

Stereochemistry in Subcomponent Self-Assembly

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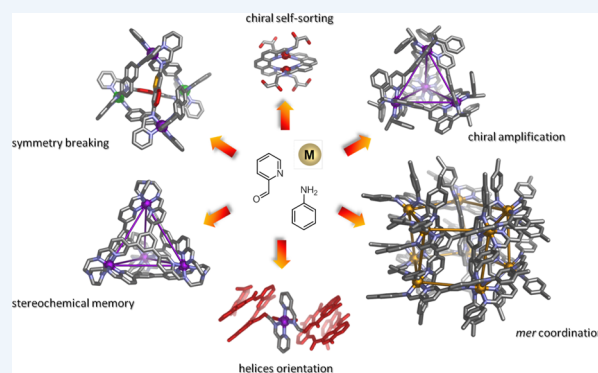
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CONSPECTUS: As Pasteur noted more than 150 years ago, asymmetry exists in matter at all organization levels. Biopolymers such as proteins or DNA adopt one-handed conformations, as a result of the chirality of their constituent building blocks. Even at the level of elementary particles, asymmetry exists due to parity violation in the weak nuclear force. While the origin of homochirality in living systems remains obscure, as does the possibility of its connection with broken symmetries at larger or smaller length scales, its centrality to biomolecular structure is clear: the single-handed forms of bio(macro)molecules interlock in ways that depend upon their handednesses. Dynamic artificial systems, such as helical polymers and other supramolecular structures, have provided a means to study the mechanisms of transmission and amplification of stereochemical information, which are key processes to understand in the context of the origins and functions of biological homochirality. Control over stereochemical information transfer in self-assembled systems will also be crucial for the development of new applications in chiral recognition and separation, asymmetric catalysis, and molecular devices.

In this Account, we explore different aspects of stereochemistry encountered during the use of subcomponent self-assembly, whereby complex structures are prepared through the simultaneous formation of dynamic coordinative ($N \rightarrow \text{metal}$) and covalent ($N=C$) bonds. This technique provides a useful method to study stereochemical information transfer processes within metal–organic assemblies, which may contain different combinations of fixed (carbon) and labile (metal) stereocenters. We start by discussing how simple subcomponents with fixed stereogenic centers can be incorporated in the organic ligands of mononuclear coordination complexes and communicate stereochemical information to the metal center, resulting in diastereomeric enrichment. Enantiopure subcomponents were then incorporated in self-assembly reactions to control the stereochemistry of increasingly complex architectures. This strategy has also allowed exploration of the degree to which stereochemical information is propagated through tetrahedral frameworks cooperatively, leading to the observation of stereochemical coupling across more than 2 nm between metal stereocenters and the enantioselective synthesis of a face-capped tetrahedron containing no carbon stereocenters via a stereochemical memory effect. Several studies on the communication of stereochemistry between the configurationally flexible metal centers in tetrahedral metal–organic cages have shed light on the factors governing this process, allowing the synthesis of an asymmetric cage, obtained in racemic form, in which all symmetry elements have been broken.

Finally, we discuss how stereochemical diversity leads to structural complexity in the structures prepared through subcomponent self-assembly. Initial use of octahedral metal templates with *facial* stereochemistry in subcomponent self-assembly, which predictably gave rise to structures of tetrahedral symmetry, was extended to *meridional* metal centers. These lower-symmetry linkages have allowed the assembly of a series of increasingly intricate 3D architectures of varying functionality.

The knowledge gained from investigating different aspects of the stereochemistry of metal-templated assemblies thus not only leads to new means of structural control but also opens pathways toward functions such as stereoselective guest binding and transformation.



1. INTRODUCTION

In recent years, *subcomponent self-assembly*¹ has emerged as a tool for the construction of increasingly complex 2D and 3D metallo-supramolecular architectures.^{1–4} This technique, an evolution of Busch's work on template synthesis,⁵ which saw key development by Hannon,⁶ involves the assembly of building blocks by the formation of coordinative ($N \rightarrow \text{metal}$) and covalent ($N=C$)^{3,7} bonds during a single overall process. Pyridyl-imine based ligands have been used by others and ourselves to assemble a wide variety of structures, from

macrocycles,³ helicates,^{3,8,9} and polymers² to metal–organic capsules^{4,10} and interlocked structures.^{11,12} In these systems, chirality arises from the spatial arrangement of the achiral pyridyl-imine ligands around the metal templates. The metal centers are C_2 -symmetric pseudo-tetrahedral bis-chelate complexes displaying Δ or Λ stereochemistry or C_3 -symmetric

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pseudo-octahedral tris-chelate complexes, which can adopt facial (*fac*) or meridional (*mer*) stereochemistry, in addition to Δ or Λ handedness. Subcomponent self-assembly, by incorporating these chiral-at-metal centers, thus generates inherently chiral structures from achiral subcomponents.

2. COMMUNICATION OF STEREOCHEMISTRY FROM CARBON (FIXED) TO METAL (FLEXIBLE) STEREOCENTERS

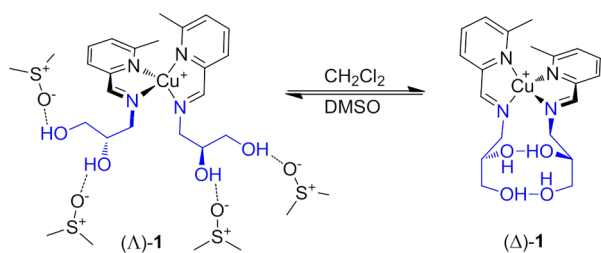
The most extensively used strategy to influence the stereochemistry of configurationally labile metal centers is the use of enantiopure organic ligands.¹³ When coordinated to metal stereocenters, such ligands render the Δ and Λ configurations of the metal diastereomeric. Energetic differences between diastereomers much greater than kT can be readily engineered, as illustrated by the examples discussed in the following sections. The ligands are thus able to predetermine the absolute configuration of the metal¹³ and often in turn to dictate the overall stereochemistry of a structure. This phenomenon has its conceptual roots in the Pfeiffer effect,¹⁴ whereby metal-centered chiroptical properties were shown to be influenced by stereocenters elsewhere within a system.

