1. INTRODUCTION

Supramolecular chemistry aims to exploit the intermolecular interaction as an alternative basis for control over chemical reactivity. Where synthetic chemists typically covalently modify functional groups to construct small molecules, supramolecular chemists instead emulate macromolecular catalysts that effect changes on encapsulated substrates. Enzymes often bind their substrates via tailored, hydrophobic cavities, activating them via the cumulative influence of many noncovalent bonds. While these intermolecular bonds are individually fragile and their formation is reversible, in aggregate they can accomplish specific and powerful catalysis, with rate enhancements of $10^{17}$-fold and higher known. In efforts to design and prepare catalysts...

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molecular hosts, despite the first examples of asymmetric induction by supramolecular hosts appearing decades ago.28,29

2. EARLY EXAMPLES OF SUPRAMOLECULAR HOSTS IN CHEMISTRY AND CATALYSIS

Pedersen’s seminal papers on alkali metal complexes of crown ethers are among the roots of supramolecular chemistry as a distinct discipline.30,31 Because the cavities of crown ethers are not strongly hydrophobic, these early supramolecular hosts were not ideal candidates for the encapsulation of organic substrates, instead demonstrating high affinities for alkali metal cations appropriate for their cavity size. Among contemporary molecular structures with defined cavities, cyclodextrins saw the earliest successful applications as simple enzyme models. Cyclodextrins are naturally occurring cyclic oligomers of α-β-glucopyranoside monomers, soluble in water but containing a defined, hydrophobic interior (Figure 1). For the most commonly applied α-, β-, and γ-cyclodextrins (6, 7, or 8 glucose units, respectively), the host cavity is ∼5.6–8.8 Å in diameter. The upper and lower rims of these cylindrical structures contain a network of hydroxyl groups, while the walls of the toroidal molecule bound a hydrophobic cavity. Lyophilic binding of organic substrates of appropriate size was observed in aqueous solution as well as organic solvents, with the orientation of guest molecules controlled by both steric constraint and the polar seam of hydrogen bonds at the cavity boundary.

Cyclodextrins had much to recommend them as supramolecular enzyme mimics: their structure had been unambiguously described by X-ray diffraction studies, and their nonspecific hydrophobic cavities allowed inclusion of varied organic small molecules.32 Kinetic studies of the decarboxylation of cyanoacetic acids by Cramer and Kampe33 demonstrated that organic reactions could be accelerated by inclusion in the cyclodextrin cavity. This catalysis was specific to β-cyclodextrin; the smaller α-cyclodextrin could not encapsulate substrates in a productive conformation. Rate accelerations observed in this study were very small ($k_{cat}/k_{uncat} = 15$), particularly in comparison to enzymatic catalysts. This is due to the nonspecific nature of the host–guest interactions in comparison to those in enzymatic catalysts with their richer variety of functional groups. Studies by Bender and co-workers29,34 established similar findings in the study of ester hydrolysis by cyclodextrins. In the presence of the cyclodextrin host, hydrolysis showed enzymelike kinetics: formation of a host–substrate complex followed by substrate conversion to product. Study of the rates of a variety of these esters within the α-, β-, and γ-cyclodextrins demonstrated that the rate of ester hydrolysis was found to vary not only with the substrate’s hydrophobicity but also with its shape, and rate accelerations ($k_{cat}/k_{uncat}$) as high as 250-fold were observed.

Encapsulation of substrates can also have powerful consequences for the regioselectivity of host-mediation transformations. Breslow and Campbell,35 studying the chlorination of anisole by hypochlorous acid, found that cyclodextrins could be used to manipulate the distribution of products. In the absence of any host, chlorination of anisole gives a mixture of α- and p-chloroanisole. Encapsulation of anisole within α-cyclodextrin, however, shields the ortho sites from substitution due to the specific orientation within the host cavity (Figure 2). The product ratio is dictated by the relative amounts of bound and unbound substrate; by measurement of the association constant and the product distribution, the relative rate of reaction for encapsulated anisole could be measured. For this transformation, $k_{cat}/k_{uncat}$ was $5.6 \pm 0.8$, a measurable but small acceleration of the reaction inside the host cavity. This study importantly demonstrated the potential for simple host structures to echo the properties of enzymatic catalysts, though the catalysis was not particularly efficient. Additionally, while this reaction can also be catalyzed enzymatically, the selectivity of the cyclodextrin-catalyzed reaction is superior,36 highlighting the opportunity for supramolecular enzyme mimics to complement the chemical versatility of enzymes.

With enzymes typically being orders of magnitude more active than these models, efforts to improve these supramolecular enzyme mimics varied both the substrate and host structure. Cyclodextrins’ amenability to specific chemical modification is a marked advantage of these host structures and continues to be a rich area of exploration.11,37 In efforts to improve the activity of cyclodextrins in catalyzing ester hydrolysis, Breslow et al.38 modified β-cyclodextrin through the addition of N-methylformamide substituents along one of the cavity edges. These nonpolar substituents were themselves encapsulated, transforming the toroidal cyclodextrin into a bowl-shaped pocket in order to disfavor dissociation of the substrate. For smaller substrates, including m-nitrophenyl acetate, this modification produced rate enhancements of about an order of magnitude. However, for larger substrates, the occupation of part of the cavity instead retarded the rate of reaction. Breslow’s studies demonstrated that high rate enhancements could be obtained by use of substrates that formed particularly strong inclusion complexes.39 Ferrocene-based substrates were deacylated most efficiently by native β-cyclodextrin, giving as high as million-fold non-catalytic rate enhancements.40

One limitation of the supramolecular catalysis presented thus far is the absence of bimolecular reactions combining two organic substrates. While hydrolytic and substitution reactions have great product ratios...
utility, particularly in biological systems, more complex reactions are essential to generating more sophisticated products. An early example of this kind of supramolecular catalysis comes from the cucurbituril-promoted cycloaddition of azides and alkynes. The cyclic hexamer cucurbit[6]uril was employed to demonstrate that the specific complementarity between host and guest could be applied in the acceleration and control of chemical reactions.40 Cucurbiturils prefer cationic substrates, as the ring of electronegative oxygen atoms interacts favorably with positive charge. Azide 2 and alkyne 3 both contain pendant ammonium groups that promote their encapsulation in 1, with the functional groups predisposed to a 1,3-dipolar cycloaddition inside the host cavity.

Quantitative kinetic study of this catalytic system revealed important enzymelike features (Figure 3c). First, it is possible to saturate the supramolecular catalyst: under high concentrations of 2 and 3, the rate depends only upon the concentration of 1.

Figure 3. (a) Structure of cyclic oligomer cucurbit[6]uril 1, represented schematically at the right. (b) Catalysis of cycloaddition of azide 2 with alkyne 3 in aqueous formic acid, resulting in regioisomers 4 and 5. (c) Cycloaddition of 2 and 3 in the presence of cucurbituril.

Figure 4. (a) Chemical identity of host monomer. (b) Skeleton drawing of capsule, reprinted with permission from ref 44. Copyright 1997 Macmillan Publishers Ltd. (c) Catalyzed Diels–Alder reaction in the cavity of hydrogen-bonded assembly 6.
The rate-limiting step for turnover is release of the product from the host, also a common feature in enzymatic catalysis.\(^{41}\) Through careful kinetic analysis, it is possible to estimate the rate acceleration induced by encapsulation. It is not inappropriate to compare the rate constant \(k_1\), corresponding to formation of the encapsulated product \([4C1]\) (where \(C\) denotes encapsulation within the host cavity) from the ternary complex \([(3-2)C1]\), to the rate constant of the background reaction \((k_0)\), as the latter is a second-order rate constant. An estimate of the catalytic acceleration can be obtained from the ratio \(k_1/k_0\), giving the appropriate second-order constant, and this measure gives a rate acceleration of \(5.5 \times 10^4\) compared to the background bimolecular reaction. Furthermore, the binding constant for incorporation of \(2\) to form the ternary \([(3-2)C1]\) complex \((K_3)\) exceeds the equilibrium constant for dissociation of \(2\) from the empty host \((K_2)\) by a factor of 120. The discrepancy is assigned to strain in accommodating both substrates in the host cavity, and this compressed state is more reactive and further improves the catalytic activity of \(1\) in this cycloaddition.\(^{42}\) More recently, this reaction has been revisited in silico,\(^{43}\) successfully reproducing the acceleration and regioselectivity of the cucurbituril-catalyzed process. This theoretical analysis of the host-catalyzed process identified coencapsulation of the substrates, and thus elimination of the entropic cost to bring the reactants into close proximity, as the basis for catalysis, with no evidence for transition-state stabilization.

