Advances in supramolecular host-mediated reactivity

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Abstract

Since the trailblazing discoveries of Lehn, Cram and Pedersen, supramolecular chemistry has established itself as a cornerstone of organic chemistry. Supramolecular hosts offer defined microenvironments that mimic the active sites of enzymes, utilizing specific host-guest interactions to enable remarkable rate enhancements and product selectivity. The development of a diverse array of self-assembled hosts, coupled with the increased demand for shorter and greener synthetic routes, have spurred significant progress in the field of supramolecular catalysis. This review covers recent advances in the field, ranging from novel organic reactivity aided by supramolecular hosts to catalytic cooperation between hosts and organometallic compounds or metal nanoparticles. Strides have also been made in the synthetic application of these hosts in site-selective substrate modifications and challenging photochemical reactions. These efforts have enabled the incorporation of non-covalent macromolecular catalysis in natural product syntheses, evidencing their unique advantages as a synthetic tool, and their powerful potential for practical applications.

Introduction

In nature, precise molecular reactivity is facilitated by a cascade of enzymes that collectively lower the activation barriers of complex, multi-step transformations under mild

conditions.[1–3] Synthetic chemists have long sought to attain such molecular precision, via tuning of reaction conditions including solvent, temperature, and catalyst design. One such approach was the development of supramolecular host molecules, whose reactivity bears clear resemblance to that of enzymatic catalysis.[4–6] Like enzymatic active sites, the defined microenvironments within these host molecules demonstrate selective guest binding and harness non-covalent interactions to induce reactivity and selectivity not observed in bulk solution.

In the decades following the initial discovery of crown ethers,[7] cryptands,[8] and carcerands,[9,10] the structural diversity of supramolecular hosts has undergone tremendous growth. Early covalent hosts including cyclodextrins and cucurbiturils remain instrumental to supramolecular catalysis, largely due to their commercial accessibility and amenability to large-scale synthesis.[11–16] A significant challenge for this class of hosts, however, is the formation of larger assemblies, which necessitates the synthesis of increasingly complex covalent scaffolds with each iteration. Multimeric resorcinarene hosts,[17,18] calixarene-based capsules,[19] and dimeric "softball" hosts by Rebek and co-workers,[20] present one solution in which higher order structures are formed through the self-assembly of multiple covalent components. Another developing class of hosts are metal coordination cages, featuring transition metal vertices and ligands that form the edges or faces of the polyhedral framework.[21,22] While generally less robust than their covalent counterparts, coordination cages offer significantly more tunability in terms of size and charge, derived from variable ligand designs and metal oxidation states. This structural diversity of supramolecular hosts has spurred their utilization in a broad range of synthetic applications, ranging from homogeneous organic reactions to nanoparticle catalysis.

Supramolecular hosts provide an accessible means for synthetic chemists to exploit non-covalent macromolecular reactivity, particularly in non-biological processes. Remarkable

reactivity has been observed within these assemblies, with some catalysts attaining rate accelerations of a million-fold or more. The ability of these hosts to stabilize reactive intermediates, transition states, and excited states has enabled a growing number of challenging transformations to proceed under unconventionally mild conditions. Additionally, guest recognition and constrictive binding have promoted size-, site-, regio-, and enantioselective catalysis, epitomized by host-mediated asymmetric photochemical reactions and late-stage functionalization of natural products. While other synthetic catalysts require complex ligand scaffolds and careful control of reaction conditions to render selectivity, supramolecular catalysts readily self-assemble from simple components, providing a tailored microenvironment even under otherwise unfavourable reaction conditions. These exceptional properties and performance of supramolecular catalysts make them worthy targets for synthesis and warrant future studies into their application and mechanisms of action.

This review covers the major advancements made in the unique reactivity promoted by supramolecular hosts in the past five years.[23-28] We begin by highlighting new variations on well-established supramolecular organic reactivity, followed by organometallic reactions facilitated by supramolecular hosts. For the sake of brevity, this review only covers the reactivity of cages that assemble around or encapsulate the entirety of the transition metal catalyst. Sterically hindered or bifunctional ligands including highly functionalized N-heterocyclic carbenes and tethered peptide scaffolds have been shown to noncovalently influence transition metal reactivity, and are covered in other reviews.[29–31] Beyond simply enabling organic and organometallic reactivity, supramolecular hosts have also been shown to direct regio- and site-selectivity, representing an emerging, application-driven direction in the field. Other avenues of catalysis, including host-

mediated photochemical reactions, are also described, demonstrating the versatility of current state-of-the-art supramolecular catalysts.

Organic Reactions Catalysed by Supramolecular Hosts

Supramolecular catalysis is hallmarked by the ability of host molecules to stabilize encapsulated reactive species through a number of non-covalent interactions, thereby decreasing the free energy gap between reactant states and transition states. Drawing on multiple stabilizing factors, remarkable catalytic activity has been observed within supramolecular hosts, inviting comparisons to the activity of enzymes. Specifically, supramolecular Brønsted acid catalysis has been enabled via favourable Coulombic and cation-pi interactions within hosts, allowing (for example) Brønsted acid catalysis to take place under usually prohibitive basic, aqueous conditions.[32] This reactivity is demonstrated by an aza-Prins rearrangement, catalysed by the triscatecholate based dodecaanionic host-**1** which has been studied extensively by Raymond, Bergman, Toste, and co-workers. This host effectively stabilizes hydrolytically unstable cationic species, including iminium ions within its core, despite water as solvent,[33] which in the aza-Prins reaction enabled the intramolecular nucleophilic addition of a pendant alkene to an *in-situ* generated iminium ion **(Figure 1a)**.[34] The encapsulated addition complex underwent an unusual 1,5-hydride shift, facilitated by the constrictive nature of the interior of host-**1**. The product generated cannot be accessed under conventional acid catalysis in the absence of the host, and demonstrates the role that supramolecular catalysts can play in accessing atypical reaction pathways by an acid catalysed mechanism.

Accessing more complex transformations to yield diverse product scaffolds has remained an outstanding challenge in supramolecular chemistry. One solution to this issue takes advantage of the stability of iminium ion intermediates within **1** to access a multicomponent aza-Darzens

reaction via intermolecular nucleophilic addition.[35] This reaction, catalysed by host-**1** (2-10 mol%), provided *trans*-substituted aziridines as the major diastereomer. However, when host-**1** was blocked with a strongly binding guest, tetraethylammonium, the opposite *cis*-substituted diastereomer was observed as the major product in low conversions. In addition, typical acid catalysed aza-Darzens reactions provided *cis*-substituted aziridines, again highlighting the ability of supramolecular catalysis to access unusual reaction pathways.

Supramolecular hosts also demonstrate the ability to modulate product selectivity in iminium catalysed reactions. Tiefenbacher and co-workers reported the selective 1,4-reduction of α,β-unsaturated cinnamaldehyde derivatives catalysed by chiral proline derivatives and resorcinarene host-**2** (**Figure 1b**).[36] Host-**2** self-assembles from six equivalents of resorcinarene in organic solvents, and is held together via phenolic hydrogen bonding. The phenolic units of **2** have a lower than expected pKa of 5.5-6 (rather than the typical pKa 10 for phenol) enabling them to function as a built-in source of acid. The polyaromatic nature of the ligands promote acid catalysis via stabilization of cationic intermediate due to favourable cation-pi interactions.[17] In Tiefenbacher and co-workers' report, a proline catalysed 1,4-reduction of α,β-unsaturated aldehydes was subjected to hexamer **2**, and a significant change in the enantiomeric excess (ee) of the product aldehyde was measured. For an *ortho*-methoxy substituted cinnamaldehyde substrate, the **2**-catalyzed reaction yielded the corresponding product with 78% ee (S), compared to 9% ee (S) in the control reaction (69% Δee). The change in the enantioselectivity of the reaction originates from host-**2** blocking the less sterically hindered face of the aldehyde, generating a "mismatched" case with the proline derivatives. This causes the Hantzsch ester to deliver the hydride from the same face into which the proline chiral information projects.[37] Acid catalysis within host-**2** was extended to a number of other transformations, such as the hydroxyalkylation reaction and cyclodehydration

reaction of alcohols with prenyl derivatives and the hydration of aryl alkynes.[38–40] Tiefenbacher and co-workers also disclosed an unusual carbonyl-olefin metathesis reaction within host-**2** enabled for the first time in the absence of strong Lewis Acids.[41] Addition of HCl as a cocatalyst in this system allowed reactions to proceed with 10 mol% host, in up to 98% yield, but with long reaction times (1-17d).