The modularity of subcomponent self-assembly has provided a straightforward method to manipulate the stereochemistry of the self-assembly processes through the incorporation of readily available enantiopure amine subcomponents, bypassing the multistep synthesis of enantiopure organic ligands such as catechols.¹⁵ This strategy has not only enabled the isolation of enantiopure mononuclear complexes,^{16–18} helicates,¹⁹ tetrahedral capsules,^{20–22} and interlocked structures^{11,12} but also provided useful platforms to study the mechanisms by which stereochemical information is relayed within these frameworks,^{20–22} a phenomenon of fundamental interest.^{23,24}

2.1. Mononuclear Complexes and Helicates

By using the subcomponent (*S*)-3-amino-1,2-propanediol in the formation of Cu^I mononuclear complex **1**, the transfer of stereochemical information from ligands to metal was observed to depend upon solvent effects (Scheme 1).¹⁶ Circular

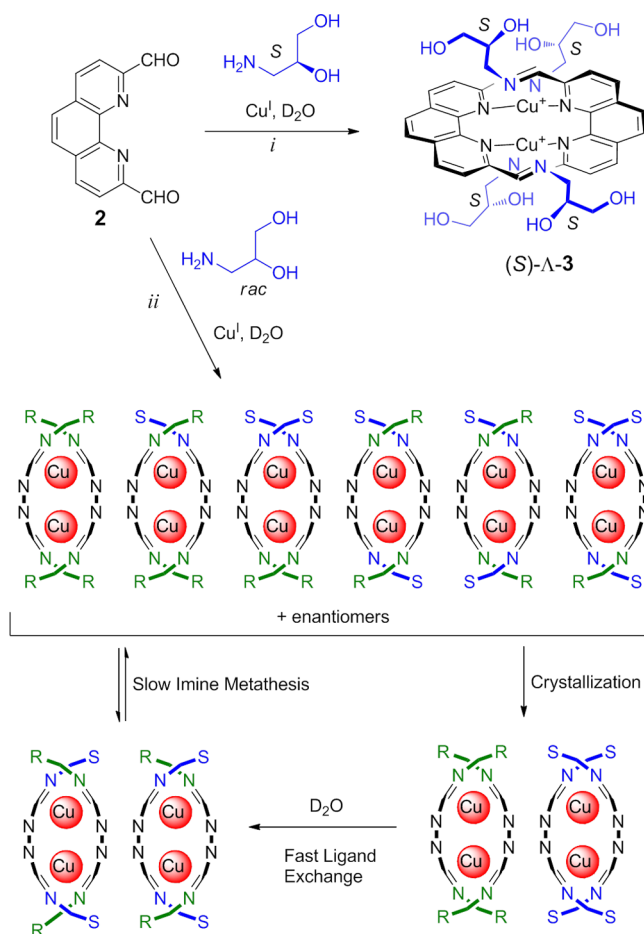
Scheme 1. Postulated Structures of **1** in DMSO (left, Λ Predominating) and CH₂Cl₂ (right, Δ Exclusively)



dichroism (CD) and NMR analyses indicated that in DMSO one diastereomer ((*S*)- Λ -**1**) was present in 20% excess, whereas in dichloromethane the diastereomer with opposite metal handedness ((*S*)- Δ -**1**), was observed. This diastereoselectivity was attributed to the difference in hydrogen-bond acceptor strength of the solvents: in dichloromethane, intramolecular hydrogen bonds rigidify the structure, leading to efficient chiral induction, whereas in DMSO hydrogen bonding with the solvent leads to an equilibrium geometry favoring the opposite metal center handedness.

The incorporation of enantiopure (*S*)-1-amino-2,3-propanediol and dialdehyde **2** into dicopper double helicate **3** resulted in quantitative induction of the helicate's twist, affording one single diastereomer (Scheme 2).¹⁹ The use of the racemic

Scheme 2^a



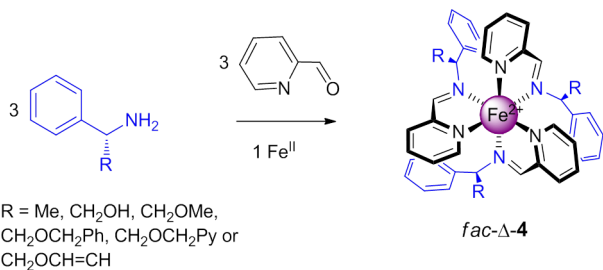
^aRoute i, synthesis of stereochemically pure helicate (*S*)- Λ -**3**; route ii, formation of the dynamic library of diastereomers of **3**, self-sorting into a single pair of enantiomers upon crystallization and proposed two-stage ligand and imine exchange following redissolution of the crystals.

amine, however, afforded a dynamic library consisting of the six possible diastereomeric pairs. This mixture self-sorted during crystallization into a single pair of enantiomers, which formed a hydrogen bonded network, which crystallized preferentially.¹⁹ This process reverted upon redissolution through initial fast ligand exchange followed by slower imine metathesis (Scheme 2). Recently, helicate (*S*)- Λ -**3** has found application in the generation of homochiral surface-confined double helical polymers through a multicomponent assembly process. The chirality of the surface-bound polymers allowed for the enantioselective recognition of the neurotransmitter 3,4-dihydroxyphenylalanine (DOPA).²⁵

In 2009, Scott and co-workers reported a novel and efficient method to prepare stereochemically pure tris-chelate complexes of octahedral metal ions. The subcomponent self-assembly of enantiopure phenylethylamine derivatives and 2-formylpyridine around Fe^{II} afforded optically pure *fac* isomers of tris-(iminopyridine) complexes of Fe^{II} following thermodynamic

equilibration, so no chiral separations were required (Scheme 3).¹⁷ This remarkable stereoselectivity originates from a

Scheme 3. Subcomponent Self-Assembly of Single Diastereomer Complexes 4



combination of steric effects and the presence of three sets of interligand parallel-offset π -stacking interactions. The looser coordination spheres of other first-row transition metals showed less efficient interligand π - π stacking, leading to lower diastereoselectivities.¹⁸ In further work, the authors applied this strategy to assemble water-soluble, optically pure “flexicates” (flexible helicites), which exhibited specific interactions with DNA and promising antimicrobial activity.⁸

2.2. Chiral Communication within Tetrahedral Cages

There is considerable interest in obtaining enantiopure metal–organic capsules,^{15,26–31} which can provide chirotopic inner phases for enantioselective guest recognition and sensing as well as stereoselective transformations.^{15,26–28} The incorporation of chiral amine residues, known to induce a single handedness in the related mononuclear complexes (see above), allowed for the straightforward preparation of stereochemically pure tetrahedral cages.^{20–22,32} Although other coordination assemblies have been synthesized from enantiopure organic ligands, we restrict our discussion to those structures prepared through subcomponent self-assembly, because the versatility of this technique has enabled us to explore the degree to which stereochemical information can be transmitted from one part of a structure to another.^{20–22} A more thorough discussion of the stereochemistry of metal–organic capsules is presented in other reviews.^{32,33}

Cage 6 assembles from 12 equiv of 1-phenylethylamine, 6 equiv of 6,6'-diformyl-3,3'-bipyridine (5), and four Fe^{II} ions (Figure 1a).²⁰ The use of the *S* enantiomer of 1-phenylethylamine brought about the formation of the single diastereomer (*S*)- $\Delta\Delta\Delta\Delta$ -6. The imine exchange reaction also allowed for the cage-to-cage transformation from racemic 7 to enantiomerically pure 6 through substitution of the more electron-poor toluidine residues at the periphery of cage 7 with the more electron-rich (*S*)-1-phenylethylamine. Sergeants-and-soldiers and majority rules experiments showed stronger nonlinear effects in this transformation than those observed in a mononuclear model complex (Figure 1b): only one or two chiral subcomponents incorporated in the cage framework were enough to induce all of the cage's Fe^{II} stereocenters to adopt the same configurational twist, and cage 6 was formed with a greater degree of stereochemical excess at the Fe^{II} stereocenters than the ee of the amine subcomponent used. This observation implies that the bipyridine linkers mediate cooperative stereochemical communication among the four metal centers in the tetrahedral structure, an effect absent in the mononuclear complex.²⁰ In a subsequent report, this stereochemical