While demonstrating that coencapsulation of reagents within supramolecular assemblies can be a powerful promoter of chemical reactivity, this system also suffers from powerful product inhibition, due to the high affinity of the catalytic host for the product. Low catalytic turnover by supramolecular catalysts has been a common limitation in reactions catalyzed by supramolecular assemblies, even as the size and shape of hosts has grown to be increasingly diverse. Prevention of catalytic turnover by strong guest binding has also been observed in the chemistry of guests bound in Rebek’s hydrogen-bonded capsules.\(^{23}\) Host \(6\) self-assembles from two monomers to form a seam of hydrogen bonds, creating a defined inner space (Figure 4). Because the seam of hydrogen bonds is an essential structural element, this “molecular softball” is more sensitive to subtle changes in host geometry, and this was exploited to catalyze the Diels–Alder addition of quinones and dienes.\(^{44}\)

Within the inner space of this cavity, both quinone 7 and Diels–Alder adduct 8 are bound in the host interior. The cycloaddition displays 200-fold rate enhancement within the host cavity, but displacement of the product \(8\) happens slowly, limiting catalytic turnover. This limitation could be overcome by judicious choice of both substrate and host structure. Deep cavitand \(9\) forms a distinct inner space via intramolecular hydrogen bonding, while also having an aperture to facilitate guest exchange (Figure 5). The cavity is strongly hydrophobic, and so the cavitand has a strong affinity for aliphatic guests. The Diels–Alder partners chosen for reaction within this cavitand were adamantylmaleimide \(10\) and anthracene \(11\). Maleimide \(10\) contains an aliphatic handle suitable to promote strong binding by cavitand \(9\), while positioning the maleimide near the hydrogen-bonding network that forms the host’s outer rim. Compound \(11\) shows no affinity for the cavitand interior, while it is reactive toward \(10\) at room temperature. The product of the Diels–Alder addition, \(12\), develops significant steric clash with the host cavity, facilitating product dissociation and allowing this transformation to be conducted with only catalytic quantities (20 mol %) of the host. The rate accelerations are modest (29–57-fold) for maleimides with varied aliphatic binding groups of appropriate size.\(^{45}\)

These selected examples of catalysis by covalent and hydrogen-bonded hosts serve to highlight both successes and recurring limitations of supramolecular hosts in promoting chemical reactions. One necessary tension in constructing efficient catalysts is the balance of substrate binding with exchange. Hosts must possess a chemically distinct inner space to attract substrates, but efficient catalysis also requires that the product be able to readily dissociate from the host structure, favoring assemblies with larger apertures. Achieving high rate accelerations along with efficient exchange has proven to be a persistent problem in the design of catalytic hosts, and we will revisit these challenges in discussing catalysis by supramolecular coordination cages.

3. METALLOSUPRAMOLECULAR HOSTS

3.1. Host Design and Synthesis

In the design of supramolecular assemblies for applications in catalysis, the development of larger and more sophisticated host structures has been an important advance. Self-assembly of symmetric host structures has proven to be a powerful technique for the synthesis of larger assemblies; for organic hosts, this approach is exemplified in the work of Rebek\(^{23}\) and others\(^{46–49}\) with hydrogen-bonded multimeric assemblies. A complementary approach is the use of metal–ligand bonding to construct nanoscale host structures. Labile metal–ligand coordination allows for the most thermodynamically favorable assembly to form, excluding structures with unfavorable geometry or stoichiometry. Careful consideration of component geometry allows for rapid construction of multimeric assemblies. The first discrete structure incorporating metal ions via self-assembly, however, was a consequence of serendipity. In 1988, Salfrank and co-workers et al.\(^{50}\) were studying the application of doubly metalated organic species as versatile synths. Ditopic bis-(magnesium) malonate \(13\) (Figure 6) was prepared from the condensation of diethyl malonate with oxalyl chloride, by use of methylmagnesium bromide as the metalating agent. The product

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**Figure 5.** Structure of Rebek’s deep cavitand, \(9\), shown (a) chemically and (b) as a space-filling model. (c) Cavitand \(9\) catalyzes the Diels–Alder cycloaddition of \(10\) and \(11\). Panel b reprinted with permission from ref 45. Copyright 2007 Royal Society of Chemistry.
of this condensation, however, was remarkably simple. This suggested that the metal salt was highly symmetric, and X-ray diffraction experiments revealed a tetrahedral “adamantoid” complex.

While this particular compound was prepared serendipitously, its synthesis demonstrated that metal–ligand coordination could be used as an organizing force for the construction of symmetric coordination cages with well-defined inner spaces. This particular ligand is much too small to create an inner cavity large enough to encapsulate organic substrates, but with larger ligands this and many other polyhedra can be prepared. To extend this observation to a general strategy, components are selected that contain the elements of symmetry present in the polyhedral compound. Individual components must be rigid in order to block the formation of unwanted geometries and stoichiometries; as long as the metal–ligand bonding is labile, the most thermodynamically favorable structure will be the dominant species.51,52

Employing these supramolecular coordination cages in the manipulation of chemical transformations requires the con-
struction of hosts able to bind small-molecule substrates. Shortly after Saalfrank’s preparation of this adamantoid supramolecular coordination cage, Fujita et al.\textsuperscript{53} reported the inclusion of organic substrates in another metal-containing framework, in this case a molecular square. Noting that many examples of inclusion complexes existed in extended solid-phase inorganic structures, a discrete soluble host was designed that incorporated capped palladium centers and linear bipyridyl ligands (Figure 7). Fujita’s molecular square self-assembles from two components: a cationic, capped (en)\textsuperscript{2+} fragment (en = ethylenediamine) and bipyridyl bridges, which combine in a 4:4 stoichiometry to form 14 (Figure 7). This combination of a rigid linear ligand and a metal complex enforcing a 90° bite angle enforces the square geometry and creates a cavity large enough for small organic molecules. This assembly was found to encapsulate 1,3,5-trimethoxybenzene in aqueous solution, forming a 1:1 inclusion complex.\textsuperscript{55} The encapsulated 1,3,5-trimethoxybenzene can be observed directly by \textsuperscript{1}H NMR, as the encapsulated guest resonances are shifted strongly upfield due to proximity to the quadrupolar aromatic walls of the ligands.

A major advantage of this methodology is its modularity: the geometric constraints of both metal complexes and the organic linkers can be designed to favor particular shapes. The Fujita laboratory has extended the methodology above to prepare an amazing variety of three-dimensional shapes with different metal–ligand stoichiometries and cavity sizes.\textsuperscript{15,54} These coordination cages encapsulate guests ranging in size from small molecules to macromolecular guests including nanoparticles\textsuperscript{55} and the protein ubiquitin.\textsuperscript{56} We will focus on those assemblies that have been applied in chemical transformations, since strategies for the synthesis of complex geometrical structures have been excellently reviewed.\textsuperscript{15,57,58} Studies of catalysis in these assemblies have largely focused on smaller cages of octahedral (15) and square-pyramidal (16) geometries, which are of appropriate size for the incorporation of small-molecule guests (Figure 8). These three-dimensional geometries are available through the use of tripodal tris(pyridyl) ligands, by variation of not only the geometry but also the volume and aperture size of the assembled hosts.

Another family of supramolecular coordination complexes that has been used in supramolecular catalysis is the family of M\textsubscript{4}L\textsubscript{6} tetrahedra designed by Raymond and co-workers. Echoing the structure of Saalfrank’s adamantoid cages, the Ga\textsubscript{4}L\textsubscript{6}\textsuperscript{12−} tetrahedron 17 [L = 1,5-bis(2,3-dihydroxybenzoylamo)-naphthalene] incorporates a ditopic ligand with catecholate moieties separated by planar aromatic spacers, chelated to octahedral trivalent metal centers (Figure 9).\textsuperscript{53} When the metal salt and deprotonated ligand are combined in a 4:6 stoichiometry, the tetrahedral assembly forms spontaneously.