In an effort to extend supramolecular catalysis to more practical applications, Tiefenbacher and co-workers also investigated terpene cyclizations within host-**2**. Supramolecular terpene cyclization is an attractive, yet challenging target, as numerous products can be generated from a single terpene.[42,43] In their seminal report, nerol, geraniol and linalool were encapsulated and ionized within **2** to generate a variety of tail-to-head terpene (THT) cyclization products.[44] **2**-catalyzed nerol cyclization provided access to eucalyptol in useful yields (~40%), previously inaccessible via direct cyclization of nerol (**Figure 1c**). To probe leaving group effects, both geraniol and geranyl acetate were subjected to host-**2** catalysed conditions, and remarkably, both provided the same major product, α-terpinene, suggesting that the initially formed transoid allylic carbocation directly isomerized to the cisoid allylic carbocation without the involvement of a linalyl intermediate. This result suggests that host-**2** facilitated a "non-stop" THT cyclization, where cationic intermediates undergo direct isomerization and addition reactions without interception by an external nucleophile, showcasing the ability of **2** to shield reactive intermediates.[45] Subsequent studies presented the concise synthesis of terpenoid natural products using THT cyclization, within host-**2,** to access the molecular skeleton of isolongifolenone,[46] δ-Selinene,[47] and (−)-Presilphiperfolan-1β-ol (**Figure 1c**).[48] These represent the shortest total syntheses to date of these natural products, demonstrating the feasibility of supramolecular catalysts as powerful reagents in complex molecule synthesis.

In many cases the source of rate acceleration in supramolecular catalysis is poorly understood. To elucidate the effect of host charge, the Raymond, Bergman, and Toste groups reported a two-cage study on the rates of an acid-catalysed Nazarov cyclization.[49] The Nazarov cyclization, which proceeds with up to 10^6-fold rate acceleration in the presence of dodecaanionic host-**1,** was subjected to the octaanionic Si^{IV}-based host-**3** (**Figure 1d**). Host-**1** accelerated the rate 680-fold more than host-**3**, due to its superior ability to stabilize the cationic intermediates and transition state of the Nazarov cyclization. For an overall charge-neutral Aza-Cope reaction catalysed by the constricted interior of the hosts, the rate should be independent of host charge because the single positive charge on the reactant does not change during the transformation—and indeed, the rates were found to be within error between hosts **1** and **3**. Despite being isostructural, hosts **1** and **3** exhibit contrasting reactivity due to their difference in charge. In a related study, Gibb and co-workers investigated the effect of charge on the macrocyclization of α, ω thioalkane halides in organic supramolecular capsules.[50] Two related capsules were synthesized: capsule **4,** containing pendant carboxylate anions, and capsule **5**, containing pendant ammonium cations (**Figure 1e**), which both self-assemble in solution to form homodimers that encapsulate hydrophobic molecules. Homodimer **5** catalysed the macrocyclization reaction to completion in a matter of minutes, while in the presence of the anionic homodimer **4**, the reaction required several weeks. This discrepancy in rate originates from stabilization of the thiolate anion (the active nucleophile), by cationic host **5**. These two studies emphasize the importance of charge and electrostatic fields in enabling catalytic pathways within supramolecular hosts.

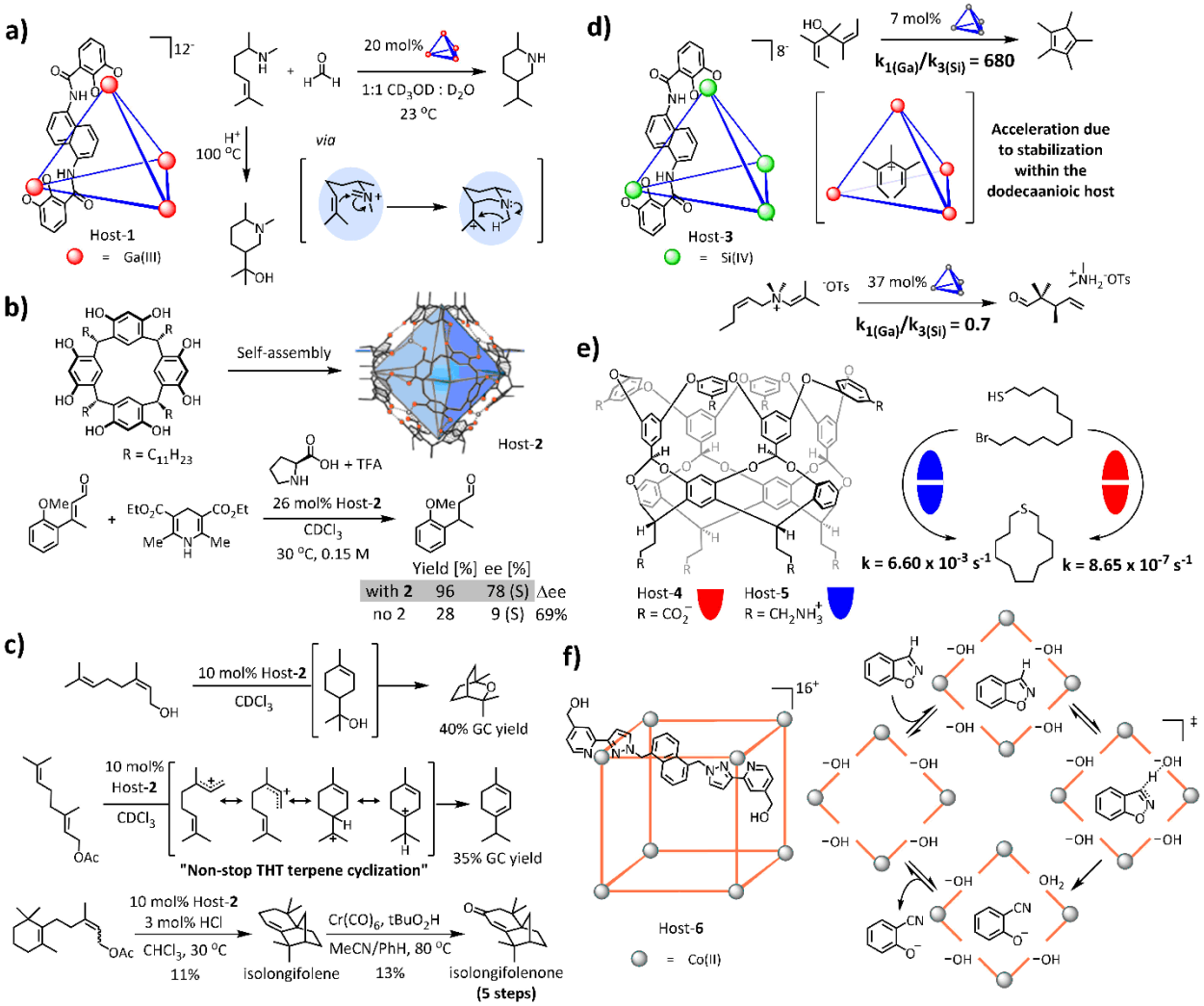

Figure 1: Organic transformations catalysed by supramolecular hosts

a) Comparison of the aza-Prins reaction catalysed by host-**1** and the formic acid catalysed cyclization. **b)** Top: Self-Assembled resorcinarene host-**2**. Bottom: The asymmetric 1,4-reduction of aldehydes facilitated by host **2**. **c)** Top: nerol cyclization to give eucalyptol as the primary product in the presence of host-**2**. Middle: the non-stop THT cyclization of geranyl acetate catalysed by **2**. Bottom: Terpene cyclization reaction in host-**2** for the concise synthesis of isolongifolenone. **d)** Charge study between host-**3** (8^- overall charge) and host-**1** (12^- overall charge). Top: Nazarov cyclization. Bottom: Aza-Cope. **e)** Charge study on the macrocyclization of thiols in the presence of polyanionic host-**4** and polycationic host-**5**. **f)** Left: Cubic Co^{II} based supramolecular host-**6**. Right: catalytic cycle for the host-**6** catalysed Kemp elimination.

