixed-ligand cages assembled from cis-protected Pt(II) centres and mixtures of a terephthalate ligand and a polypyridyl ligand.\(^{[39]}\)

This charge-separation approach has subsequently been utilized to assemble a variety of metallo-supramolecular structures with ambidentate ligands. Use of elongated variants of isonicotinate, namely 4-(pyridin-3-yl)benzoate (33) and 4-(pyridin-3-ylylethynyl)benzoate (34), with cis-\([\text{Pt(PEt}_3]_2]^{2+}\) units gave \((2 + 2)\) metallacycles with exclusive formation of the head-to-tail isomers (Figure 16c).\(^{[40]}\)

In comparison to the report by Hor, combining the isomeric nicotinate ligand (35) with cis-\([\text{Pd(PEt}_3]_2]^{2+}\) in equimolar amounts resulted in formation of molecular triangle \([\text{Pd}_3(35)_2(\text{dppf})]^{1+}\), with the unsymmetrical ligands again shown to bind in a head-to-tail fashion both in solution and the solid state (Figure 17a).\(^{[41]}\) Interestingly, when 5-pyrimidinecarboxy-
interactions to gain control over the assembly of lower structures (e.g. DNA, proteins). Inspired by these natural processes, self-assembled systems into the desired isomerically pure product, with high fidelity (Figure 18). Formation occurring with high fidelity (Figure 18).

Nature extensively exploits non-covalent interactions (hydrogen-bonding, π-π interactions, other electrostatic interactions, and dispersion forces and steric interactions) to "correctly" orient self-assembled systems into the desired isomerically pure structures (e.g. DNA, proteins). Inspired by these natural systems, there have been some efforts to use non-covalent interactions to gain control over the assembly of lower symmetry heteroleptic metallo-assemblies. While most of the methods developed to date have used two or more, different, symmetrical ligands to synthesize hetero-ligand assemblies \cite{18a,66–69}, the same type of principles can and have been applied to try and control the assembly of metallo-systems with lower symmetry ligands.

**Steric Control**

The concept of using steric hindrance to promote formation of heteroleptic assemblies could arguably be traced back to the work of Sauvage and co-workers. The use of a macrocyclic phenanthroline ligand, incapable of forming homoleptic complexes due to mechanical constraints, ensured formation of a Cu(I)-directed pseudo-rotaxane complex in combination with an acyclic phenanthroline ligand, \cite{70} the subsequent cyclization or stoppering of which yielded mechanically interlocked catenane \cite{71} or rotaxane \cite{72} molecules, respectively.

Following this, Schmittel and Ganz were able to generate heteroleptic Cu(I) phenanthroline complexes with two acyclic components through incorporation of bulky aryl substituents into one of the ligands (Figure 19a), effectively inhibiting homoleptic assembly (and thereby promoting formation of the heteroleptic species) through steric repulsion (Figure 19b).\cite{73} This motif, labelled the HETPhen (heteroleptic phenanthroline) approach, has been used to generate a range of heteroleptic complexes, and has been extended to other coordinating motifs and metal ions. As an example, ligand 45 features both a bulky 2,9-disubstituted phenanthroline and a terpyridine unit (Figure 19c). Upon addition of Cu(I) a single species was observed to form, identified as the triangle \([\text{Cu(45)}]^{3+}\) (Figure 19d), with each metal centre coordinated to one phenanthroline and one terpyridine moiety. Interestingly, coordination of the same ligand to Zn(II) resulted in a mixture

![Figure 17. SXRD structures of a) molecular triangle \([\text{Pd}(\mathbf{35})]^{2+}\) and b) metallacycle \([\text{Pd}(\mathbf{38})]^{2+}\) assembled from cis-protected Pd(II) ions and nicotinate (35) and isonicotinate-N-oxide (38) ligands, respectively. Hydrogen atoms have been omitted and dppf ligands shown as stick models for clarity.](image1)

![Figure 18. a) Diplatinum clip 40 and pyridylbenzoate ligands 32/41/42 assemble to give \([2+2]\) metallacycles with exclusively head-to-tail arrangement of ligands. b) SXRD structure of tetraneutral metallacycle formed from reaction of 40 and 32. Hydrogen atoms have been omitted and PEt₃ ligands shown as stick models for clarity.](image2)