While topologically similar to the octahedral M\textsubscript{6}L\textsubscript{4} cage 15, Ga\textsubscript{4}L\textsubscript{6} assembly 17 has much smaller apertures and an interior more strictly segregated from bulk solution. Tetrahedral host 17 can encapsulate a wide range of monocationic and neutral organic species. Cationic species are strongly bound in a variety of polar solvents: association with the host exterior is driven enthalpically by favorable Coulombic interaction with the −12 charge of the host. Encapsulation in the host interior, while enthalpically unfavorable, is entropically driven by expulsion of solvent from the host cavity.\textsuperscript{59} This entropic effect also drives encapsulation of neutral guests, allowing uncharged species to be encapsulated in aqueous solution.\textsuperscript{60} The cavity of the assembly can vary from approximately 250 to 400 Å\textsuperscript{3} in volume, and guests as small as NMe\textsubscript{4}° and as large as Co(Cp*)\textsubscript{2}° have been encapsulated by 17.\textsuperscript{61}

### 3.2. Stoichiometric and Catalytic Chemistry in Supramolecular Coordination Complexes

Among covalent and hydrogen-bonded supramolecular hosts, Diels−Alder reactions have been successful model reactions for demonstration of host-activated reactivity.\textsuperscript{44,62} Acceleration of a bimolecular Diels−Alder reaction was accomplished with each of two different three-dimensional coordination cages based upon the Pd(en)\textsubscript{2} fragment, 15 and 16. Both cages have favorable π-stacking interactions with aromatic guests, and for this reason substrates 9-hydroxymethylanthracene (11) and N-cyclohexylmaleimide (18) were chosen as Diels−Alder substrates.\textsuperscript{63} For the closed octahedral cage 15, the [11–18C15]\textsuperscript{2+} complex forms stably at room temperature and does not undergo cycloaddition efficiently below 80 °C (Figure 10). At 80 °C, the Diels−Alder reaction of the encapsulated substrates proceeds; the orientation of the substrates is dictated by the cavity environment, and the product of the cycloaddition is the unusual regioisomer 19. The entropic cost of forming ternary complex ([11–18C15]\textsuperscript{2+}) is compensated by the enthalpy of substrate binding, which acts as a thermodynamic sink. Within the cavity of 15, however, the cycloaddition was not efficiently catalytic due to retention of 19 within the cavity of 15, exacerbated by slow exchange of 19 through the pores of the cage.

Remarkably, this problem was averted through the use of open cage 16. With 10% catalyst loading, near-quantitative conversion to cycloadduct 20, the regioisomer ordinarily obtained from Diels−Alder addition of 11 and 18, was observed. Host 16 has a much larger pore for substrate exchange, while π-stacking interactions between the anthracene substrate and assembly walls mitigate the entropic cost of assembling the host and two substrates into a ternary complex. The Diels−Alder cycloaddition then breaks the planarity of the anthracene substrate, promoting dissociation of product 20 to allow catalytic turnover. This was the first example of a supramolecular coordination cage efficiently discerning between substrate and product, allowing weak product binding and efficient catalysis.\textsuperscript{63}

Catalytic turnover was also later achieved by use of supramolecular tetrahedron 17 in the aza-Cope electrocyclization of allylenammonium salts (Figure 11).\textsuperscript{64,65} Allylenammonium cations are tightly bound within the assembly, displacing the more weakly bound NMe\textsubscript{4}° cation readily. Once bound in the cavity of 17, the opposite ends of the substrate, which must come...
together for electrocyclization to take place, are forced into close proximity. Restricting the substrate to a more reactive population of conformations drives cyclization, affording iminium ions that are strongly bound guests inside 17, though the presence of NMe₄⁺ promotes their extrusion from the assembly. Once these iminium cations are hydrolyzed, the product aldehydes cannot compete with the starting material (or the NMe₄⁺ cation) for encapsulation in the host cavity, enabling efficient turnover. Unlike the previous example, here turnover is enabled by a change in the chemical reactivity of the product, rather than a change in the geometry. Because the immediately formed product is vulnerable to subsequent hydrolysis, the secondary product aldehydes can be efficiently expelled from the host, for which they have a much lower affinity than does the substrate.

The scope of this catalysis was general, particularly in comparison to other supramolecular catalytic systems: seven different substrates all showed significant rate accelerations, up to 864-fold, while displaying high conversion and catalytic turnover. This same principle was later extended to the more challenging propargylic enammonium substrates, further demonstrating the scope and versatility of this catalytic system. This process was also unique in circumventing the problem of turnover by use of differently charged substrate and product, leading to large thermodynamic preference for substrate binding to eliminate product inhibition.

The strong affinity of Ga₄I₆⁻ for cationic guests can also drive the protonation of weakly basic species, allowing encapsulation to drive acid-promoted chemistry. This capacity was first exploited for catalysis in the proton-catalyzed hydrolysis of orthoformates (Figure 12). While orthoformates are stable in neutral or basic aqueous solution, encapsulation in 17 promotes protonation of an ethereal oxygen by stabilizing the conjugate acid of these guests. Hydrolysis of the protonated species to the corresponding carboxylic ester is then possible inside the assembly cavity, followed by base- or acid-catalyzed hydrolysis of the ester. The product carboxylates are anionic and are repelled by the assembly, so this catalysis is again largely free from product inhibition due to the change in charge state. Four

Figure 10. (a) Diels–Alder addition of 11 and 18 within the cavity of octahedral supramolecular assembly 15 (host represented by square), yielding unusual regioisomer 19. (b) Catalysis of Diels–Alder addition of 10 and 11 by use of bowl-shaped host 16, yielding regioisomer 20.

Figure 11. Aza-Cope electrocyclization of allylenammonium cations as catalyzed by 17.
different orthoformates could be hydrolyzed catalytically inside the Ga₄L₆ assembly, the largest being trisopropylorthoformate; this substrate also displayed the highest rate acceleration ($k_{cat}/k_{uncat} = 3900$), an improvement upon the accelerations observed in theaza-Cope rearrangement. This methodology was later extended to include the hydrolysis of acetals. Zhang and Teifenbacher have recently reported a related hydrolysis of acetals promoted by a highly acidic ($pK_a \sim 5.5-6$) hexameric resorcinarene capsule.

In order to improve the catalytic efficiencies observed in these transformations, an acid-catalyzed pericyclic rearrangement was targeted in order to obtain large rate enhancements. The Nazarov cyclization of pentamethycyclopentadienol is used in the synthesis of the common ligand pentamethycyclopentadiene (Cp*H), and requires both protonation of a weakly basic alcohol and cyclization of the resulting pentamethyldienyl cation intermediate (Figure 13). This combines the features of both aforementioned catalytic transformations in 17: protonation of the substrate is favored within the cavity of 17, and the subsequent electrocyclization is favored by the constrained environment of the host interior. This synergistic catalysis results in the highest rate accelerations observed thus far in a supramolecular coordination cage, up to 2.1 million-fold. The transition state for water ionization, and possibly that for cation formation, are bound to form a complex in solution. Formation of adduct 26 proceeds poorly (<10% yield) in aqueous solution or methanol, but in an aqueous solution of 24 and 25 with 1 mol % cage 15, the cyclization gives 96% yield of adduct 26 (Figure 15). In contrast to the Diels–Alder reaction earlier, the reactivity of open, square-pyramidal cage 16 is starkly different. While substrate 24 also forms an inclusion complex with coordination cage 16, the condensation proceeds very poorly with this square-pyramidal host under the same conditions. This stands in contrast to studies of Diels–Alder reactions, which are promoted by both supramolecular coordination cages 15 and 16, and demonstrate that geometric changes can have profound consequences for catalytic activity.

3.3. Stabilization of Reactive Species within Supramolecular Coordination Cages

The design of supramolecular receptors and engineering of catalysts are closely linked, as catalysts bind to the transition state of a chemical reaction in a manner analogous to substrate–receptor association. Binding of guests within the cavities of these host structures has the capacity to powerfully perturb chemical equilibria. Noting the strong binding of alkylammonium cations, Raymond and co-workers demonstrated that this preference could allow the trapping of iminium cations in aqueous solution (Figure 16). The disfavored equilibrium between ketone and iminium is shifted by the encapsulation of the iminium cation, though it is ordinarily unstable in aqueous solution. Trapping the iminium species in assembly 17 allows observation of the encapsulated species by $^1$H NMR.