In contrast to acid catalysis, Ward and co-workers have investigated base catalysis within host-**6,** which forms a molecular cube in solution from eight Co^{II} atoms and twelve ligands (**Figure 1f**). This host has an overall cationic charge of 16^+, which enables it to bind anions such as chloride, fluoride and hydroxide to its surfaces in water. The host is an efficient catalyst for the Kemp

elimination of benzisoxazole to 2-cyanophenolate, with 2×10^5 rate acceleration.[51] This elimination reaction is facilitated by an increase in local concentration of hydroxide ions around the host. In addition, this reaction is autocatalytic in the absence of a strong base, as the phenolate ion generated in the Kemp elimination binds to the outer face of the host, deprotonating an equivalent of starting material.[52]

In addition to increasing the local activity (in the thermodynamic sense) of reactive species such as hydroxide, supramolecular hosts have also been designed with specific activating groups for enabling catalysis. One such example is host-**7** reported by Hooley and co-workers, which contains endohedral carboxylic acids for the purpose of enabling Brønsted acid catalysis.[53] Host-**7** is an efficient catalyst for acetal deprotection, giving high conversions even in neutral water (**Figure 2a**). By compartmentalizing the Brønsted acid source, this cage enabled a multistep, one-pot synthesis with acid-sensitive reagents such as imine-based helicate-**8**. Helicate-**8** underwent ligand substitution with pyridyl aldehydes that are *in situ* deprotected by host-**7**, to give non-brominated helicate-**9**. Another example of a host containing activating groups for catalysis is the supramolecular trigonal prism synthesized by Mukherjee and coworkers.[54] Host-**10** self-assembles from six equivalents of urea-containing pyridyl ligands, six equivalents of Pd^{II}, and six equivalents of a shorter ligand to "clip" the supramolecular prism together (**Figure 2b**). Hydrogen bonding interactions from the urea functionalities activated Michael additions of nitro-olefins to 1,3-dimethylbarbituric acid and Diels-Alder reactions of anthracene at 5 mol% loading of the catalyst in water. In the absence of host, little to no reactivity was observed. In another example of a host containing activating functionalities, Lusby and co-workers synthesized Pd^{II} helicate host-**11**, designed to activate dienophiles for chemoselective Diels-Alder reactions (**Figure 2c**).[55] This host contains two distal hydrogen bonding sites at the polarized *ortho*-C–H bonds of the Pd-bound

pyridine, which selectively bind and activate *para*-quinone. With 20 mol% host-**11**, 1,3-pentadiene underwent a chemoselective Diels-Alder reaction with *p*-quinone, even in the presence of a competing diene, anthracene.

Multi-cage systems with preinstalled activating groups can also promote a multi-catalyst, one-pot, cascade reaction. Fujita and co-workers reported hosts **12** and **13** as catalysts for a tandem oxidation-Diels-Alder reaction (**Figure 2d**).[56] Host-**12** contains pendant oxidation catalyst TEMPO, while host-**13** contains a chiral amine Diels-Alder catalyst for enones. This chiral amine is incompatible with TEMPO in bulk solution, but within host-**13**, the amine is physically separated from the oxidation catalyst imbedded in host-**12**. This two-cage system oxidized an allylic alcohol to the corresponding α,β-unsaturated aldehyde, which underwent selective cyclization to Diels-Alder adduct **14** with high ee in host-**13**. This example highlights the capability of synthetic hosts to mimic cascade reactions found in enzymatic systems, enabling multi-step transformations to occur in a single pot.

A recent report by Fujita and co-workers presents another way to generate reactivity within a host: by accessing mechanically strained intermediates.[57] The Pt^{II} based host-**15** encapsulated two equivalents of aromatic amides in a *cis*-twisted conformation with up to a 34-degree dihedral angle between the carbonyl and N–H bond (**Figure 2e**). This conformation disrupts the stabilizing resonance interactions within the amide bond, causing these encapsulated amides to hydrolyse faster than observed for the free *trans* isomer. On subjecting the host-guest system to basic conditions, the twisted s-*cis* conformer hydrolysis was accelerated up to 14-fold. This example demonstrates the ability for supramolecular hosts to destabilize ground states to accelerate reactions.