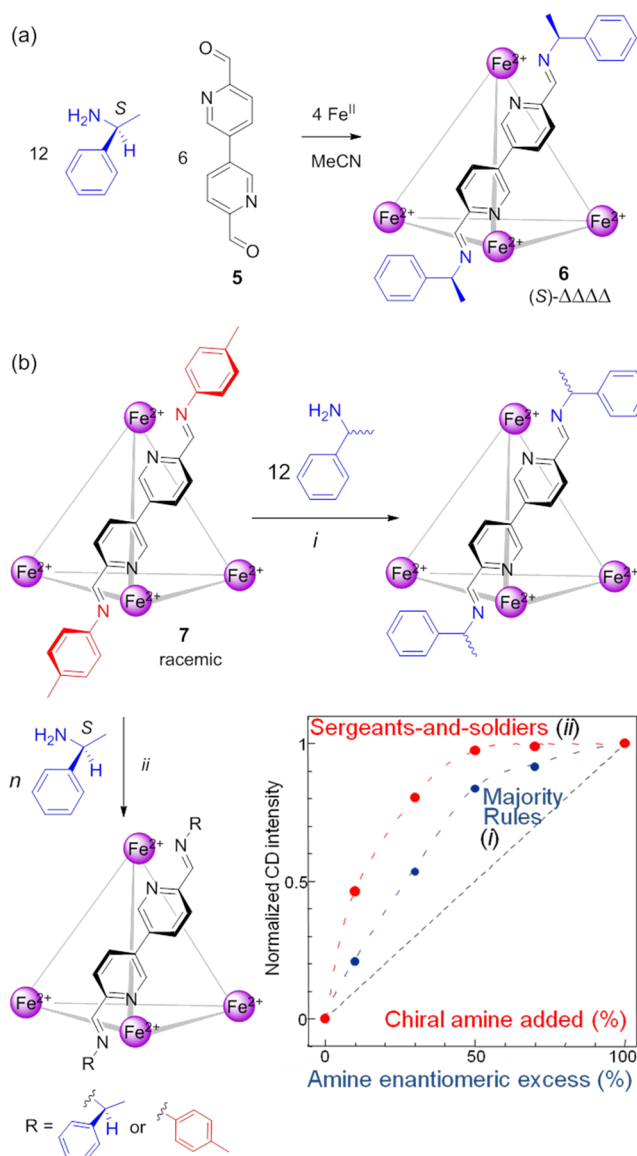
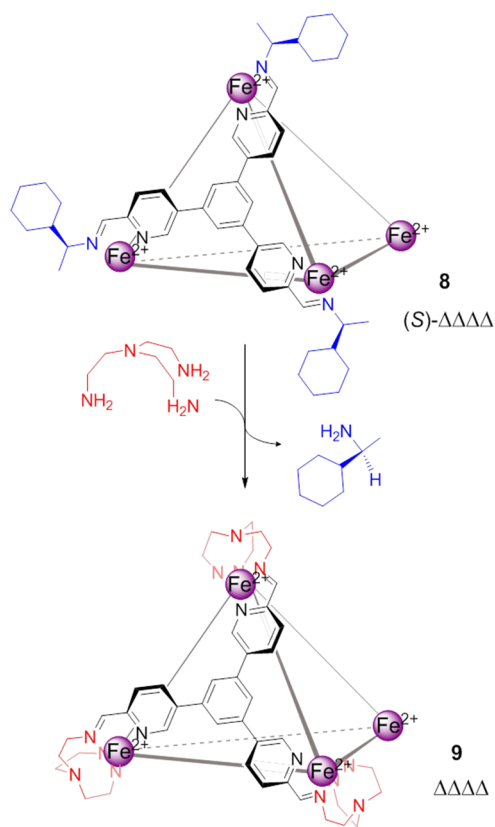


Figure 1. (a) Diastereoselective formation of tetrahedral cage 6; (b) conversion of racemic 7 into cage 6 and plots of normalized CD intensities at 610 nm for 6 with 1-phenylethylamine as a function of the % ee of 1-phenylethylamine (majority rules experiment, route i) and as a function of (*S*)-1-phenylethylamine content (sergeants-and-soldiers experiment, route ii).

communication was found to take place even in the larger cages, with Fe–Fe distances exceeding 2 nm (see below).²¹

As a consequence of the understanding gained of the cooperative chiral communication between metal centers in tetrahedral assemblies, we were able to achieve the enantioselective synthesis of a face-capped tetrahedron that contains no fixed carbon stereocenters via a chiral memory effect (Scheme 4).²² Systems with chiral memory are able to retain the information first imprinted by a chiral auxiliary after its removal or replacement, the key step in this strategy.^{29,34,35} Fe₄L₄ capsule 8, based upon a tritopic trialdehyde subcomponent, was prepared diastereoselectively through the incorporation of an enantiopure amine residue, (*S*)-1-cyclohexylethylamine. This amine was displaced by achiral tris(2-aminoethyl)amine (tren), while maintaining the stereochemistry of the cage framework (Scheme 4). In the presence of free Fe^{II} in solution

Scheme 4. Enantioselective Synthesis of Cage 9 through the Chiral Memory Effect



(to suppress the dissociation of cage 8 during the substitution reaction), cage 9 was isolated with 99% enantiopurity, which was retained even after extended heating. Mechanistic studies indicated the memory displayed by this capsule to be the result of the effective stereochemical communication between the metal centers mediated by the rigid 3-fold-symmetric faces, in combination with a stepwise substitution mechanism.

The subcomponent self-assembly method has also proven effective for the construction of topologically complex molecules with interlocked and intertwined subunits.^{11,12} A discussion of these structures is beyond the scope of the present Account, but it is worth noting that subcomponents with fixed chiral centers have also been used to control the stereochemistry of these structures. An enantiopure Borromean link¹² and pentameric cyclic helicate¹¹ have been reported by the groups of Stoddart and Leigh, respectively.

3. COMMUNICATION OF STEREOCHEMICAL INFORMATION WITHIN SYSTEMS HAVING NO "FIXED" STEREOCENTERS

In another line of enquiry, we seek to understand stereochemical communication between configurationally labile metal centers connected through rigid organic ligands in three-dimensional architectures prepared through subcomponent self-assembly. In this context, we have explored the mutual influences between metal-centered stereochemistry and ligands with axial or helical chirality.