Analogously, the equilibrium between amines and their conjugate acids (protonated ammonium species) can also be perturbed by encapsulation in assembly 17 (Figure 17). The negatively charged hydrophobic cavity of 17 has a strong thermodynamic preference for ammonium cations, driving
protonation. Selective inversion—recovery $^1$H NMR experiments demonstrated that the amines freely exchange between the interior of 17 and exterior association. Rather than acting as a kinetic trap for the protonated species, the host assembly accomplishes the increase in basicity by thermodynamic bias of the amine/ammonium equilibrium. Shifts in basicity as large as 4.5 $pK_a$ units were observed, representing free energy perturbations as large as 6.1 kcal/mol. Compared to shifts in

Figure 13. (a) Nazarov cyclization as catalyzed by 17. Depending on the site of elimination, either the exocyclic or endocyclic isomer of Cp*H is produced.73 (b) Proposed reaction coordinate for host-catalyzed Nazarov cyclization.74

Figure 14. Cyclization of monoterpene citronellal (21), giving diastereomer 23a as the major product in the presence of the Ga$_4$I$_{12}^-$ assembly, while Brønsted acid catalysis instead gives diol 22.
The basicity that has also been observed in different covalent hosts, the basicity increase observed in \( \text{Ga}_4\text{L}_6^{12-} \) are substantially larger, reflecting the host’s greater affinity for cationic guests in preference to neutral organic guests.80–83

An important and potentially practical application of these hosts in stabilizing reactive guest species was the encapsulation of white phosphorus.84 This material is normally explosive upon interaction with atmospheric oxygen, but Nitschke and co-workers were able to sequester it within tetrahedral anionic assembly 27 (Figure 18). The encapsulated \( \text{P}_4 \) molecule is unreactive in the host cavity, as oxygenated intermediates are not able to fit inside the assembly interior. Furthermore, the phosphorus could be extruded readily from the host by replacement with benzene, extracting \( \text{P}_4 \) into the organic phase. Expelled from the confines of the host, \( \text{P}_4 \) is then available for oxidation by atmospheric oxygen to phosphoric acid in the mixed-phase system. While this storage system is inefficient on a mass basis ([\( \text{P}_4\text{C}27 \)] is 3.5% \( \text{P}_4 \) by mass), the water-soluble host is easily isolated from its organic substrate and can be reused. The ability of 27 to serve as a “protecting group” for reactive species was further demonstrated by its ability to prevent the Diels–Alder reaction of maleimide with encapsulated furan. “Deprotection” was then easily accomplished by displacement with an alternative guest (benzene), allowing the reaction to proceed.85

4. TRANSITION METAL CHEMISTRY AND CATALYSTS IN SUPRAMOLECULAR HOSTS

Complementing the design of new host structures, the incorporation of transition metal catalysts can impart new activities to these supramolecular assemblies. The first efforts to integrate transition metal catalysis and supramolecular encapsulation were published by Breslow and Overman in 1970,86 using cyclodextrins as the supramolecular host. Drawing analogy to metalloenzymes, which bind substrates principally by use of hydrophobic pockets as many enzymes do, the authors reasoned that attachment of a suitable hydrophobic host could increase the rate of a transition metal catalyst by binding the substrate near the reactive center. Metalloenzyme model 28 was constructed by covalent attachment of pyridine-2,5-dicarboxylic acid to \( \alpha \)-cyclodextrin (Figure 19), followed by treatment with \( \text{NiCl}_2 \) and pyridinecarboxaldehyde (PCA). The authors then examined the hydrolysis of \( \text{p-nitrophenylacetate} \) by both free nickel complex and artificial metalloenzyme 28. Supramolecular catalyst 28 demonstrates almost 4-fold rate acceleration over the nickel–PCA complex, and this acceleration is not restored by the presence of free \( \alpha \)-cyclodextrin. Furthermore, competitive inhibition of catalysis by 28 is observed in the presence of cyclohexanol, where hydrolysis by the nickel–PCA complex was not affected by addition of cyclohexanol.
As the ligands applied in organometallic chemistry have become progressively more sophisticated, noncovalent ligand−substrate interactions have become common. This necessarily blurs the distinction between different types of supramolecular transition metal catalysts where either complete encapsulation or strong steric shielding drives substrate selectivity and reactivity. Consider the chiral organometallic triangle 29, prepared as a C₃-symmetric ligand by coordination of a ditopic alkyne to cis-capped Pt²⁺ centers (Figure 20). This strategy is certainly akin to the aforementioned work in the Fujita and Stang laboratories, using transition metal complexes and organic linkers of appropriate geometry to prepare geometric 2-D cages. Instead of encapsulating substrates in the cavity, however, a Ti⁴⁺ center was introduced, producing a chiral complex with no clearly defined inner space. While this complex was a versatile and highly enantioselective catalyst, that selectivity is produced by the chiral ligands used to construct 29, rather than being a consequence of encapsulation in a discrete host cavity.

The Reek laboratory has developed a family of symmetric, supramolecular transition metal catalysts with defined cavities for selective catalysis. Self-assembly of C₃-symmetric ligand 31 and zinc porphyrin 30 in a 3:1 ratio yields a free phosphine nested in a symmetric cavity formed by the porphyrins (Figure 21a). This tris(pyridyl)phosphine can be coordinated to a triad of Zn²⁺−porphyrins, creating a cavity with a single phosphine to act as a ligand for transition metal complexes. The organometallic complex chosen to impart catalytic activity was Rh(acac)(CO)₂, and the supramolecular catalyst [(30)₃31]Rh(CO)₃H was active in the hydroformylation of alkenes. This supramolecular catalyst displayed substantially different activity and selectivity in comparison to the porphyrin-free catalyst system when 1-octene was used as a model hydroformylation substrate (Figure 21b). If PPh₃ is instead used as the ligand for the rhodium complex, the catalyst displays a turnover frequency (TOF) of only 6 h⁻¹, while the supramolecular catalyst [(30)₃31]Rh(CO)₃H has a TOF of 126 h⁻¹. Additionally, the
selectivity for branched hydroformylation product 32 versus linear aldehyde 33 is different: the PPh₃Rh(CO)₃H complex gives a 3:1 ratio of linear/branched products, while the supramolecular catalyst [(30)₃(31)]Rh(CO)₃H gives inverted selectivity, favoring the branched aldehyde 32 in a 3:2 ratio. Binding to the cavity of this supramolecular host thus created a spatial environment for the rhodium center that was different enough for the selectivity of this transition-metal catalyzed reaction to be significantly altered.

An important virtue of these multicomponent systems is the ease of generating new structures. By use of the same zinc porphyrin but a different isomer of the tripodal phosphine, the structure of the host assembly can be modified, with significant consequences for catalysis (Figure 22). The [(30)₃4]Rh(CO)₃H complex is more active than the unencapsulated rhodium species and also displays high selectivity in the hydroformylation of internal alkenes. While the unencapsulated rhodium complex is nonselective in the hydroformylation of trans-3-octene at room temperature, the encapsulated transition metal complex forms 2-propylhexanal preferentially in 3:1 ratio over 2-ethylheptanal, the minor product. Further demonstrating the generality of this modular strategy, other hydroformylation catalysts can be prepared by instead altering the structure of the metal complexes used to form the host walls, as the authors have demonstrated by coordination of zinc–salen complexes to form distinct host assemblies.

By application of these same principles, more elaborate multicomponent hosts were designed, taking advantage of the selectivity of different coordinating motifs to engineer complex porphyrin-containing hosts. Phosphite ligand 35, containing three zinc–porphyrin substituents, self-assembles in the presence of 1,4-diazabicyclo[2.2.2]octane (DABCO) to coordinate and encapsulate a transition metal. The rhodium complex of ligand 35 alone is an efficient hydroformylation catalyst,
though it shows poor selectivity in producing linear versus branched aldehydes (2.5:1 ratio). Addition of the monotopic nitrogen donor quinuclidine slightly improves the turnover frequency of the Rh(35)₂ complex, but the selectivity of hydroformylation is slightly worse. Only in the presence of 1.5 equiv of DABCO, allowing for formation of the Rh-(35)₂(C₆H₁₂N₂)₃ complex, is the selectivity improved to give more than a 15-fold excess of the linear product isomer (Figure 23). This establishes the importance of the intact supramolecular assembly for improvement in selectivity; multicomponent systems allow experiments isolating the effect of encapsulation on selectivity and activity.