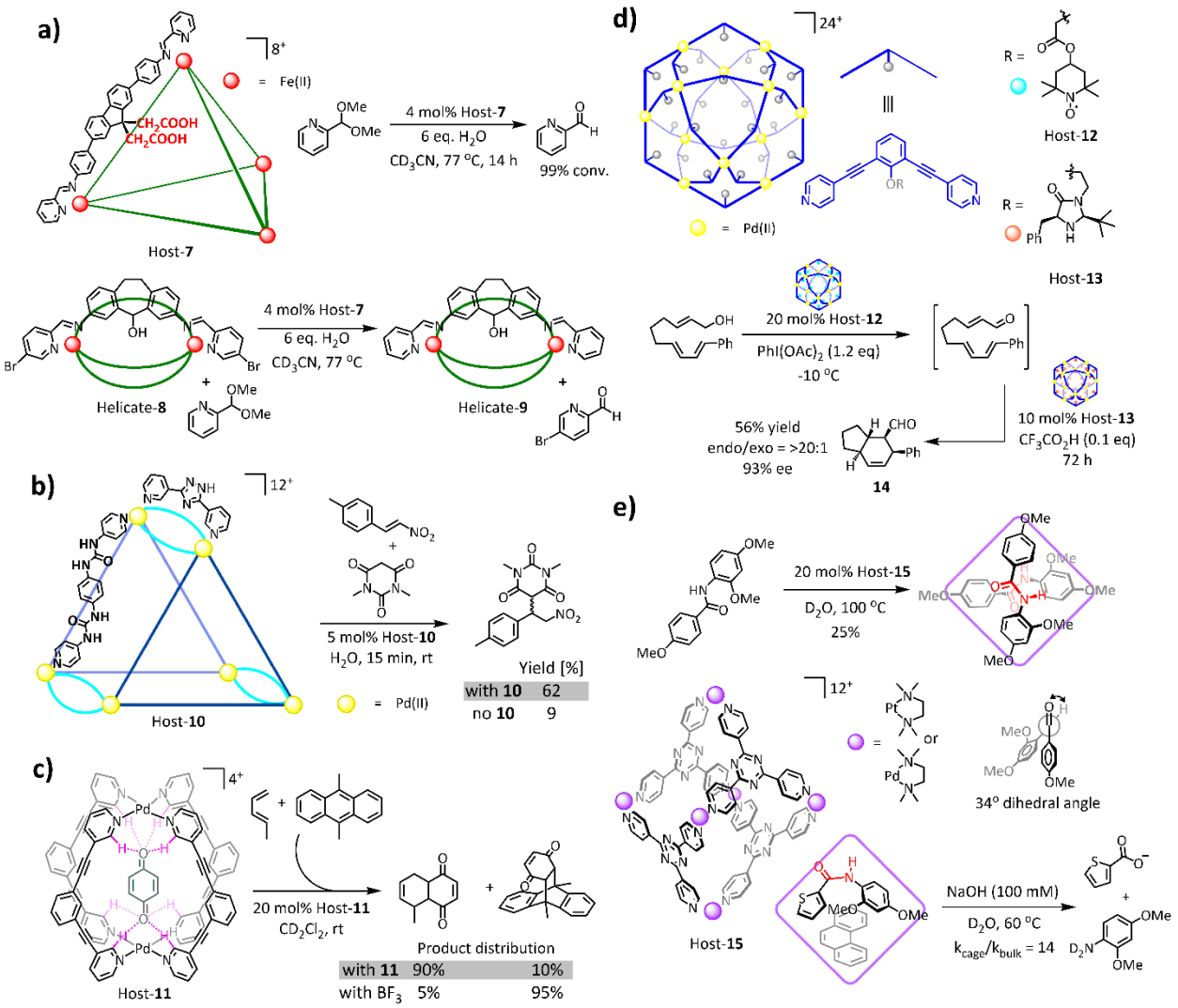

Figure 2: Organic transformations promoted by supramolecular hosts

a) Acetal hydrolysis catalysed by acid functionalized host-**7**, followed by helicate substitution reaction to generate helicate-**9**. **b)** Self-assembled host-**10** containing urea activating groups, and the 1,4-addition to nitro-olefins, promoted by the urea functionalities. **c)** Supramolecular host for a catalytic Diels-Alder reaction, illustrating the selectivity for the smaller diene in the Diels-Alder reaction with *para*-quinone. **d)** Tandem reaction catalysed by hosts **12** and **13** to generate Diels-Alder adduct **14** selectively in one pot. **e)** Top: Encapsulation of aryl amides enforces a twisted-*cis* conformation within host-**15**. Bottom: The twisted-cis conformation of encapsulated amides accelerates hydrolysis.

Organometallic Reactions Catalysed by Supramolecular Hosts

Supramolecular hosts enable novel reactivity for organometallic catalysts in ways otherwise inaccessible by traditional ligand scaffolds, much as proteins can alter the secondary coordination sphere in enzymes. Charged hosts can stabilize oppositely charged reaction intermediates to accelerate or favour a particular reaction pathway, as highlighted by the acceleration of elementary organometallic steps within the anionic tetrahedral host-**1** studied by the Raymond, Bergman and Toste groups (**Figure 1a**).[58] Host-**1** catalysed the reductive elimination of a dimethyl monophosphine Au^{III} iodide (**16**) to form ethane with a $1.9x10^7$-fold rate acceleration (**Figure 3a**).[59] This dramatic rate acceleration has been attributed to constrictive binding and stabilization of the positively charged transition state by the anionic host.[60] Similarly, the rate of reductive elimination from an encapsulated Pt^{IV} complex (**17**) was increased 2.6×10^4-fold (**Figure 3a**). Host-**1** has a turnover number (TON) of 312 for the reductive elimination from **16**, but this TON was increased to 947 for related host-**18**, which is made more stable to alkyl halides by chiral amides at its vertices. Host-**18** behaved as a cocatalyst with platinum complex **19** in a dual catalytic mechanism for the sp^3-sp^3 cross coupling of an alkyl tin and alkyl halide, accelerating the prohibitively slow reductive elimination step of the catalytic cycle (**Figure 3a**).[61] Notably, this represents a unique example in which an organometallic complex shuttles between cooperative catalytic cycles occurring both inside and outside of the host cavity. Host-**1** also accelerates β-hydride elimination from an ethyl dimethyl Pt^{IV} complex to form ethylene, and reductive elimination from an acyl dimethyl Pt^{IV} complex to yield acetone. The scope of this system is limited by the size of the host cavity, which excludes a larger benzyl dimethyl Pt^{IV} complex.

Besides acceleration of reductive elimination, host-**1** likewise accelerates oxidative addition. Host-**1** promoted the oxidative addition of aryl halides to encapsulated Cu^{I} and Pd^{II} complexes (**Figure 3b**).[62] Control experiments showed that these oxidative additions occur uniquely within the host, as the metal complexes are either unreactive or follow decomposition pathways in its absence. Reaction selectivity was also altered due to the confined nature of the cavity microenvironment—*para*-iodotoluene is typically more reactive toward oxidative addition than *ortho*- and *meta*-iodotoluene, but this trend was reversed under host-mediated reaction conditions, due to the sterically-limited binding affinity of *para*-iodotoluene. These results highlight the ability of supramolecular hosts not only to accelerate the elementary steps of organometallic catalysis but also to exhibit atypical selectivity resulting from differential binding.

Supramolecular hosts have also demonstrated the ability to enhance enantioselective transformations induced by single metal catalysts. Notably, Reek and co-workers reported an enantioselective hydroformylation reaction for branched aldehyde products, catalysed by a supramolecular Rh complex.[63] Catalyst-**20** consists of a Rh-ligated chiral phosphoramidite, which is coordinated to a mixed Zn^{II} porphyrin and Pd-based coordination host (**Figure 3c**). **20**⊂Host-**21** provided up to 71% ee and high conversion to the branched product, significantly out-performing the free phosphoramidite Rh catalyst. Cui and co-workers also reported highly enantioselective catalysis with host-**22** (**Figure 3d**)**.** Host-**22** self-assembles from three equivalents of chiral Cr- and Mn-salen based ligands and Zr vertices.[64] This multi-metal host catalysed the tandem epoxidation and nucleophilic ring opening to give product **23** in high conversions and enantioselectivity. While the host did not increase the inherent ee provided by the free Mn-salen catalyst, it led to increased overall conversions. This example thus highlights the ability of supramolecular hosts to stabilize catalysts at lower loadings and increase their TON.

In addition to providing rate acceleration to mononuclear catalysts, supramolecular hosts have demonstrated the ability to pre-organize multiple metal catalysts and enhance their catalytic behaviour, as shown by Reek and co-workers. Through hydrogen bonding interactions between host-bound guanidinium moieties and pyridine-bound sulphate moieties, host-**24** can encapsulate up to twelve pyridine-ligated ruthenium complexes (**25**), creating a local ruthenium concentration of up to 0.54M within its cavity—a condition difficult to attain in bulk solution due to solubility and cost considerations (**Figure 3e**).[65] The host-catalyst complex accelerated electrochemical water oxidation by two orders of magnitude through facilitation of the rate-limiting step, dinuclear coupling of molecular oxygen, which was favoured by the increased local concentration of catalyst (**Figure 3e**). Similarly, host-**24** can bind up to twelve copper Xantphos-based catalysts, modified to contain sulphate groups to interact with the host, and accelerate the copper-catalysed cyclization of 4-pentynoic acid.[66] This reaction also involves a rate-limiting dinuclear coupling step, which was accelerated 50-fold despite the low average concentration of catalyst in solution. Additionally, the host increased the turnover number by 2.5-fold compared to the unencapsulated copper catalyst under the same reaction conditions. In a recent study, host-**24** not only pre-organized gold catalyst **26**, but the substrate as well in the intramolecular cyclization of acetylenic acids (**Figure 3e**).[67, 68] Aided by the addition of catalytic base, interactions between the substrate's deprotonated carboxylic acid groups and the host's guanidinium groups led to selective formation of a five-membered ring (**27b**) over a six-membered ring (**27a**), which was favoured in absence of the host. Conversion decreased when the number of encapsulated gold complexes in each host cavity exceeded four, as binding sites for the substrate were blocked, further evidencing the influence of host-induced conformational pre-organization.