3.1. Metal-Directed Orientation of Helices

In collaboration with Ivan Huc's group, we demonstrated subcomponent self-assembly to be an efficient approach to

assemble helically folded, aromatic–amide oligomers and to set their relative orientations, as with a peptide turn, but at different angles. The pseudo-tetrahedral Cu^I complex 10 (Figure 2a) assembled from amine-functionalized tetrameric

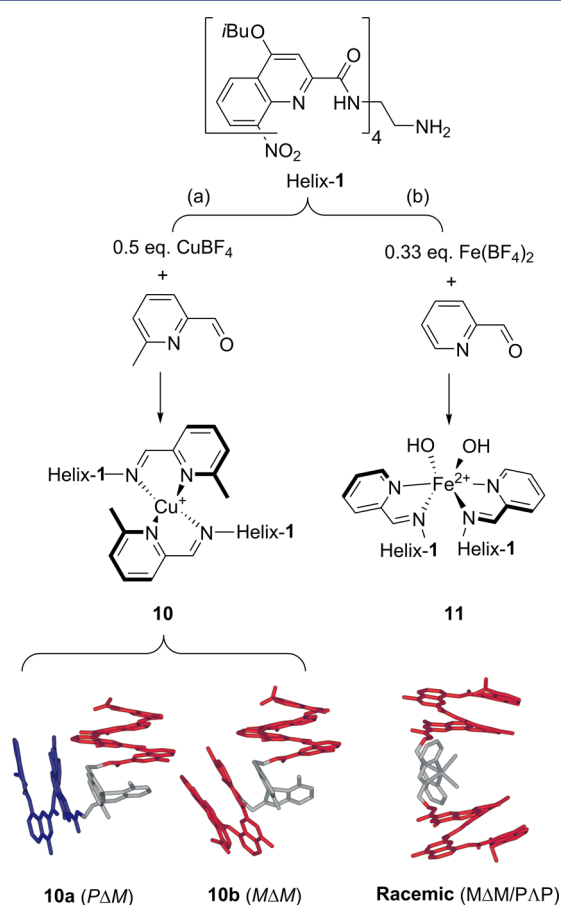


Figure 2. Formation of (a) Cu^I (**10**) and (b) Fe^{II} (**11**) complexes from the tetrameric helix 1 subcomponent and their X-ray structures, showing the orientation of helices in each complex (*M* helices are shown in red and *P* in blue).

helix 1. Complex **10** was found to exist as a mixture of three diastereomeric pairs of enantiomers: *P*Δ*M*/*P*Δ*M* (**10a**), *P*Δ*P*/*M*Δ*M* (**10b**), and *P*Δ*P*/*M*Δ*M* (**10c**), where *M* or *P* refers to the handedness of the helical segments and Δ or Λ designates the configuration of the metal center. The X-ray structures of racemic **10a** and **10b** diastereomers revealed the geometry of the Cu^I complex to dictate an unusual, roughly perpendicular, orientation between the two helices (Figure 2a). In contrast, the use of Fe^{II} as metal template resulted in the helices orienting in a roughly linear fashion (Figure 2b). X-ray crystallography confirmed the formation of a racemic *M*Δ*M*/*P*Δ*P* Fe^{II} complex **11** bearing only two helix-iminopyridine ligands as well as two hydroxide counterions bound directly to the metal center. The two hydroxide ligands appeared to play a role in orienting the helices in a parallel fashion by preventing them from folding back on the iminopyridine moieties.³⁶

3.2. Stereochemical Communication between Vertices of Polyhedra

The utilization of octahedral metal ions (such as Fe^{II}, Co^{II}, Zn^{II}, Ni^{II}, or Cd^{II}) in subcomponent self-assembly has generated a wide variety of high-symmetry architectures with *fac*-coordi-

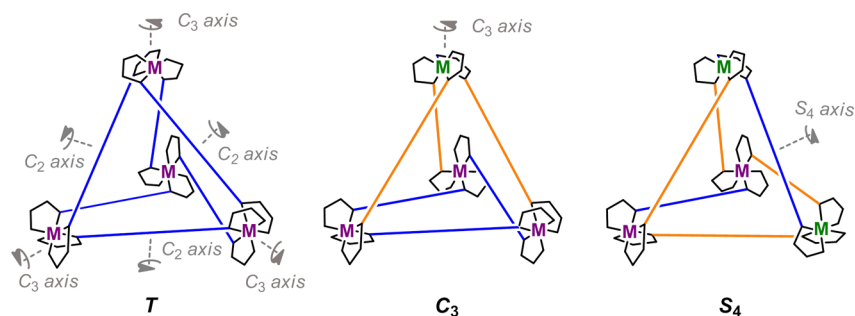


Figure 3. Representation of the three diastereomers of a tetrahedral M_4L_6 capsule. Purple (Δ) and green (Λ) metal centers are of opposite stereochemical configuration, blue lines represent *anti*-linkages between homochiral metal centers, and orange lines represent *syn*-linkages between heterochiral metal centers. Reproduced from ref 39. Copyright 2011 American Chemical Society.

nated vertices, including M_3L_3 and M_3L_3 helicates,^{37,38} M_4L_6 and M_4L_4 tetrahedra,^{4,20–22,37,39,40} and M_8L_6 and M_8L_{12} cubic cages.^{41–44} Our research on the transfer of stereochemical information between vertices of polyhedra has focused on M_4L_6 tetrahedral cages, because they have been observed to exhibit the richest stereochemistry.^{32,45} Depending on the Λ or Δ configuration of each metal center, a tetrahedral ensemble (M_4L_6 or M_4L_4) can adopt homochiral T ($\Lambda\Lambda\Lambda\Lambda/\Delta\Delta\Delta\Delta$), heterochiral C_3 ($\Delta\Delta\Delta\Lambda/\Lambda\Lambda\Lambda\Delta$), or achiral S_4 ($\Lambda\Lambda\Delta\Delta$) overall symmetry, as shown in Figure 3 for the M_4L_6 case. These three diastereomers (plus their enantiomers) exist in a statistical distribution (12.5%, 50%, and 37.5%, respectively) in solution if the metal centers do not influence each other stereochemically.

An initial inquiry aimed to control the stereochemistry of a series of terphenyl edged Fe_4L_6 cages (16–19, Figure 4)

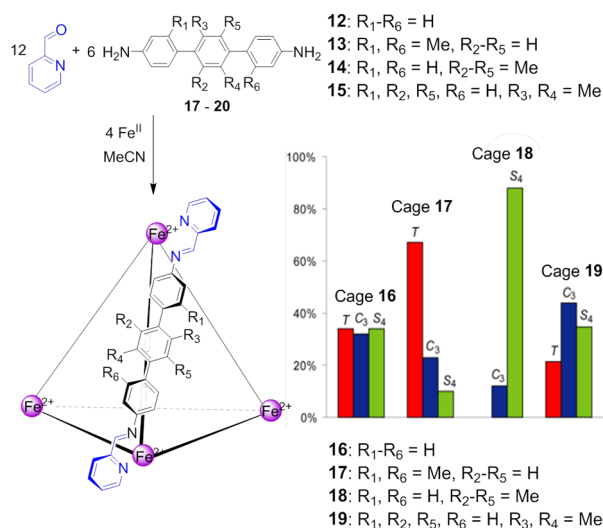


Figure 4. The self-assembly of tetrahedral cage complexes 16–19, which expressed different equilibrium distribution of diastereomers at 298 K. Reproduced with permission from ref 32. Copyright 2014 The Chemical Society of Japan.

through subtle ligand tailoring.³⁹ Cage 16 prepared from *p*-terphenyldiamine 12 exists in solution as a roughly equal mixture of the three cage diastereomers. Such small deviation from a statistical distribution reflects the presence of only slight stereochemical coupling between metal centers. Methylated terphenyl derivatives (13–15) were utilized in the preparation of cages 17–19 to investigate how variations in the methyl groups' placements influenced stereochemical communication

between metal centers and therefore the diastereomer populations (Figure 4). The T -symmetric diastereomer was observed to predominate (17) when 2,2''-dimethylterphenylenediamine (13) was used, whereas the S_4 cage diastereomer (18) was generated predominantly with the use of 2',3',5',6'-tetramethylterphenylenediamine (14); the use of 2',5'-dimethylterphenylenediamine (15) produced the C_3 -symmetric cage (19) to a greater degree than the other two diastereomers (Figure 4). The relative spatial arrangement of the terminal phenylene rings in dianilines 12–15, as influenced by the methyl groups' steric effects, preferentially stabilized the *syn* or *anti* orientation of the ligands and thus the distribution of the three diastereomers, which contain different proportions of *syn* and *anti* ligand orientations.