A related strategy for the incorporation of catalytically active transition metal complexes into supramolecular hosts is exemplified by the work of Lee and Hupp, who used metalloporphyrins as subunits for the construction of supramolecular assemblies. By use of catalytic metalloporphyrins that also contain coordinating substituents, supramolecular coordi-
nation cages can be assembled around the catalytic center to create encapsulated transition metal complexes (Figure 24).\textsuperscript{93} The first such example described was a molecular square \textsuperscript{36}, containing four zinc porphyrins bridged by capped rhenium centers, encapsulating manganese porphyrin \textsuperscript{37}, an established olefin epoxidation catalyst. Encapsulation of catalyst \textsuperscript{36} increases both its activity and its lifetime: turnover number (TON) is increased 10-fold upon formation of the encapsulated complex, and the lifetime under reaction conditions is extended from 10 min to 3 h, though encapsulated \textsuperscript{[37⊂36]} displays a catalytic rate about a third that of the free porphyrin complex. This is not attributed to electronic deactivation of the catalyst but rather the steric hindrance of the host cavity and the restricted exchange of reactants at the catalytic center. Furthermore, replacing manganese porphyrin \textsuperscript{37} with a tetrapodal Mn(III)–porphyrin yields a higher-turnover catalyst (1500 turnovers). This increased lifetime is attributed to the stronger complexation of this porphyrin by the supramolecular host.\textsuperscript{94}

Accrued expertise in the design and construction of these porphyrin boxes has yielded increasingly complex materials. The self-sorting metalloporphyin assemblies of Hupp and co-workers\textsuperscript{95} are among the most complex discrete catalysts developed from these building blocks. Utilizing the differing thermodynamics of metal–ligand interaction, the assembly of metalloporphymins \textsuperscript{38–40} yielded a large, discrete assembly with multiple cavities containing catalytic sites assembled from three different components (Figure 25).\textsuperscript{95} The inclusion of the well-studied Mn–porphyrin catalyst into component \textsuperscript{40} incorporates oxidative catalytic activity into the host, allowing for size-selective oxidation due to sequestration of the catalytic metal center in the host cavity.

The use of metal–ligand coordination to incorporate catalytically active transition metals into supramolecular hosts has thus been an effective strategy for preparing catalysts with unusual selectivity and activity. Only recently, however, has the encapsulation of transition metal catalysts emerged as a strategy for preparing similar catalysts. The first transition metal complexes to be encapsulated were iridium piano-stool complexes incorporated into the Ga\textsubscript{4}L\textsubscript{6} assembly.\textsuperscript{96} Iridium complex \textsuperscript{[Cp\textsuperscript{*}(PMe\textsubscript{3})Ir(Me)OTf] (43, OTf = OSO\textsubscript{2}CF\textsubscript{3} = triflate) is known to activate the C–H bonds of a broad variety of organic substrates at low temperatures, first forming the \textsuperscript{[Cp\textsuperscript{*}(PMe\textsubscript{3})Ir(Me)]\textsuperscript{+}} cation.\textsuperscript{97,98} Efforts to form this active species in aqueous solution by encapsulation in \textsuperscript{17}, however, did not succeed in forming the aquo complex, likely due to the cost of desolvating aquo complex \textsuperscript{[Cp\textsuperscript{*}(PMe\textsubscript{3})Ir(Me)(OD\textsubscript{2})\textsuperscript{+}}. This was circumvented through addition of an ethylene ligand, favoring encapsulation via both increased hydrophobicity of the solvated cation and possibly favorable \pi-stacking with the aromatic walls of the host. Encapsulated iridium complex \textsuperscript{[(44)C\textsubscript{17}]\textsuperscript{+–}} induces quantitative C–H bond activation/decarbonylation of aldehydes able to fit in the assembly cavity (Figure 26). Shape selectivity is also displayed by the encapsulated complex, as isovaleraldehyde is reactive as a substrate while the unbranched valeraldehyde is not. Iridium complexes incorporating other olefins have also been applied in these C–H activations,\textsuperscript{99} and ethers have also been applied as C–H activation substrates, though all reactions are stoichiometric rather than catalytic.

Encapsulation of a catalytically active transition metal catalyst was first accomplished by hydrogenation of a rhodium precatalyst for the isomerization of allylic alcohols.\textsuperscript{100} After it was demonstrated that cationic rhodium precatalyst \textsuperscript{(PMe\textsubscript{3})\textsubscript{2}Rh(COD)*} (COD = 1,5-cyclooctadiene) was encapsulated in \textsuperscript{17}, the catalytically active \textsuperscript{[(PMe\textsubscript{3})\textsubscript{2}Rh(OD\textsubscript{2})\textsubscript{3}]\textsuperscript{C\textsubscript{17}}} species was generated by addition of 1 atm of H\textsubscript{2}. The encapsulated catalyst rapidly isomerizes allylic alcohols and ethers, displaying restricted substrate scope due to the steric restrictions within
the host cavity (Figure 27). The encapsulated catalyst, however, is not stably bound to the host interior; with the hydrogenation of its hydrophobic COD ligand, the cationic rhodium species is much more readily solvated in aqueous solution and is only kinetically trapped by the host. Nonetheless, dissociation of the catalyst does not infringe upon the selectivity of isomerization in the presence of the host.

The first report of a stably bound, active transition metal catalyst was the encapsulation of a gold(I)−NHC catalyst (NHC = N-heterocyclic carbene) in a hexameric assembly of resorcin[4]arene subunits. A network of hydrogen bonds drives the self-assembly of the resorcin[4]arene subunits, creating a cavity with a volume of approximately 400 Å³. Gold complex 46 is bound inside the cavity of the (45)₆ host, occupying only 30% of the host volume, less than the approximately 55% usually optimal for encapsulation. This leaves room for solvent molecules or substrates to access the encapsulated catalyst. The catalytic activity of the [46C(45)₆] complex was studied in hydration of the alkyne 4-phenyl-1-butyne (47). In wet organic solvent, free catalyst 46 promotes Markovnikov addition of water to this terminal alkyne, giving methylketone 48 almost exclusively; under anhydrous conditions, 1,2-dihydronaphthalene is obtained via intramolecular rearrangement (Figure 28).

Encapsulation of complex 46 in assembly (45)₆ radically alters the catalyst’s activity and selectivity. The catalyst is much slower, converting only 5% of 47 in 30 min, while 46 converts the substrate to 48 quantitatively in the same period under the same conditions. While less active, the encapsulated catalyst is capable of anti-Markovnikov addition of water, though Markovnikov addition is still preferred 3:1. Additionally, the “anhydrous” pathway producing 50 is active with the [46C(45)₆] catalyst. This could be due to limited availability of water, or promotion of the intramolecular rearrangement in the confined space of the host cavity. The unusual selectivity of the encapsulated catalyst demonstrates the potential for encapsulation to access

Figure 28. (a) Formation of supramolecular host (45)₆ from six monomeric resorcin[4]arene units. The assembled host encapsulates gold(I)−NHC complex 46. (b) Hydration of alkyne 47 by encapsulated catalyst [46C(45)₆] in wet benzene at 70 °C yields Markovnikov (48, 12%) and anti-Markovnikov (49, 4%) products, as well as intramolecular rearrangement product 50 (12%). Reprinted with permission from ref 101. Copyright 2011 American Chemical Society.

Figure 29. Hydroalkoxylation of allene 51 to yield allylic ether 52 and diene 53.
unprecedented reactivity with established transition metal catalysts.

While it could be anticipated that encapsulation of transition metal complexes in supramolecular hosts might reduce the reaction velocity, encapsulation of the PMe₃AuX (X = Cl, Br) complex in the Ga₄L₆ assembly 17 instead displays more efficient catalysis than the free gold complex. When incubated with assembly 17 in D₂O solution, PMe₃AuX is encapsulated as a mixture of two species, thought to be the cationic PMe₃Au⁺ and hydrated PMe₃Au(D₂O)⁺. These encapsulated catalysts were studied in the hydroalkoxylation of allene 51 to give allylic ether 52 along with small quantities of diene 53 (Figure 29). Remarkably, the encapsulated complex [PMe₃Au⁺⊂17] displays more efficient catalysis, with an approximately 8-fold increase in the reaction rate. This increase in catalytic efficiency upon encapsulation is unique so far but presents the tantalizing possibility that supramolecular encapsulation may be able to make transition metal complexes more active while also imparting chemo- and regioselectivity.