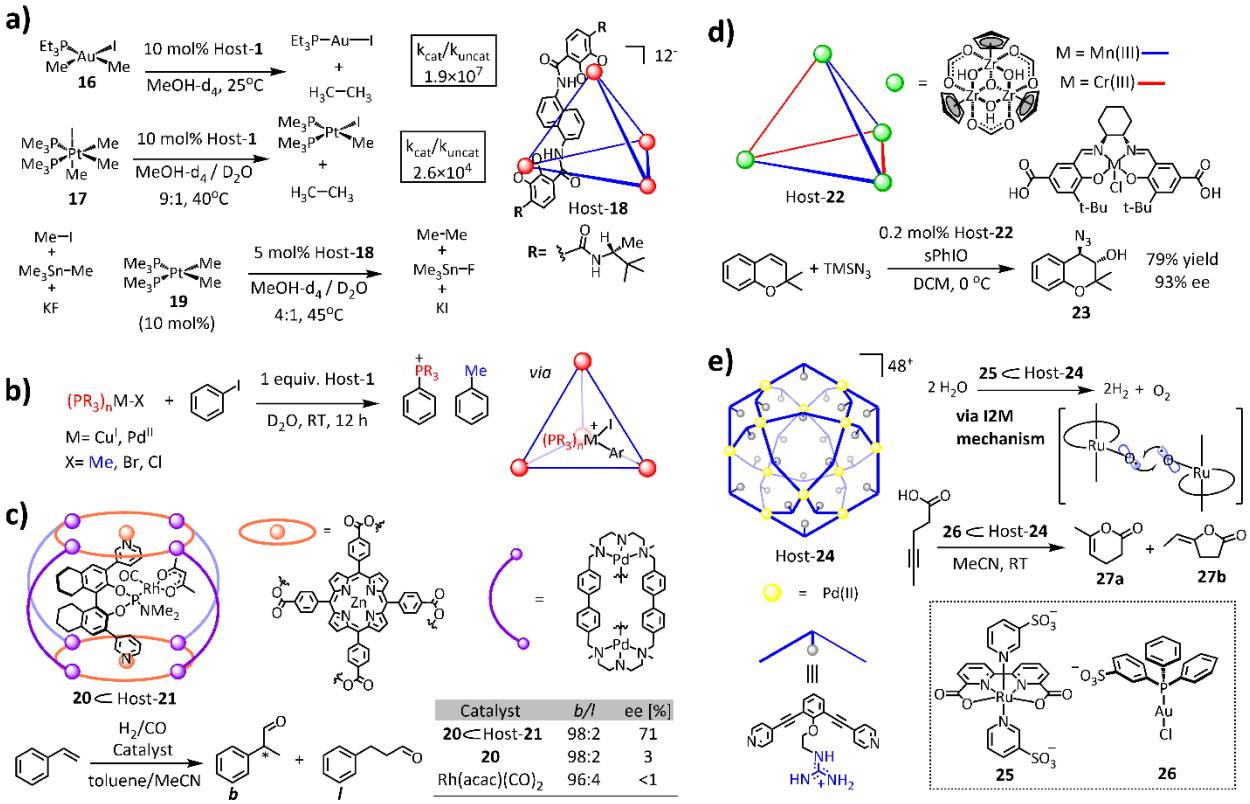

Figure 3: Organometallic transformations promoted supramolecular hosts

a) Reductive elimination of Au^{III} and Pt^{IV} catalysed by host-**1,** and dual catalytic reaction for sp^3-sp^3 cross coupling to give ethane catalysed by Pt^{IV} and host-**18**. **b)** Oxidative addition of aryl halides to Cu^{I} and Pd^{II} catalysed by host-**1**. **c)** Top: Chiral phosphoramidite Rh catalyst **20** encapsulated by host-**21**. Bottom: hydroformylation conditions highlighting the enhanced selectivity for the encapsulated catalyst over the free Rh catalyst **20. d)** Top: Chiral salen-based tetrahedral host-**22**. Bottom: Conditions for the tandem asymmetric epoxidation, azide addition reaction catalysed by Host-**22**. **e)** Left: Host-**24** containing endohedral guanidinium functionalities. Right: Dinuclear Ru water oxidation and dinuclear Au cycloisomerization promoted by host-**24.**

Supramolecular hosts have also proven useful in metal nanoparticle and nanocluster catalysis. The host cavity provides a protecting scaffold for the formation of uniform nanoclusters, improving catalytic performance and preventing decomposition, agglomeration, or other disorganizing pathways. In one example, Chen and co-workers reported a trigonal prismatic coordination cage with thiophene ligands that bind Pt^{IV} precursors to form Pt^{0} nanoclusters, which demonstrated higher electrocatalytic performance than Pt/C for the hydrogen evolution reaction

(HER) (**Figure 4a**).[69] Host-**28** had higher current density, longer durability, and stronger corrosion resistance than Pt/C.

The Zhou group also reported a porous coordination cage (host-**29**) that encapsulates metal cations in solution, which were reduced to form neutral metal nanoclusters within its pores. Composite cobalt nanoclusters within host-**29a** showed superior catalytic activity in the hydrolysis of ammonia-borane compared to other first row transition metal nanocluster catalysts (**Figure 4b**).[70] The negatively charged host-**29a** coordinates and organizes Co^{II} cations into smaller and more uniform particles within its cavity, preventing the detrimental agglomeration of the particles, even after reduction to Co^0. The significance of charge was evidenced by comparison to an overall neutral analogue, host-**29b**, in which the sulphate groups were replaced with tert-butyl groups, leading to instant agglomeration, followed by slower reaction times and slower turnover frequency (**Figure 4b**). Zhou and co-workers also reported encapsulation of Ru^{III} cations in host-**29a** to form uniform Ru^0 nanoclusters with improved catalytic activity in the methanolysis of ammonia borane.[71] These examples highlight the possibilities of cooperation between supramolecular chemistry and metal nanoparticles for small molecule catalysis.

In another instance of supramolecular nanoparticle catalysis, Mukherjee and co-workers reported host-**30a** and host-**30b**, with multiple interior diamine binding sites that aid in the synthesis of Pd^0 nanoparticles. The nanoparticles exhibited improved stability and catalytic performance in the cyanation of aryl halides compared to other common palladium catalysts (**Figure 4c**).[72] Host-**30a** has a significantly smaller cavity than host-**30b**, which led to the formation of smaller Pd nanoparticles. As a result, host-**30a** demonstrated superior catalytic activity, evidencing the influence of supramolecular hosts through modulation of particle size. Another covalent organic cage (host-**31**) reported by Mukherjee and co-workers promoted the

formation of Au^0 nanoparticles within its cavity, which act as heterogeneous photocatalysts for the conversion of nitroarenes to their corresponding azo- compounds (**Figure 4d**).[73] Host-**31** contains photosensitizing phenothiazines, and prevented the agglomeration of the gold nanoparticles by regulating particle size, which improved their photocatalytic activity and reusability. Catalysis proceeded under mild conditions with >99% selectivity for the azo-product, followed by easy separation of the catalyst (**Figure 4d**). In summary, supramolecular hosts show great potential in transition metal catalysis, enhancing the catalytic abilities of the metal through electrostatic stabilization, pre-organization, and protection from degradation pathways.