Following on from insights gained in the previous study,³⁹ subsequent work demonstrated a method of systematic symmetry-breaking within a series of M_4L_6 cages through modification of linker geometry (Figure 5).⁴⁰ The use of rigid

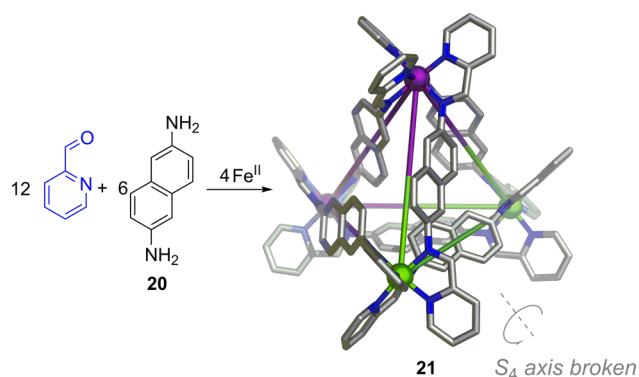


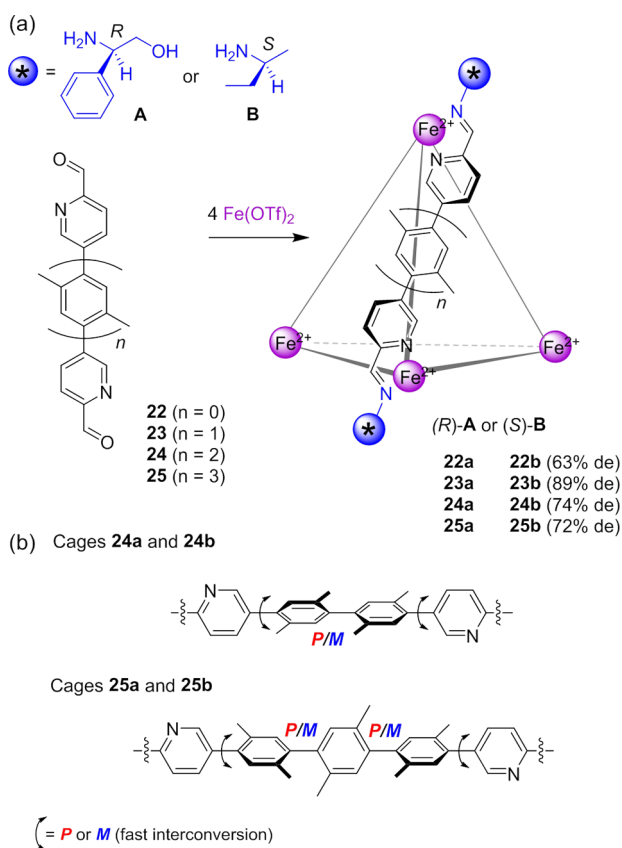
Figure 5. The self-assembly of 21 yielded an S_4 -symmetric framework that contains two Δ (purple) and two Λ (green) Fe^{II} metal vertices, wherein the S_4 axis was broken by the ligands' geometry, yielding a cage with no symmetry.

diamine 20 was predicted to form an S_4 -symmetric framework because the enforced coplanarity of the two terminal phenyl rings of the spacer favored the *syn* ligand arrangement that predominates for S_4 -symmetric M_4L_6 structures. The offset geometry of the naphthyl spacers of 20 caused them to adopt an arrangement within cage 21 whereby within each ligand one ring is orientated inward, roughly toward the center of the cage, and one ring points outward; the S_4 symmetry axis is thus broken with an offset introduced between the two coordination sites within the same linear bis-bidentate ligand, and the cage is therefore asymmetrical, albeit racemic. The generation of larger

asymmetrical cages in enantiopure form, in order to enantioselectively encapsulate asymmetrical guests, is a high-value goal.

In collaboration with the Stoddart group, we aimed to investigate the stereochemical communication and cooperativity within a series of large Fe_4L_6 cages incorporating both flexible axial stereochemical elements in the cages' edges and fixed stereocenters in the amine residues at the vertices (Scheme 5).²¹ These optically active cages were prepared from

Scheme 5. (a) Diastereoselective Formation of Tetrahedral Fe_4L_6 Cages 22a–25a (Enantiopure) and 22b–25b (de Indicated) and (b) Possible Axial Conformations of Each Ligand in the Cages



linear 5,5'-bis(2-formylpyridines) incorporating varying numbers ($n = 0-3$) of oligo-*p*-xylene spacers (22–25) and either a bulky chiral amine residue (cages 22a–25a) or less bulky chiral amine residue (cages 22b–25b). The moderate barrier to bond rotation between the xylene rings leads to slow interconversion between *P* and *M* axial conformations of the ligands on the NMR time scale, which allowed us to infer details as to the axial conformations of the xylene ligand moieties in the cages. Although cages 24a,b and 25a,b have Δ -stereochemistry at each Fe^{II} center induced by the enantiopure amines (A or B), their ^1H NMR spectra presented a large number of peaks, which we attributed to different axial conformations (many possible diastereomers exist for each cage; for 24, $\Delta\Delta\Delta\Delta$ - $(PPPPPP)$, $(PPPPPM)$, $(PPPPMM)$, $(PPPPMM)$, and so on). The preferential formation of only one diastereomer (or rapid rate of axial isomerization on the NMR time scale) should produce only one set of ^1H NMR peaks. The Fe^{II} -centered configuration thus did not dictate the ligands' axial config-

urations, that is, no gearing effect was observed between cage vertices and edges. This study also revealed that the length of the ligands in these cages had only a moderate impact upon the chiral information transfer between Fe^{II} stereocenters; effective communication of stereochemistry was observed even in the larger cages with $\text{Fe}-\text{Fe}$ distances >2 nm.