![Figure 19. Coordination of a) bulky phenanthroline ligand, 43, and unsubstituted phenanthroline, 44, with Cu(I) results in b) the heteroleptic complex \([\text{Cu(43)(44)]}^{+}\) (SXRD structure; hydrogen atoms omitted for clarity). c) 45 self-assembles in the presence of Cu(I) ions to give d) the triangular complex \([\text{Cu(45)]}^{3+}\) through formation of heterotopic Cu(I) coordination environments (calculated structure).](image3)
of the homologous trinuclear triangle and also a tetranuclear molecular square assembly.[74]

The Schmittel group have extensively utilized the HETPhen approach, and its variants, in combination with other, orthogonal, heteroleptic coordination modes to prepare a host of elaborate mixed-ligand and heteronuclear metallo-supramolecular structures. An intimate examination of this raft of work is outside the purview of this article; the reader is directed to reviews on the topic for a fuller overview of the impressive versatility of structures that can be obtained from these design methods.[75]

Fujita and co-workers have reported a philosophically similar, although practically simpler, approach to mixed-ligand assemblies using steric parameters to drive heteroleptic coordination about cis-protected square planar metal ions. Self-assembly of [Pt(en)(ONO$_2$)$_2$] (en = ethylenediamine), tritopic ligand 46 and ditopic pyrimidine 47 in the presence of template 48 resulted in quantitative formation of heteroleptic cage [Pt$_3$(en)$_4$(46)$_2$(47)$_3$] (Figure 20a). The template was essential for assembly of the heteroleptic complex; in its absence, a mixture of the homoleptic structures was produced.[76] To assist in the formation of larger cages capable of binding multiple π-stacked guests, additional directing factors were deemed necessary. When stoichiometric amounts of 2,6-lutidine and pyridine were combined in the presence of template 49, mixture of the homoleptic structures was produced.[77] Subsequently self-assembly of [Pd(en)(ONO)$_2$], 46 and 49 in the presence of a pyrene template (50) was shown to quantitatively form the heteroleptic cage [Pd$_4$(en)$_8$(46)$_2$(49)$_3$]$_2^{2+}$, capable of binding two π-stacked aromatic guests (Figure 20c).[78] This method has been termed the ‘side-chain directing’ approach.

Through incorporating this motif into a single 4,4’-dipyridyl ligand, 51, featuring an unsubstituted pyridine at one end and a 2,6-lutidine unit at the other, Stang and co-workers were able to engineer formation of a single isomer of a tetranuclear metallacycle upon self-assembly with a cis-protected Pt(II) precursor. As a result of each cis-protected Pt(II) binding to one lutidine and one pyridine ligand, exclusive formation of the head-to-tail isomer (Figure 21; isomer D) of the molecular square was observed, with calculations suggesting this product to be over 20 kcal mol$^{-1}$ lower in the energy than the next lowest energy isomer. Repeating the self-assembly reaction using ligand 52, in which the 2,6-dimethyl-4-pyridine was replaced with 3,5-dichloro-4-pyridine, gave a complicated mixture of isomeric square complexes, clearly demonstrating the effect of moving the steric side groups to a more remote location. Calculations indicated very small differences in energy between the isomers (<3 kcal$^{-1}$), supporting the conclusion from experimental data that the distal steric groups were ineffective at promoting exclusive formation of heterotopic metal centers.[79]

This side-chain directing approach is not limited to cis-protected metal ions. Lewis and co-workers have extended this to the self-assembly of Pd$_4$L$_4$ cages from ‘naked’ Pd(II) ions and unsymmetrical dipyridyl ligands. Taking inspiration from heteroleptic Pd$_6$L$_6$L’$_2$ cages, reported by the groups of Clever[80] and Crowley[81] in which sterically crowding ortho methyl or amino groups, respectively, were used to direct formation of the mixed-ligand assemblies, ligand 53 (Figure 22a) was combined with a ‘naked’ Pd(II) source to give a potential mixture of Pd$_4$L$_4$ cage isomers. Surprisingly the observed speciation of isomers was dependent upon the solvent: in acetonitrile a single major isomer was formed, identified as likely to be the trans isomer (Figure 22b) by DFT calculations; in DMSO a mixture of the trans and cis (Figure 22c) cages was obtained.[31]