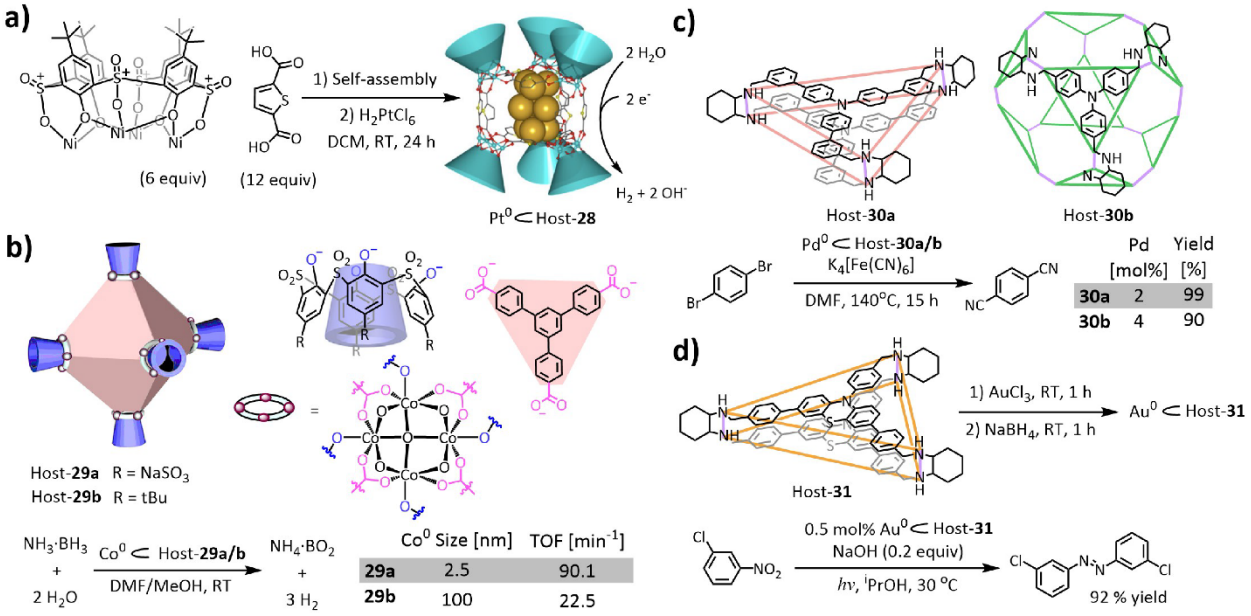

Figure 4: Host mediated metal nanoparticle synthesis and reactivity

a) Self-assembly of host-**28** reported by Chen and workers, which catalyses hydrogen evolution reaction (HER) through encapsulated Pt^0 nanoclusters. **b)** Top: anionic and neutral hosts **29a/b** self-assembled from three components. Bottom: Conditions for oxidation of borane catalysed by metal nanoclusters within host-**29a/b**. **c)** Top: two differently-sized covalent cages synthesized by Mukherjee and co-workers. Bottom: Conditions for cyanation catalysed by Pd^0 nanoparticles within hosts **30a** and **30b**. **d)** Top: phenothiazine-containing covalent cage synthesized by Mukherjee and co-workers. Bottom: azo-formation reaction catalysed by gold particles within host-**31**, which also acts as a photosensitizing agent.

Regio- and Site-Selective Reactivity Enabled by Supramolecular Hosts

Reactions made regio- or site-selective by supramolecular catalysis represent ongoing efforts toward bridging the gap between proof-of-concept reactivity and synthetic application. For these reactions the primary purpose of the host is not to provide overall rate acceleration, but instead a secondary sphere in which selective binding and guest recognition promote a significant rate differential between desired and competing undesired reaction trajectories. Two general approaches have been undertaken to attain this supramolecular-controlled selectivity. The first approach uses the host as a stoichiometric supramolecular "protecting group" to bind lipophilic portions of the substrate, while the reactive species is directed to a distal portion of the substrate *outside* of the host. The second approach involves the encapsulation of a transition metal catalyst, which provides a secondary environment to direct chemo and regioselectivity *inside* the host.

The Rebek group has been a leader in implementing the first approach, exemplified by the selective macrocyclization and mono-functionalization reactions mediated by cavitand host-**32a/b** (**Figure 5a**).[74–80] The deep pocket formed by the aromatic scaffold enables strong hydrophobic binding to the lipophilic portion of bolaamphiphiles such as α, ω-amino acid **33**.[75] When bound, the substrate adopts a U-shaped conformation, projecting the polar, reactive end groups close together at the solvent-exposed rim (**A**). Upon subjecting this system to conventional amide-bond forming conditions using NHS (N-hydroxysuccinimide) and EDC (N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide), the corresponding cyclic lactam product **34** was selectively observed. In the absence of super-stoichiometric host-**32a**, oligomeric products formed despite high-dilution conditions, indicating that the host not only reduces the entropic barrier of macrocyclization, but functions as a sterically-hindered protecting group to prevent intermolecular reactivity. Similar reactivity was observed with α, ω-dienes, in which host-**32a** facilitated an

intramolecular olefin-metathesis reaction leading to the selective formation of cyclooctene in the presence of Hoveyda-Grubbs-II catalyst.[76] This system was extended to the mono-functionalization reaction of difunctional alkanes by subjecting α, ω-diazide **35** to Staudinger reduction conditions in the presence of stoichiometric quantities of N-methyl urea cavitand, host-**32b**.[77] Remarkably, mono-reduction product **36** was exclusively formed, even with excess phosphine, whereas a mixture of reduction products form in the absence of the host. This selectivity is attributed to a shift in the equilibrium towards conformation **B**/**C** upon mono-reduction, where the amine extrudes from the cavity and the more lipophilic azide is shielded from further reduction. Selective mono-functionalization and macrocyclization was also accomplished successively in a one-pot fashion, as shown by the host-**32a** mediated transformation of diamine **37** to di-lactam **38**.[80]

Fujita and co-workers extended this supramolecular "protecting group" approach further by investigating its application to a simple natural product (**Figure 5b**).[81] Previously reported Pd host-**15** (**Figure 2e**) self-assembles from four triazole ligands, forming a highly hydrophobic, octahedral cavity. Geranyllinalool **39** forms a 1:1 inclusion complex with host-**15** under aqueous conditions in which it adopts a U-shaped conformation, evidenced both by ^{1}H-^{1}H NOESY correlation experiments and X-ray crystallography. The terminal prenyl moiety extrudes from the cavity, whereas the two internal trisubstituted double bonds are well-encapsulated. Subjecting host-guest complex **39⊂15** to an aqueous solution of N-bromosuccinimide (NBS) yielded a single product, with exclusive bromination at the exposed prenyl site. Subsequent bromonium ring-opening by NO_3^- counterions formed 14,15-nitratobrominated product **40** in 82% yield. Control experiments in the absence of the cage yielded a mixture of bromination products due to competing reactivity at the internal (10, 11) alkenyl group. High site-selective reactivity was also observed

upon addition of *m*-chloroperoxybenzoic acid to **39⊂15**, where epoxidation occurred exclusively at the prenyl end group to give product **41** in quantitative yield.

While the previous examples demonstrated modification of a single, solvent-exposed site, a recent report from Ribas and co-workers presents a modular approach that enables access to a range of selectively modified fullerene products.[82] Controlled functionalization of C_{60} is an important challenge in the design of improved perovskite thin layers in solar cell devices. Tetragonal prismatic host-**42**, consisting of two Zn^{II}-porphyrin moieties and four Pd^{II}-molecular clips, was previously reported to form 1:1 inclusion complex C_{60}⊂**42** in acetonitrile.[83] While fully encapsulated, portions of the guest remain exposed to the solvent through four lateral apertures (**Figure 5c**). Subjecting C_{60}⊂**42** to standard Bingel-Hirsch conditions with one equivalent of ethyl bromomalonate (Nuc **A**) resulted in the formation of the regioisomerically pure mono-adduct, where cyclopropanation occurred exclusively at a solvent-exposed, equatorial [6,6] bond. Subsequent additions of Nuc **A** resulted in the stepwise formation of bis-, tris-, and tetrakis-equatorial *homo*-adducts, and addition of methylmalonate (Nuc **B**) enabled formation of the corresponding *hetero*-adducts, showcasing the modularity of this strategy.