Sequestration of transition metal complexes can also be used to protect or stabilize unstable catalytic materials. This application was demonstrated in the encapsulation of ruthenium piano-stool complex [RuCp(PMe₃)(MeCN)₂]+ in Ga₄L₆, generating a supramolecular transition metal complex (54) capable of high-turnover catalysis in aqueous solution (Figure 30). The unbound ruthenium catalyst is unstable in aqueous solution, decomposing with a half-life of approximately 1 h; solutions of the encapsulated catalyst 54, however, are stable for days. Encapsulation has only minimal effect on the rate of catalysis: supramolecular catalyst 54 displays approximately half the catalytic rate of free complex at the same concentration. The increased lifetime of catalyst 54, however, allows very high catalytic turnover: over 1000 turnovers can be achieved with extremely low catalyst loadings (0.05 mol %). This is itself a particularly strong example of a more general virtue of encapsulated transition metal complexes: where supramolecular catalysts usually require relatively high catalyst loadings, incorporation of transition metal catalysts has provided cases where catalysis with extremely low loadings is possible. A similar impact on catalyst lifetime was recently observed with cubic M₄L₆-encapsulated cobalt porphyrin catalysts. The encapsulated cobalt catalysts gave a turnover number (TON) of 33 for the cyclopropanation of styrene with ethyl diazoacetate, compared with a TON of 9 for an unencapsulated catalyst. Additionally, encapsulation improves the water solubility of the transition metal complex by an order of magnitude, and the improved solubility and stability suggest that this methodology may be more generally applicable in the preparation of “green” catalysts for organic synthesis.

Encapsulation of transition metal complexes also has the potential to stabilize unusual geometries or stoichiometries, as Fujita and co-workers have demonstrated by the encapsulation of a dinuclear ruthenium complex in Pd₆L₄ cage 15. Encapsulation of this complex in Pd₆L₄ cage 15 stabilizes the cis-bridged isomer, confirmed by IR and X-ray crystallography (Figure 31). The unbound dinuclear complex 55 is also quite photosensitive and will decompose under ambient light in a matter of days. The encapsulated complex, in contrast, displays no decomposition under the same conditions. While this complex is not implemented in catalysis, the preferential stabilization of unusual geometries is certain to find application in generating novel supramolecular transition metal catalysts.

More recently, Fujita and co-workers have shown that the Pd₆L₄ cage 15 is capable of simultaneous encapsulation of palladium(II) or platinum(II) halides and organic hydrocarbons. When terminal alkynes were encapsulated with bis(phosphine)-palladium(II) dichloride, activation of the alkynyl C–H bond occurred to produce a palladium acetylide. The authors...
hypothesize that capsule-induced proximity is responsible for the facile sp-C–H activation.

In addition to impacting rates and selectivities, encapsulation of transition metal complexes has the potential to protect the catalyst from detrimental interactions and events. To take advantage of this property, Ga₄L₆-encapsulated gold and ruthenium catalysts were successfully paired with the enzymes with transition metals imparted by encapsulation was clearly demonstrated in the presence of Me₃PAu⁺, indicating that the unencapsulated gold complex interferes (probably irreversibly) with enzymatic hydrolysis. The rate of esterase catalysis was reduced in the presence of Me₃PAuCl, demonstrating that these supramolecular catalysts are compatible with enzymes to enable concurrent tandem catalysis.

5. ENANTIOSELECTIVE SUPRAMOLECULAR CATALYSTS

While size- and shape-based chemoselectivity has certainly been achieved by use of supramolecular catalysts, the engineering of highly enantioselective catalysts has been a much more difficult challenge. As we have returned to several times in this review, important early efforts were made with cyclodextrins as hosts. Because these cyclic oligomers are made of enantiopure monomers, they are promising candidates for enantioselective chemistry. One of the earliest examples of enantioselective supramolecular chemistry was demonstrated by use of a transaminase model constructed by covalent attachment of pyridoxamine (56) to β-cyclodextrin to create supramolecular host 57 (Figure 33). The reductive amination of keto acids 58–60 by free pyridoxamine 56 was studied in the presence of 1 equiv of cyclodextrin. With 56 alone, the three keto acids all display similar reactivities, forming the corresponding amino acids in equal yields under 1:1 competition experiments. In the presence of β-cyclodextrin, aromatic substrate 59 became relatively less reactive than pyruvic acid, due to competitive binding by β-cyclodextrin. Fused catalyst 57, however, reacted approximately 200 times faster with 60 than did 56, while pyruvic acid displayed no change in reactivity between host 57 and small-molecule catalyst 56. Binding to the cyclodextrin cavity drives the reaction, and because the cavity is chiral, it is reasonable to imagine that enantioselectivity could be observed with chiral acids. Two such amino acids were reductively aminated with 57, DL-dinitrophenyltryptophan and DL-dinitrophenylphenylalanine. The former yields only 12% enantiomeric excess while the latter achieves 51% ee, preferring to react with the L enantiomer. Efforts to apply cyclodextrins as both supramolecular hosts and a basis for optical induction have continued with some success, but the enantioselectivities have been modest. Studies of enantioselectivity in other, metal-free supramolecular hosts have also been modest (<60% diastereomeric or enantiomeric excess).

The first reported examples of enantioselective reaction chemistry within a supramolecular coordination cage employed chiral components to generate chiral host structures. Fujita’s supramolecular coordination cages 15 and 16 contain no intrinsic elements of chirality. The capping ethylenediamine units on the metal centers, however, can be replaced with chiral diamines to yield cage 61 (Figure 34). While the element of chirality is on the periphery of the cage structure, the walls of the assembly distort slightly because of this substitution.

This cage was applied to the photochemical [2 + 2] cycloaddition of fluoranthene 62 and N-cyclohexylmaleimide (10), which produces a four-membered ring with multiple chiral centers (Figure 35). Ternary complex [62·10C55]₆ is formed in 60% yield (measured by 1H NMR), and this complex was isolated by filtration to remove excess substrate. Irradiation of the isolated ternary complex gives the encapsulated product complex in 55% yield based on the starting host–guest complex. The transformation is carried out on the isolated host–guest complex [62·10C61]₁₂, which gives the product complex upon irradiation, in 33% overall yield and 50% ee.

As the first asymmetric reaction mediated by a chiral supramolecular host, this work represented an important advance in supramolecular enantioinduction. The potential for
chiral space to provide asymmetric induction is tantalizing, but this system suffers from a lack of catalytic turnover and very limited scope (three other examples, none with >20% ee). It is perhaps unsurprising that decoration of the assembly exterior would have only limited influence on the interior space of a supramolecular host.

An example of asymmetric catalysis with supramolecular coordination cages was reported by Hupp and co-workers, using metalloporphyrin boxes (Figure 36). The catalyst was similar to the metalloporphyrin box discussed earlier (see Figure 25), but the tin porphyrin 64 contains a chiral ligand, rendering the pentameric assembly 65 chiral (Figure 36). This chiral host was then evaluated as an enantioselective catalyst. The host is...
catalytically competent in the oxidation of methyl p-tolyl sulfide and does so enantioselectively, giving the sulfoxide product in 12% enantiomeric excess. This has the advantage over supramolecular cage 61 of being a truly catalytic system, but the enantioselectivity is very mild, likely due to the small size of the chiral ligand relative to the large cavities in host 65. Together, these examples of enantioselective supramolecular materials indicate that the inclusion of chiral components can provide a basis for asymmetric induction, but these effects may be weak and a broader variety of chiral components will need to be incorporated to discover highly enantioselective materials. Much larger enantioselectivities have recently been reported by the Reek group in the asymmetric hydroformylation of styrene derivatives occurring in a metal-ligand cage.124

An alternative strategy for the preparation of chiral supramolecular coordination is the generation of chirality via self-assembly. The Ga4L6 tetrahedron 17 prepared by Raymond and co-workers is an example of this strategy; rather than incorporating chiral components, host 17 is a chiral architecture made from only achiral components. Binding of the three catecholate ligands to the trivalent metal center can form either a right-handed (Δ) or left-handed (Λ) helix (Figure 37).

Figure 37. Chirality in the coordination of three catecholate ligands in an octahedral geometry around a metal center, as in supramolecular coordination cage 17.

Mechanical coupling between the four vertices of 17 prevents the formation of any diastereomer with a mixture of Δ and Λ chirality, and as a result only the ΔΔΔΔ and ΛΛΛΛ structures are observed. This supramolecular assembly thus exists as a pair of enantiomers, though the components of the assembly are themselves achiral and so the host is synthesized as the racemate. In the presence of a chiral guest, diastereomeric host–guest complexes are formed, which can be distinguished readily by 1H NMR (Figure 38).