We attributed this unexpected long-range communication to a thermodynamic preference for the *T*-symmetric cage framework, shown by cages constructed from linear 5,5'-bis(2-formylpyridines). This situation contrasts with our observations for cages formed from linear dianiline derivatives, which appear to favor the three diastereomers equally, as discussed above. Based on molecular modeling studies, we postulate this divergent behavior to be due to differences in the linker's degree of offset (Figure 6).²¹ There is a difference in

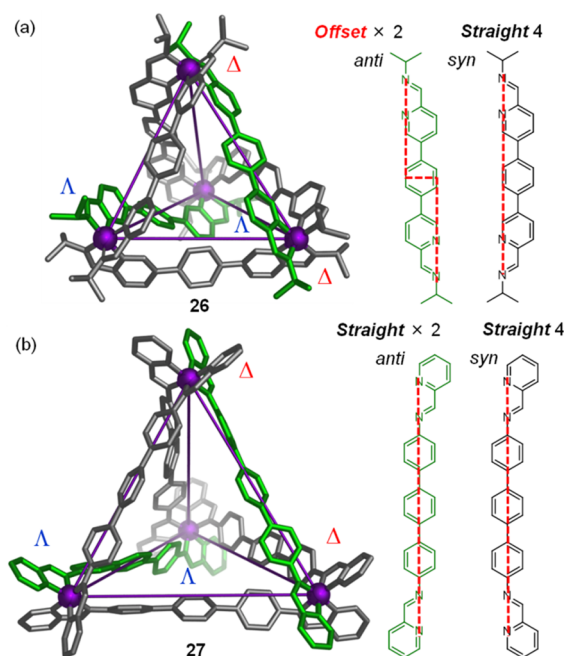


Figure 6. Molecular models of the S_4 -symmetric diastereomer of tetrahedral cages assembled from linear (a) bis-formylpyridine and (b) dianiline derivatives.

metal–metal distances between the *syn*- and *anti*-conformations of the ligands based on bis-formylpyridine in cage 26, which is present to a lesser extent in the dianiline ligands of cage 27. As a result the C_3 - and S_4 -diastereomers of cage 26, which contain ligands in both conformations, are more distorted than those in 27, leading to a greater energetic penalty to cage 26 adopting these diastereomers than that for 27. The *T*-diastereomer, in contrast, has symmetry-equivalent metal–metal distances in both 26 and 27, suffering from no distortion. This stronger cooperative stereochemical coupling for 26, thus, originates from geometric effects within the framework as a whole.

4. STRUCTURAL COMPLEXITY THROUGH STEREOCHEMICAL DIVERSITY

4.1. Copper Tubes

The use of tetrahedral Cu^{I} as a metal template in subcomponent self-assembly has generated a variety of 2D structures, such as grids,⁴⁶ helicates,¹⁹ polymers,² and a three-dimensional host.⁴⁷ This host provides an illustrative example

of how the stereochemistry of the ligand arrangement around the metal centers plays a key role in defining the cavity of the structure and therefore its host–guest behavior (Figure 7).⁴⁷

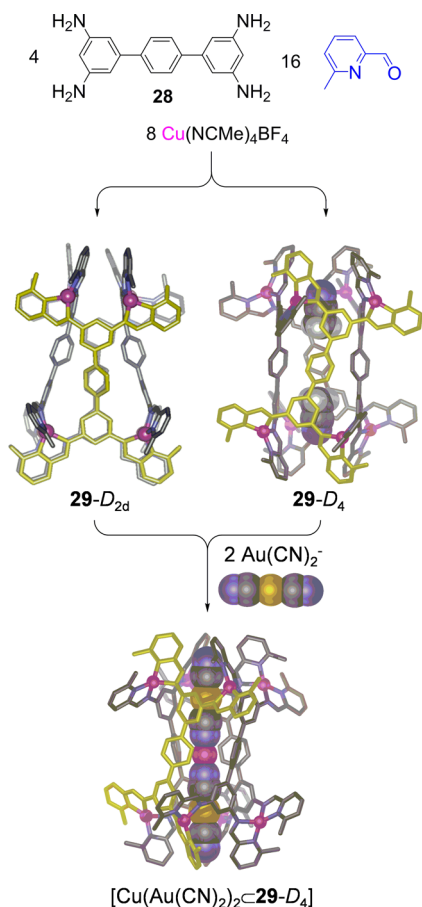


Figure 7. Subcomponent self-assembly of the two diastereoisomers of Cu_8L_4 complex **29** and the inclusion of $\text{Cu}(\text{Au}(\text{CN})_2)_2^-$ within D_4 -**29**.

The reaction between tetra-amine **28**, 6-methyl-2-formylpyridine, and Cu^{I} in acetonitrile solution afforded a mixture of two isomeric products. X-ray crystallography revealed these isomers to be M_8L_4 tube-like structures with approximate D_{2d} and D_4 point symmetries, in which the Cu^{I} ions define the vertices of elongated cuboids having different ligand conformations (**29- D_{2d}** and **29- D_4**). In **29- D_{2d}** , the arrangement of the ligands eliminates the internal void volume. In contrast, **29- D_4** approximates a right square prism in which one of the square faces is twisted by 40° with respect to the other. This ligand arrangement results in a narrow tubular channel having a radius of ca. 2.1 Å and a volume of 193 Å³, in which two acetonitrile molecules were found to be encapsulated in the crystal. The addition of a suitable linear guest, $\text{Au}(\text{CN})_2^-$, to a solution of **29** produced a new host–guest species, which was identified as $[\text{Cu}(\text{Au}(\text{CN})_2)_2^- \text{C} \text{29-} D_4]$, wherein the central Cu^{I} was obtained from destruction of a portion of the host if further Cu^{I} was not added. The diastereoisomer population of **29** in solution thus shifted toward the D_4 isomer to generate the lowest energy host–guest configuration, which stabilized an otherwise unstable guest.

4.2. Cubic Cages

In addition to defining the vertices of tetrahedral capsules, octahedral metal centers having *fac* stereochemistry may be

used to generate cubic structures from carefully designed subcomponents. Several face-capped M_8L_6 cubic structures have been prepared from fourfold-symmetric tetrakis-bidentate ligands,^{41–43} in which eight tris(pyridylimine) Fe^{II} vertices all had the same Δ or Λ stereochemistry. An edge-bridged Fe_8L_{12} cube was also prepared from a bidentate, linear ligand in which the coordinate vectors were forced into an obtuse orientation of ca. 120° . The subcomponent self-assembly of 3,3'-diformyl-4,4'-bipyridine **30** and different anilines around Fe^{II} ions thus yielded cubic structure **31** as confirmed by single-crystal X-ray diffraction (Figure 8).⁴⁴ Each metal center of Λ stereochemistry