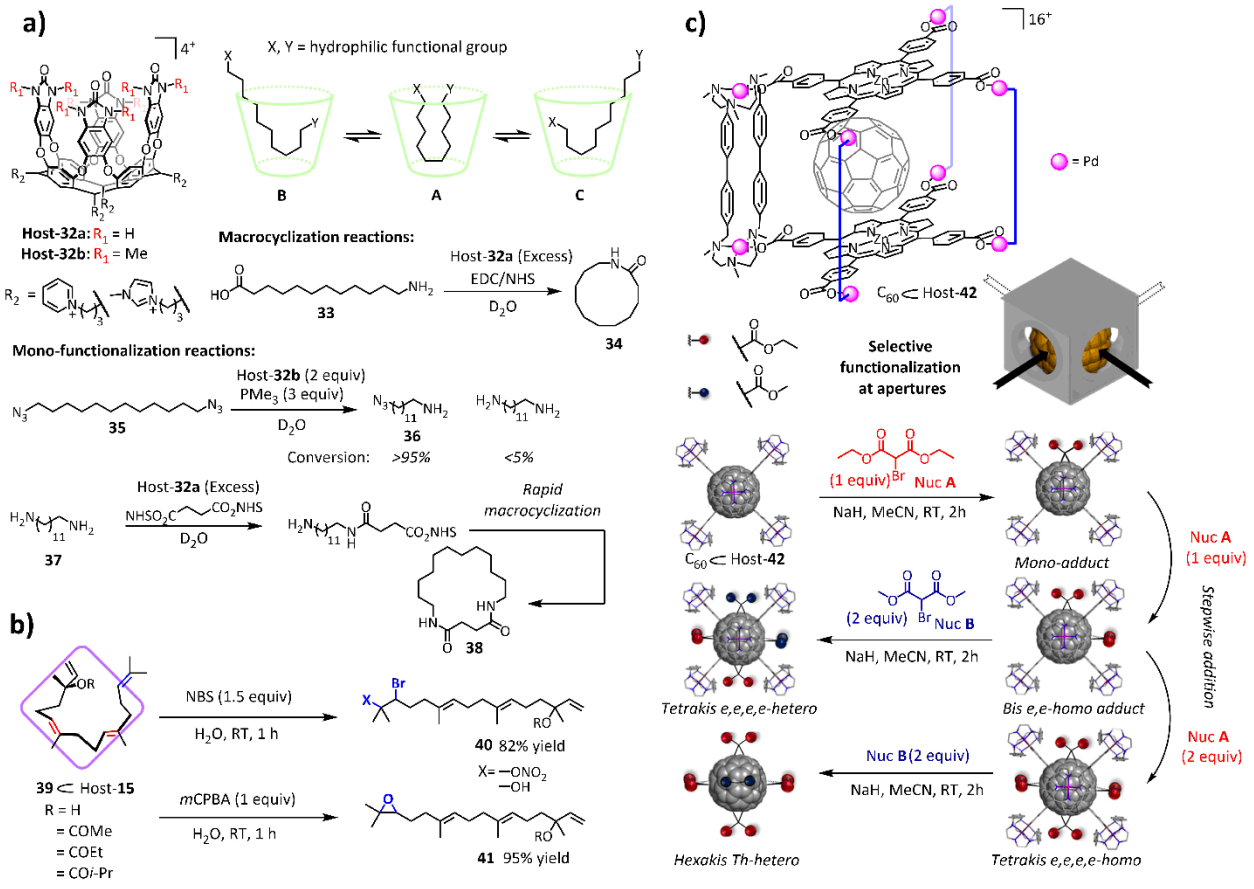

Figure 5. Regio- and site-selective reactivity rendered by stoichiometric amounts of supramolecular hosts

a) Top left: Cavitand host-**32a** synthesized by Rebek and co-workers. Top right: Binding equilibria within host-**32**, showing yo-yo like motion. Bottom: Macrocyclization and mono-functionalization reactions facilitated by stoichiometric encapsulation in host-**32a/b**. **b)** Quantitative encapsulation of diterpenoid renders site-selective electrophilic bromination and epoxidation outside the cage. **c)** Top: Tetragonal prismatic host-**42** synthesized by Ribas and co-workers. Bottom: Stepwise addition of bromomalonate nucleophiles renders modular site-selective Bingel-Hirsch cyclopropanations.

The supramolecular protecting group approach enables high levels of selectivity across different host-guest platforms and organic reactions, but its application requires quantitative formation of the host-guest complex and super-stoichiometric concentrations of host, which can limit its scope and scalability. An alternative approach that promotes high selectivity at catalytic loading of host involves anchoring a reactive metal catalyst internally, thereby restricting the size and conformations of substrates that can co-encapsulate. Host-**43a**-catalyzed regioselective

hydroformylation, first reported by Reek and co-workers in 2001, is a well-established example.[63,84–89] Host-**43a** self-assembles from three Zn^{II}-tetraphenylporphyrin (Zn-TPP) moieties that coordinate to the pyridyl units of tris(*m*-pyridyl)phosphine (**Figure 6a**). Addition of a Rh^{I} precursor results in the formation of an encapsulated mono-phosphine Rh complex, an active catalyst in the hydroformylation of 1-octene. While the free Rh complex was selective for the linear aldehyde product, the [Rh]⊂**43a** complex reversed selectivity, forming the branched product in larger quantities (*l*/*b*<1). In a subsequent study, the size of the cage was modulated to further elucidate the effect of confinement on the selectivity of the reaction.[85] Smaller host-**43b** was synthesized by replacing the Zn-TPP ligands with electron-deficient tetraphenylporpholactone (Zn-TPPL), which resulted in a stronger and shorter Zn-pyridyl interaction and a calculated 44% decrease in cavity volume compared to **43a**. In parallel hydroformylation reactions of 1-octene and propene, host-**43a** exhibited a higher *b*/*l* ratio for 1-octene, whereas host-**43b** was more selective for propene. These observations are attributed to match/mismatch effects, where the smaller host-**43b** is configurationally "matched" with the smaller propene substrate, and **43a** with the larger octene. Modular reactivity can thus be achieved by fine-tuning the steric and electronic properties of the supramolecular coordination sphere.

In another example by Reek, Nitschke, and co-workers, a Rh hydroformylation catalyst was encapsulated within host-**44**, a zinc-porphyrin analogue of a previously reported Fe_4L_6 host (**Figure 6b**).[87] The cage assembles around two phosphine ligands, which together chelate a single Rh complex. Upon subjecting a series of terminal olefins to supramolecular hydroformylation conditions, smaller substrates (1-hexene) underwent significantly higher conversions than larger substrates (styrene). Control reactions in the absence of **44** showed a narrower range of conversions

regardless of substrate size. This example demonstrates that supramolecular host-mediated regioselectivity can be extended to size-selective transformations as well.

While previous examples involved multi-component syntheses of novel supramolecular hosts, Sollogoub and co-workers demonstrated regioselective reactivity using covalent *N*-heterocyclic carbene (NHC)-capped α-cyclodextrin host-**45a** and β-cyclodextrin host-**45b** (**Figure 6c**).[90] NHC coordination to $Cu^{I}Cl$ creates an active encapsulated catalyst for the borylation of phenylalkynes.[91] Subjecting substituted and unsubstituted terminal and internal phenylalkynes to host-**45a**-mediated borylation conditions resulted in excellent selectivity for the linear products, yielding *b/l* ratios as low as 0.02. In contrast, the larger host-**45b** catalysed the formation of the branched product as the major isomer under otherwise identical conditions. NMR studies of the reaction intermediates revealed that the selectivity-determining *syn*-borylcupration step occurs within the host cavity. DFT analyses suggested that the smaller cavity size of **45a** enforces an orthogonal, horizontal approach of the acetylene, whereas **45b** promotes a vertical approach, in which the alkyne projects directly into the larger cavity.