Chiral discrimination between bound guests was first demonstrated with ruthenium complexes 66a–g (Figure 39).116 After combination of an aqueous solution of Ga4L6 host 17 and an ethereal phase containing CpRu(diene)Cl, aquo complexes 66a–g can then be isolated from the aqueous layer. 1H NMR can be employed to distinguish the diastereomeric host–guest complexes [66a–g]1711− and quantify the host’s selectivity for one diastereomer over the other. Small changes in the size or shape of the ruthenium complex have large consequences for the selectivity observed, and these findings are summarized in Table 1.

Study of the diastereoselectivity of host 17 in reaction chemistry, rather than guest binding, employed the cationic half-sandwich iridium complex 44. Complex 44 is bound tightly by 1, and [44C17]11− reacts with aldehydes at room temperature to form chiral complexes 67a–i. The degree of selectivity varies significantly depending on the size and shape of the aldehyde (Table 2).44–46 The modest scope of this reaction demonstrates the size and shape selectivity of assembly 1, as aldehydes bearing more than five carbons are unreactive with [44C17]11−, while isobutyraldehyde does react to form [67C17]11−. Diastereoselectivities range from very slight to modest (up to 40% de), competitive with the aforementioned enantioselectivities with other supramolecular coordination cages.

Application of host 17 in enantioselective chemistry requires separation of the host isomers. Rather than incorporating chiral components to drive formation of one isomer, this was accomplished through resolution of the ΔΔΔΔ and ΛΛΛΛ enantiomers. Addition of (−)-N′-methylnicotininium iodide (S-nic) causes the spontaneous resolution of the two enantiomers, allowing access to ΔΔΔΔ-[S-nicC17], or ΛΛΛΛ-[S-nicC17],117,118 Ion-exchange chromatography allows isolation of each enantiomer as the tetramethylammonium salt. While very few chiral supramolecular hosts have been prepared, the resolution of the host enantiomers provides a unique opportunity to explore supramolecular hosts as chiral nanoscale materials for enantioselective synthesis.

Aza-Cope rearrangement of enammonium substrates was selected to evaluate 17 as an enantioselective catalyst. Encapsulation of these substrates within 17 enforces a reactive conformation.14 The product iminium ions are vulnerable to hydrolysis, producing neutral aldehydes that are weakly encapsulated in 17. As long as R is different from R, the rearrangement generates a chiral center and could be enantioselective within chiral assembly 17. Additionally, reactivity compatible with (NMe)12-17 is required, because obtaining suitable quantities of the enantiopure potassium salt of 17 is not practical.117 Enammonium substrates 68 are more tightly bound than NMe12+, allowing efficient catalysis within (NMe)12-17. Treatment of these allyl enammonium tosylates (68a–g) with catalytic amounts of (NMe)12[ΔΔΔΔ-17] did yield enantioenriched product aldehydes (Table 3). Enantioselectivities of 60% or higher were observed for the cis-ethyl (68b) and trans-isopropyl (68f) salts (Table 3). Small changes in substrate size and shape produced large variation in the enantioselectivity of rearrangement within ΔΔΔΔ-17. The enantioselectivity obtained with substrate 68b (64% ee) declined rapidly with addition of a single carbon (68d, 9% ee) or changing the geometry of the double bond (68c, 25% ee). Shape selectivity was demonstrated by the different enantioselectivities observed for isopropyl-substituted substrate 68f, which exhibited much higher enantioselectivity than its isomer, n-propyl-substituted substrate 68e.

Lower temperatures improved the enantioselectivity of the rearrangement. Substrate 68f was used to test the rearrangement
down to 5 °C. A steady decline in the yield and longer reaction times were observed at lower temperatures, but the enantioselectivities improved significantly, up to 78% ee. A remarkable element of this catalyst is the substantial difference in selectivity when comparing catalysis to product binding. Using the racemic potassium salt of the assembly, the product iminium ions can be observed bound to the interior of the assembly and the potassium salt of the assembly, the product iminium ions can be evaluated by 1H NMR. For this element of this catalysis is the substantial di

Curtin–Hammett situation in which the distribution of products in the enantioselective rearrangement is controlled by the energy difference between the transition states that lead to the two product enantiomers; the diastereoselectivities of binding for the product are much smaller, reflecting a small energy difference for the iminium host–guest complexes.

Until recently, expanding enantioselectivity of catalysis by 17 was limited due to racemization of the enantiopure assembly under conditions used for neutral-substrate catalysis. Recently, this problem was obviated through the synthesis of a Ga₄L₆-assembly (69) replacing the catecholate ligand moieties with terephthalimides incorporating enantiopure amines (Figure 40). Where, in Fujita’s assembly 55, an external element of chirality was incorporated at the edges of an achiral assembly, here the external chiral element is used to bias the intrinsic chirality of the M₄L₆ tetrahedron. As a result, assembly 69 is synthesized as a single diastereomer, with the helical chirality at the metals dictated by the chiral amine. In addition to affording an enantiopure host, the terephthalimide-based assembly is much more stable to increased temperature and oxidation by air. Host 69 could then be applied in the monoterpene-like cyclization of 21 to give enantioselectivities competitive with those observed in theaza-Cope cyclization, as high as 69% (at 20 °C).

Nitschke and co-workers prepared an enantiopure analogue of their Fe₃⁺-tetrahedron 27, incorporating enantiopure linker 70 to prepare the chiral assembly 71 (Figure 41). The enantiopure terphenylene linker was prepared in an expedient synthesis from diiodohydroquinone and enantiopure 3-chloro-1,2-propanediol. These chiral organic ligands bias the helical chirality of assembly 71, with (R,R)-70 yielding only the ΔΔΔΔ-71 assembly, while

Table 1. Diastereoselectivities of Binding for Ruthenium Complexes 66a–g by Host 17

<table>
<thead>
<tr>
<th>substrate</th>
<th>R₁</th>
<th>R₂</th>
<th>de (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>66a</td>
<td>H</td>
<td>Me</td>
<td>4</td>
</tr>
<tr>
<td>66b</td>
<td>H</td>
<td>Et</td>
<td>72</td>
</tr>
<tr>
<td>66c</td>
<td>H</td>
<td>i-Pr</td>
<td>28</td>
</tr>
<tr>
<td>66d</td>
<td>H</td>
<td>n-Pr</td>
<td>54</td>
</tr>
<tr>
<td>66e</td>
<td>Me</td>
<td>H</td>
<td>15</td>
</tr>
<tr>
<td>66f</td>
<td>Et</td>
<td>H</td>
<td>18</td>
</tr>
<tr>
<td>66g</td>
<td>n-Pr</td>
<td>H</td>
<td>17</td>
</tr>
</tbody>
</table>

“Diastereoselectivities were measured by 1H NMR integration and have estimated ±3% error.

Table 2. Diastereoselective Formation of Host–Guest Complexes 67a–i via C–H Activation by Encapsulated Cationic Iridium Complexes

<table>
<thead>
<tr>
<th>R</th>
<th>product</th>
<th>diastereoselectivity (de) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me</td>
<td>67a</td>
<td>60:40 (20)</td>
</tr>
<tr>
<td>Et</td>
<td>67b</td>
<td>65:35 (30)</td>
</tr>
<tr>
<td>n-Pr</td>
<td>67c</td>
<td>70:30 (40)</td>
</tr>
<tr>
<td>i-Pr</td>
<td>67d</td>
<td>55:45 (10)</td>
</tr>
<tr>
<td>n-Bu</td>
<td>67e</td>
<td>nr</td>
</tr>
<tr>
<td>i-Bu</td>
<td>67f</td>
<td>58:42 (4)</td>
</tr>
<tr>
<td>s-Bu</td>
<td>67g</td>
<td>nr</td>
</tr>
<tr>
<td>t-Bu</td>
<td>67h</td>
<td>nr</td>
</tr>
<tr>
<td>Ph</td>
<td>67i</td>
<td>nr</td>
</tr>
</tbody>
</table>

“de = (% major diastereomer – % minor diastereomer). Diastereomeric ratios were evaluated by 1H NMR integration. nr = no C–H activation was observed.