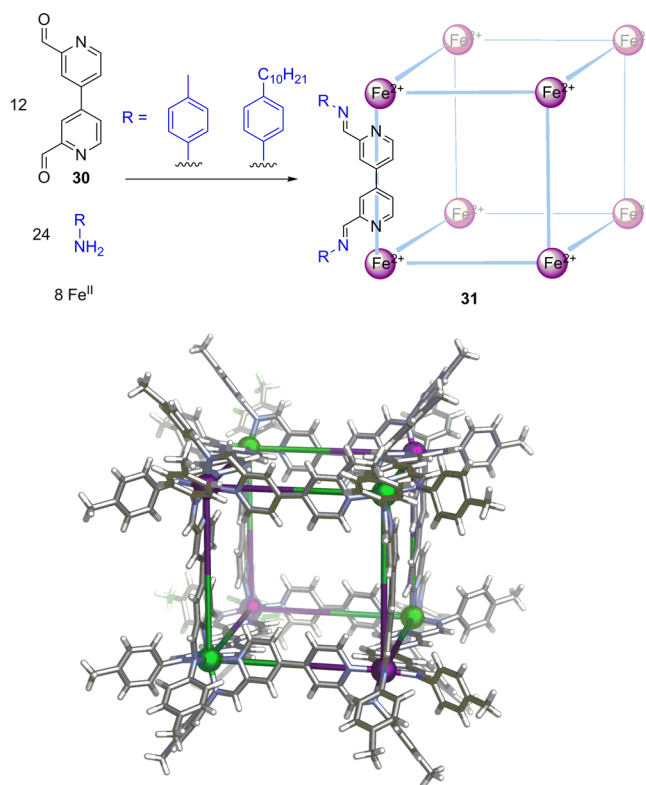


Figure 8. Preparation and X-ray structure of edge-bridged cube **31** with approximate T_h point symmetry; green spheres correspond to Λ stereochemistry, and purple spheres depict Δ .

in **31** was adjacent to three Δ centers and vice versa, lending the capsule approximate T_h point symmetry as opposed to the O (chiral octahedral) point symmetry found for other M_8L_6 ^{41–43} and M_8L_{12} ^{48,49} cube structures. The T_h -symmetrical arrangement for **31**, which forces the bipyridine rings into an eclipsed coplanar configuration, appears to allow the ligands to bow slightly away from the Fe – Fe vectors, relieving strain more effectively than would be possible in an O -symmetric arrangement.

4.3. New Forms through Meridional Stereochemistry

In all of the structures discussed above that are knit together using octahedral metal templates, these metal centers possess uniquely *facial* (*fac*) stereochemistry. The advent of more recent examples containing *meridional* (*mer*) metal centers has resulted in an increase of structural diversity and complexity over what may be obtained using only *fac* stereochemistry, albeit at the cost of predictability. Key foundations were laid by Ward et al., who have shown how the combination of both *fac*

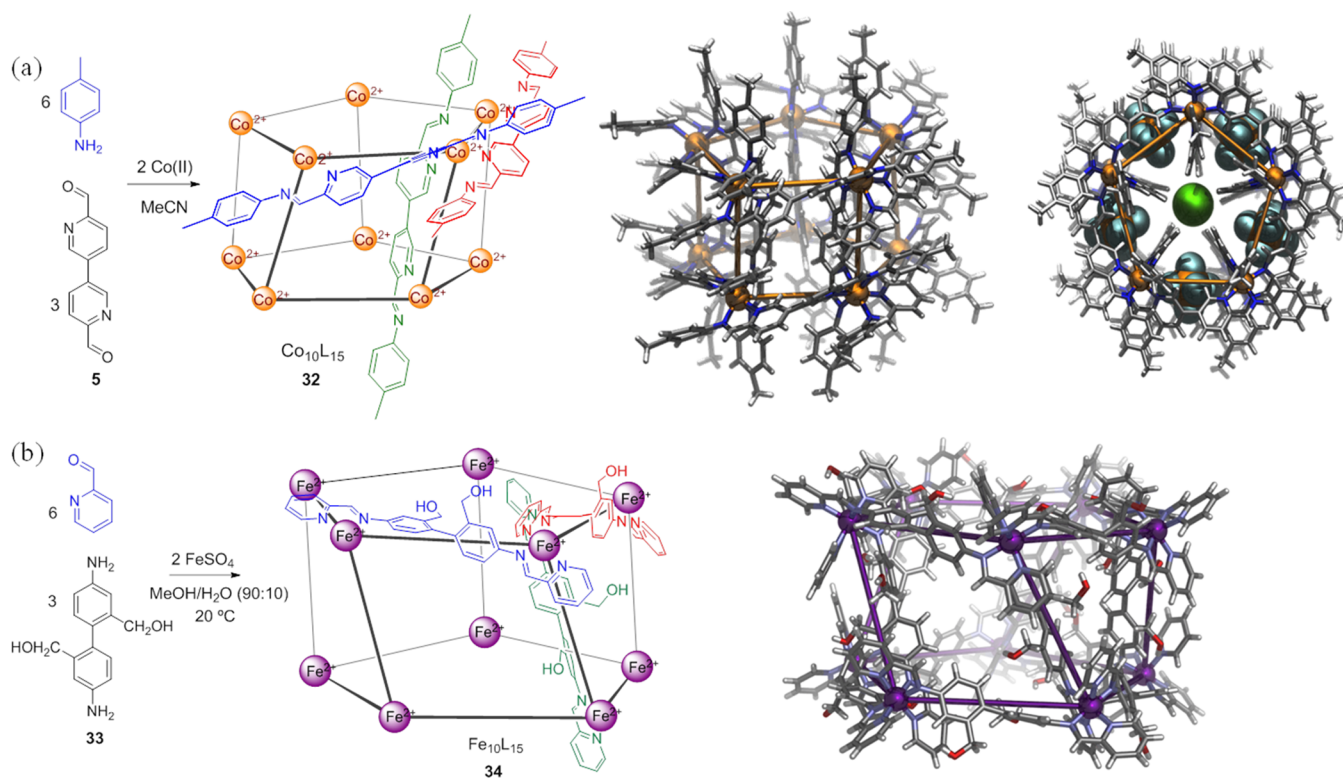


Figure 9. Subcomponent self-assembly and crystal structure of barrel-like structures (a) $\text{Co}_{10}\text{L}_{15}$ (32), showing encapsulated PF_6^- and Cl^- , and (b) $\text{Fe}_{10}\text{L}_{15}$ (34).

and *mer* stereochemistries with flexible ligands leads to the formation of highly intricate structures.^{48,49}

We first reported the self-assembly of a $\text{Co}_{10}\text{L}_{15}$ pentagonal prism (32) from a more rigid ligand than Ward's (formed from 6,6'-diformyl-3,3'-bipyridine, 5, and *p*-toluidine subcomponents), in which the octahedral Co^{II} centers are *mer* coordinated.⁵⁰ X-ray crystallography revealed a barrel-like structure with idealized D_5 point symmetry that consists of two Co_5L_5 circular helicates stacked one above the other, bridged by five additional axial ligands (Figure 9a). The interweaving of the ligands creates six anion-binding pockets. Five such pockets are located between the two pentagonal rings and are occupied snugly by anions, such as ClO_4^- , PF_6^- , or BF_4^- . A sixth pocket in the central channel of the structure was found to bind chloride with high affinity (Figure 9a). We determined that while the former anions serve as first-order templates for the pentagonal prism, chloride binding is the result of second-order templation and is not required to stabilize the structure. In addition to Coulombic attraction between the anion templates and the Co^{II} cations, the structure is further stabilized by extensive π - π stacking between ligands.