![Figure 20](image_url)

**Figure 20.** a) Self-assembly of cis-protected Pt(II) with ligands 46 and 47 in the presence of template 48 yielded heteroleptic architecture [Pt$_3$(en)$_4$(46)$_2$(47)$_3$] (SCXRD structure). b) Steric repulsion between two cis-oriented 2,6-lutidine ligands drives the equilibrium towards the heteroleptic complex. c) Self-assembly of cis-protected Pd(II) with ligands 46 and 49 in the presence of template 50 yielded heteroleptic architecture [Pd$_4$(en)$_8$(46)$_2$(49)$_3$] (SCXRD structure). Hydrogen atoms have been omitted from SCXRD structures for clarity.
Attractive Interactions

Sen and Natarajan recently reported the self-assembly of dipyrindyl ligand 54 (Figure 23a), incorporating a steroid-based backbone, with Pd(II). Using NMR analysis the authors suggested selective formation of a single one of the four potential cage isomers. The lack of through-space interactions between the inequivalent ends of the ligands in the complex, as observed by NOESY NMR, combined with DFT calculations suggested that the “all-up” conformation had been formed (Figure 23b). The selective formation of this isomer was rationalized as resulting from inter-ligand hydrogen-bonding interactions between endohedral hydroxyl groups (Figure 23c), only possible with a syn arrangement of neighboring ligands. Repeating the self-assembly with ligands lacking one or both of these hydroxyl groups resulted in formation of isomeric mixtures, confirming the importance of the additional non-covalent interactions in driving biased isomer formation.[80]

If the energy difference between isomers of self-assembled systems is insufficiently large, a mixture of metallo-supramolecular architectures is likely to result. Whilst on the face of it this may be assumed to be an undesirable outcome, it does provide the opportunity to bias isomer formation through the influence of stimuli. This offers the potential to develop adaptable systems that respond to external effectors.

An example of structural adaptability controlled through host-guest chemistry was reported by Fujita and co-workers. The self-assembly of [Pd(en)(ONO₂)]₄⁻ and the tritopic ligand 55 can yield two products: isomeric cages 56 and 57 (Figure 24). In the absence of any additional components during the self-assembly process, a mixture of these two cages was obtained. However, addition of 1,3,5-benzenetricarboxylic acid as a guest drove formation of cage 57 selectively. Conversely, if the self-assembly was undertaken in the presence of CBr₃Cl or CBr₄, 56 was obtained as the major product; this was sufficiently kinetically stable to allow purification by crystallization. Reversible conversion between the isomers was also shown to be possible. Addition of excess CBr₃Cl to a solution of 57 templated by p-xylene resulted in guest exchange and subsequent rearrangement of the host to cage 56; addition of excess p-xylene effected reversion to cage 57. The difference in isomer speciation driven by the guest molecules was rationalized in terms of maximizing interactions between the two. Cage 57 possessed a flat structure, with the aromatic surfaces of the ligands more parallel to each other, suitable for π–π interactions between the host and guest. Conversely the more spherical cavity of 56 was better adapted to the encapsulation of guests such as CBr₃Cl and CBr₄.[81]

Conclusion

Much of the early work on metallo-supramolecular architectures used highly symmetrical ligands and symmetrical metal complexes/ions to facilitate the self-assembly process and avoid formation of mixtures of products. While these symmetrical systems have been used for a wide range of interesting applications there is a growing realization that lower symmetry architectures may provide enhanced properties. There have now been several different approaches developed that allow the controlled assembly of unsymmetrical ligands and metals ions to generate (controllably) lower symmetry architectures. Herein we have discussed the different approaches that have been used to control self-assembly with low symmetry ligands, including the use of mixed-denticity ligands, geometric constraints, charge separation strategies and the use of repulsive or attractive non-covalent interactions between ligands. With these new methods now available, and others being developed, it is only a matter of time before interesting new properties of these lower symmetry architectures are discover. In particular, these lower symmetry metallo-macrocycles and cages may display more selective molecular recognition properties. Similarly, they may also be able catalyze/facilitate different, more complex, types of reactions within their cavities.
**Conflict of Interest**

The authors declare no conflict of interest.

**Keywords:** host-guest systems • low-symmetry ligands • metallo-supramolecular architectures • non-covalent interactions • self-assembly

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