Table 3. Evaluation of Asymmetric Induction in the Aza-Cope Rearrangement Catalyzed by 17

<table>
<thead>
<tr>
<th>substrate</th>
<th>R₁</th>
<th>R₂</th>
<th>yield (%)</th>
<th>ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>66a</td>
<td>H</td>
<td>Me</td>
<td>45</td>
<td>0</td>
</tr>
<tr>
<td>66b</td>
<td>Et</td>
<td>H</td>
<td>58</td>
<td>64</td>
</tr>
<tr>
<td>66c</td>
<td>H</td>
<td>i-Pr</td>
<td>69</td>
<td>25</td>
</tr>
<tr>
<td>66d</td>
<td>Pr</td>
<td>H</td>
<td>68</td>
<td>9</td>
</tr>
<tr>
<td>66e</td>
<td>H</td>
<td>Pr</td>
<td>21</td>
<td>23</td>
</tr>
<tr>
<td>66f</td>
<td>H</td>
<td>i-Pr</td>
<td>74</td>
<td>60</td>
</tr>
<tr>
<td>66g</td>
<td>H</td>
<td>i-Pr</td>
<td>49</td>
<td>78</td>
</tr>
<tr>
<td>66h</td>
<td>H</td>
<td>n-Bu</td>
<td>82</td>
<td>6</td>
</tr>
</tbody>
</table>

“Yields were measured by 1H NMR with CHCl₃ as an internal standard after extraction of the reaction mixture into toluene-d₈.

°Reaction at 5 °C. 50% catalyst loading.

Yields were measured by 1H NMR with CHCl₃ as an internal standard after extraction of the reaction mixture into toluene-d₈.

°Reaction at 5 °C. 50% catalyst loading.
Instead gives the \( \Lambda \Lambda \Lambda \Lambda \) -71 enantiomer. Small, hydrophobic guests (\( \sim 8 \)–\( 12 \) non-hydrogen atoms) are encapsulated in the host and display slow exchange on the NMR time scale. In particular, the chiral guest \((\pm\)\)-limonene is observed to form diastereomeric host–guest complexes by \(^1\)H NMR, though no selectivity is observed when racemic limonene is encapsulated in the enantiopure assembly. Host 71 also demonstrates catalytic activity, driving the hydrolysis of the organophosphate dichlorides in the presence of catalytic \( \Delta \Delta \Delta \)-71. This portends the intriguing possibility that, with chiral substrates, these enantiopure hosts might ultimately also find application in enantioselective catalysis.

6. CONCLUSIONS AND OUTLOOK

Early studies in supramolecular chemistry and catalysis established that weak host–guest interactions could be a powerful driving force for the manipulation of guest molecules. The first generation of supramolecular hosts were limited primarily to natural cavity-containing molecules and increasingly elaborate—and synthetically challenging—covalent architectures. The rise of supramolecular coordination complexes as modular host structures has provided a richly diverse array of host structures. This has been a direct consequence of their modular design, allowing for combinatorial variance of host structure and chemical environment through the substitution of simple components. Larger host cavities have enabled more bimolecular reactions and greater substrate complexity, as well as improved substrate scope for host-catalyzed reactions. As the mechanisms of catalysis have become better characterized, more efficient reactions have been developed and examples of enzymelike rate accelerations have been discovered. Unusual chemo- and stereoselectivity have been observed in many transformations mediated by supramolecular coordination cages, with some intriguing examples of enantioselective catalysis appearing more recently. Development of highly enantioselective supramolecular catalysts remains a challenging prospect and an area of substantial disparity between enzymes and these artificial catalysts.

The incorporation of active transition metal complexes and catalysts is a recent and exciting area of study. Echoing the modular nature of host design, transition metal complexes can be incorporated through encapsulation or coordination to impart new chemical activity on supramolecular coordination cages. Control of the outer-sphere environment of transition metal catalysts has drawn increasing interest recently, and the first examples of encapsulated transition complexes have demonstrated their potential for unusual chemoselectivity and increased efficiency. While there are still very few examples of these systems, the possibilities for incorporation of metal complexes into host structures are very exciting. We anticipate that the interplay between organometallic chemistry and supramolecular catalysis will be fertile ground for the advent of catalysts with unique and exciting reactivity.

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Figure 40. Enantiopure chiral M\(_4\)L\(_6\) assembly 69.

Figure 41. Enantiopure tetrahedral supramolecular coordination cage 70 incorporates enantiopure organic linkers between the Fe\(^{2+}\) centers.
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Notes
The authors declare no competing financial interest.

Biographies

Casey J. Brown obtained a B.A. in biochemistry in 2005 from Swarthmore College under the mentorship of Professor Robert S. Paley. After a two-year appointment through Teach for America, he received his Ph.D. in 2011 from the University of California, Berkeley, working in the laboratories of Professors Robert G. Bergman and Kenneth N. Raymond. His graduate work focused on application of supramolecular hosts in organometallic and asymmetric catalysis. He is currently an NIH postdoctoral fellow in the laboratory of Virginia W. Cornish at Columbia University.

F. Dean Toste obtained his B.Sc. in chemistry and biochemistry (1993) and M.Sc. in organic chemistry (1995) from the University of Toronto. He moved to Stanford University where he completed his Ph.D. in 2000 under the guidance of Professor Barry Trost. After a postdoctoral appointment with Professor Robert Grubbs at the California Institute of Technology, he took a position as an assistant professor of chemistry at the University of California, Berkeley, in 2002. He was promoted to associate professor in 2006 and to professor of chemistry in 2009. Professor Toste’s honors include an Alfred P. Sloan Research Fellowship (2005), the Cope Scholar Award (2006) and the E. J. Corey Award (2008) from the American Chemical Society, BASF (2007) and Mitsui (2014) Catalysis Awards, the Organometallic Chemistry Directed towards Organic Synthesis (OMCOS) Award (2007) and Thieme-IUPAC Prize in Synthetic Organic Chemistry (2008) from IUPAC, the Merck Award (2010) from the Royal Society of Chemistry, and the Mukaiyama Award (2011) from the Society of Synthetic Organic Chemistry Japan.

Robert Bergman received his Ph.D. at the University of Wisconsin in 1966 under the direction of Jerome A. Berson. He spent 1966–1967 as a postdoctoral fellow in Ronald Breslow’s laboratory at Columbia and afterwards joined the faculty of the California Institute of Technology. In 1977, he accepted a professorship at the University of California, Berkeley, and a joint appointment at the Lawrence Berkeley National Laboratory; in 2002 he was appointed Gerald E. K. Branch Distinguished Professor at Berkeley. Among his previous honors are a Sloan Foundation fellowship (1969), a Dreyfus Foundation teacher–scholar award (1970), election to membership in the U.S. National Academy of Sciences and American Academy of Arts and Sciences (1984), the American Chemical Society Award in Organometallic Chemistry (1986), the U.S. Department of Energy E. O. Lawrence Award in Chemistry (1994), the American Chemical Society Arthur C. Cope Award (1996), and the ACS James Flack Norris Award in Physical Organic Chemistry (2003), the ACS George Olah Award in Hydrocarbon Chemistry (2013), and the Welch Award in Chemistry (2014).

Kenneth N. Raymond attended Reed College, where he received a B.A. in 1964. His Ph.D. research at Northwestern University, under the direction of Professors Fred Basolo and James A. Ibers, concerned the synthesis and structure of five-coordinate metal complexes. Upon completing his Ph.D., he began his faculty appointment at the University of California at Berkeley in 1967, becoming associate professor in 1974 and professor in 1978. His work has been recognized with several awards, including the Ernest O. Lawrence Award of the Department of Energy (1984), a Humboldt Research Award for Senior U.S. Scientists (1991), and the American Chemical Society Alfred Bader Award in Bioinorganic or Bioorganic Chemistry (1994). He has been an Alfred P. Sloan research fellow (1971–1973), a Miller research professor at the University of California (1977–1978, 1996), and a Guggenheim fellow (1980–1981). He was elected to the National Academy of Sciences in 1997 and the American Academy of Arts and Sciences in 2001. In 2008,
Professor Raymond was honored with the ACS Award in Inorganic Chemistry. In addition to his academic appointment at the University of California, he is a co-founder of Lumiphore Inc., which utilizes new luminescent agents developed in his laboratory, and faculty senior scientist and interim director of the Seaborg Center at Lawrence Berkeley National Laboratory. He is the author of 18 patents and more than 500 research publications.

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