The serendipitous discovery of 32 and rationalization of the driving forces for its formation motivated a more systematic study into the metal and anion templation effects in the outcome of self-assembly reactions with rigid ligand 5.⁵¹ Templation effects could be optimized to stabilize *mer* stereochemistry over *fac* to prepare pentagonal prisms also from Fe^{II} , Ni^{II} , and Zn^{II} , as well as other new structures having mixed metal stereochemistry: an S_4 -symmetric M_8L_{12} ($\text{M} = \text{Co}^{\text{II}}$, Ni^{II} , or Zn^{II}) distorted cuboid, having four *fac* and four *mer* centers per structure, and a D_2 -symmetric M_6L_8 extended circular helicate ($\text{M} = \text{Ni}^{\text{II}}$ or Zn^{II}), containing four *mer* coordinated metal centers.⁵¹ In a later study, a $\text{Cd}_{12}\text{L}_{18}$

hexagonal prism belonging to the same structural family was also isolated.⁵² Kwong and co-workers have also reported $\text{Cd}_{12}\text{L}_{18}$ and $\text{Mn}_{12}\text{L}_{18}$ hexagonal prisms prepared through subcomponent self-assembly of *m*-xylenediamine and 2-formylpyridine. These structures have overall D_3 symmetry, containing both *fac*- Δ and *mer*- Λ metal centers in a 1:1 ratio.⁵³

A further example of a pentagonal antiprism was prepared from geometrically similar subcomponents to those of 32 (Figure 9b). The Fe^{II} -templated assembly of diamine 33 and 2-formylpyridine in water generated an Fe_4L_6 tetrahedron (with all-*fac* coordination) and also an $\text{Fe}_{10}\text{L}_{15}$ prism (34, with all-*mer* coordination).⁵⁴ Changing the solvent system and temperature was found to enable the selective preparation of each structure and to achieve their interconversion. X-ray analysis revealed a structure for 34 analogous to that of 32, but having longer metal-to-metal distances and a 36° twist between the two parallel Fe_5 pentagons, thus approximating the structure of a pentagonal antiprism. The increased ligand length also results in a more open structure, thereby eliminating the well-defined guest binding pockets observed in the previous architectures.

Metal-organic capsule 36, which is based on an icosahedral array of metal ions, is the largest architecture prepared to date using subcomponent self-assembly (Figure 10).⁵⁵ The tritopic triamine 35 was found to self-assemble with 2-formylpyridine and Fe^{II} to form three different architectures under different reactions conditions: an Fe_2L_3 triple helicate, a face-capped Fe_4L_4 tetrahedral capsule, and $\text{Fe}_{12}\text{L}_{12}$ structure 36. The 12 Fe^{II} centers in 36 form an approximately icosahedral framework with the tris-bidentate ligands capping only 12 of the 20 faces. The C_5 symmetry axes of regular icosahedra are thus lost, lending the structure overall T symmetry. All the Fe^{II} centers in 36 display lower-symmetry *mer* stereochemistry (being all Δ or all Λ within each capsule), in contrast to the *fac* coordination

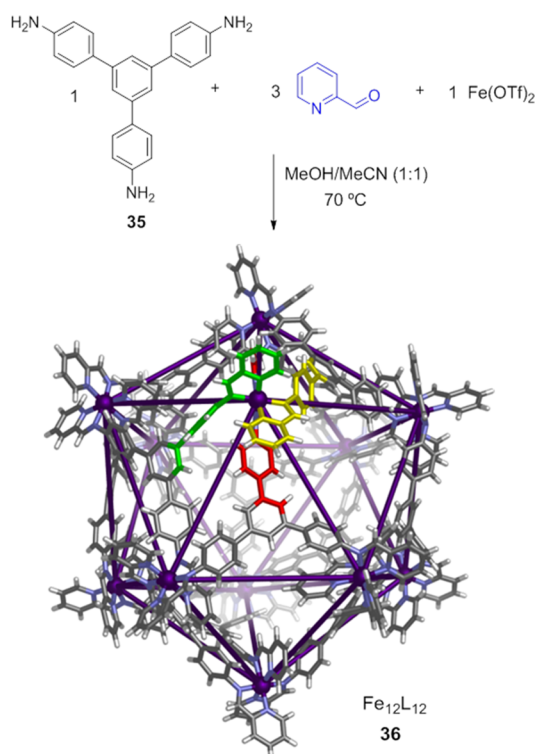


Figure 10. Preparation of icosahedral capsule **36**, showing the crystal structure. The three different ligand environments are highlighted in different colors.

required to define the C_3 axes of the smaller tetrahedral capsule or the helicate. Consequently, despite the incorporation of the same building blocks in the same ratios, differing metal stereochemistry between the observed structures leads to drastic differences in cavity volumes, shapes, and sizes, leading to the selective encapsulation of different guests.

5. CONCLUSION

The potential for error correction provided by the reversibility of the metal–ligand and imine-bond-forming reactions, acting in concert with the geometrically defined metal coordination spheres, make subcomponent self-assembly a particularly powerful technique for the construction of complex chiral structures from simple building blocks. These structures have served as useful platforms for the investigation of aspects of stereochemistry in metal–organic systems. From initial studies of the stereochemistry of mononuclear complexes, this method has evolved to allow the synthesis of an asymmetric capsule, to explore the mechanisms involved in the transfer of stereochemical information within tetrahedral cages, and to allow the enantioselective synthesis of a capsule via chiral memory. The simple change from *fac* to lower symmetry *mer* geometry around a metal center in subcomponent self-assembly has also resulted in an increase in structural complexity and enabled new functions to be exhibited by these intricate structures. In this Account, we illustrate how we have started to understand and progressively replace chance by rational design in the control of stereochemistry during self-assembly, but many of the parameters relating to stereochemical information transfer require further examination. The examples and studies discussed here also provide groundwork to develop yet more complex chiral metal–organic structures and isolate them in optically pure form. The chirotopic inner phases of these

structures can potentially be put to some of the same uses as natural chiral binding pockets, in stereoselective substrate recognition and catalytic transformations.

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Notes

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Biographies

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William J. Ramsay was born in Edmonton, Alberta, Canada. In 2011, he received his B.Sc. (Specialization) in chemistry at the University of Alberta where he conducted research in the area of metallacycle transfer reactions with Eric Rivard. He obtained his M.Phil. under the supervision of Jonathan Nitschke at the University of Cambridge in October of 2012 and is currently working towards a Ph.D. in the same group, focusing on synthesis and host–guest behavior of metallo-supramolecular structures.

Jonathan R. Nitschke was born in Syracuse, New York, USA. He received his bachelor's degree from Williams College in 1995 and his doctorate from the University of California, Berkeley, in 2001 under the supervision of T. Don Tilley. He then undertook postdoctoral studies with Jean-Marie Lehn in Strasbourg under the auspices of a US NSF fellowship, and in 2003, he started his independent research career as Maître-assistant (fixed-term independent PI) in the Organic Chemistry Department of the University of Geneva. In 2007, he was appointed Lecturer at Cambridge, where he now holds the position of Reader (Associate Professor, approximately). His research program investigates the self-assembly of complex, functional structures from simple molecular precursors and metal ions.

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