In another example by Sollogoub and co-workers, host-**45a/b** were utilized in the regioselective hydrosilylation of conjugated enones (**Figure 6c**).[92] The generation and stabilization of a distinct, monomeric Cu-H species within the host cavity enabled asymmetric reduction of acetophenone in good yields and enantiomeric excess using phenylsilane as the reductant. Furthermore, host-**45a** was selective for the 1,2-reduction product for benzylideneacetone derivatives, whereas the larger host-**45b** generated the 1,4-reduction product. This example again demonstrates the ability of the two cyclodextrin-based ligands to stabilize and select for different orientations of the substrate as it approaches the reactive metal centre.

While regioselective transformations at a single reactive site have been successfully demonstrated by encapsulated metal catalysts, site-selective reactivity in the presence of multiple reactive sites is a longstanding challenge. A recent report by Raymond, Bergman, and Toste and co-workers addresses this challenge by demonstrating a rare example of site-selective hydrogenation of poly-enols utilizing the Ga naphthalene host-**1** (**Figure 6d**).[93] The active hydrogenation catalyst was formed *via* halide abstraction from (DMPE)RhCl and encapsulation of the resulting Rh cation. Under host-catalysed hydrogenation conditions, various hexen-1-ol substrates yielded high conversions of olefins in which the double bond is remote from the hydroxyl group (5- and 4-hexen-1-ol), but little to no conversions of more proximate double bonds (3- and 2-hexen-1-ol). In stark contrast, the free Rh catalyst resulted in quantitative conversion of all hexen-1-ol substrates, regardless of alkene position. Increased site-selectivity was attributed to the preferential binding of the more lipophilic alkyl end of the pendant alcohol substrate within the host. Similarly, a linolenic acid derivative underwent selective hydrogenation in the presence of larger pyrene-based host-**46**. These examples demonstrate the potential of encapsulated metal catalysis to address synthetic challenges in the selective functionalization of natural products and biomolecules.

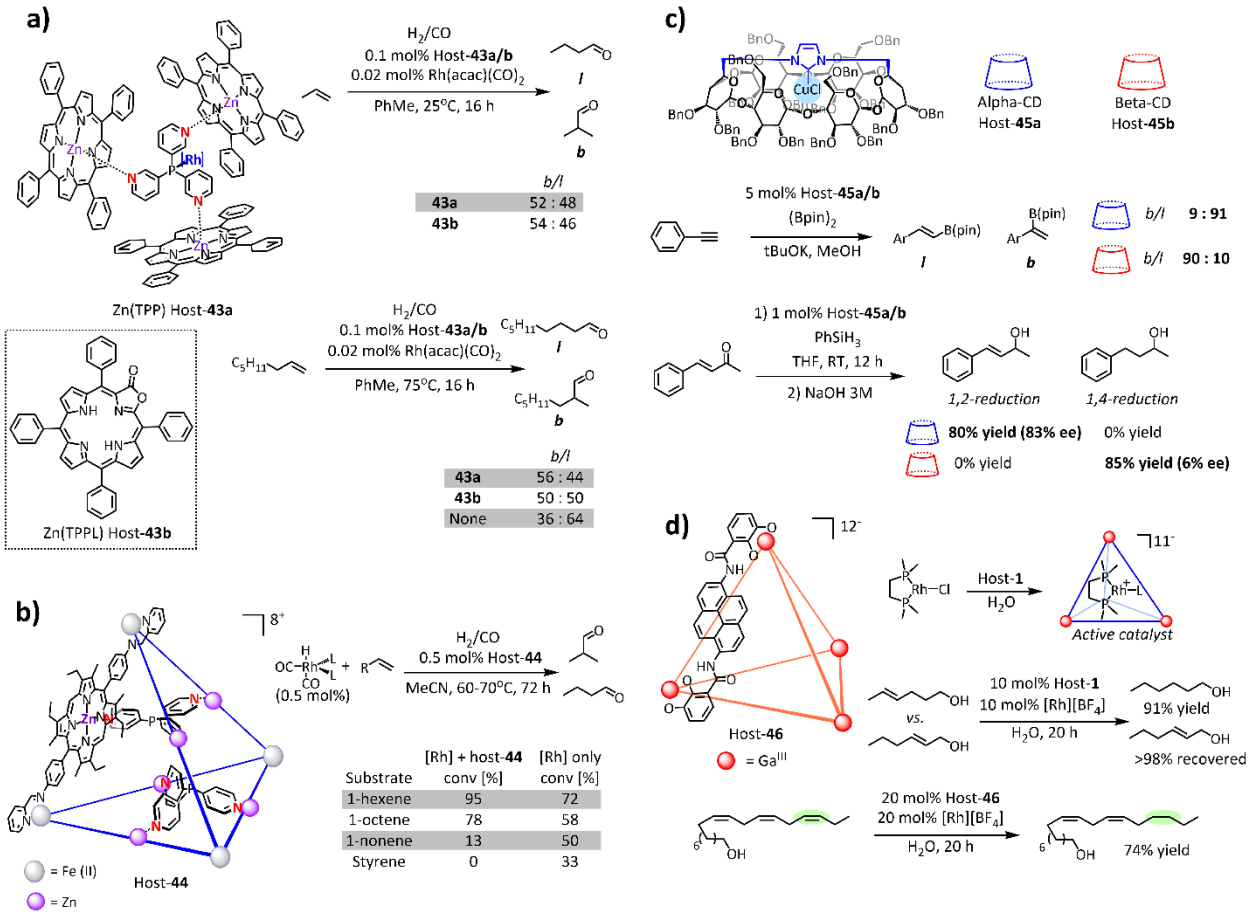

Figure 6. Regio- and site-selective reactivity catalysed by supramolecular hosts

a) Left: Zn(TPP) host-**43a** and smaller Zn(TPPL) host-**43b**. Right: linear vs. branched hydroformylation of 1-octene and propene, in which host-**43a** and **43b** give different selectivities. **b)** Left: Host-**44** by Reek, Nitschke and co-workers, which integrates Zn porphyrin moieties into Fe_4L_6 cage previously reported by the Nitschke group. Right: Smaller substrates generally result in higher conversion, though some anomalous conversions were observed for 1-heptene and 1-decene. **c)** Top: α- and β-cyclodextrin hosts-**45a** and **45b**, a bridging covalently tether NHC chelates a molecule of CuCl. Bottom: **45a** and **45b** gives opposite selectivity in a copper-catalysed borylation and hydrosilylation. **d)** Left: Larger pyrene host-**46** by Toste and co-workers. Right: Active cationic Rh complex formed inside the cage selectively hydrogenates terminal olefins.

Photochemical Reactivity Enabled by Supramolecular Hosts

Photochemical reactions are notoriously difficult to control due to their intrinsically low reaction barriers upon excitation and highly reactive intermediates. Supramolecular hosts provide an opportunity to control such reactions through pre-organization of reactive species, and in some cases modifying the photophysical properties of participating reagents. Supramolecular chemistry has historically been used in conjunction with photochemistry—nearly three decades ago, Cram and co-workers used a hemicarcerand host to stabilize and characterize antiaromatic cyclobutadiene, formed through a photochemical 4 pi-electrocyclic ring closure from 2-pyrone, followed by a retro-[2+2] to release CO_2.[94] More recently, a host-guest system was shown to enhance the yield and enantioselectivity in a similar organic photoreaction. Aitken and co-workers reported the photochemical 4 pi-electrocyclization of lactam **47** assisted by heterogenous β-cyclodextrin (**β-CD**) (**Figure 7a**).[95] The chiral **β-CD** formed a 1:1 complex with **47** in the solid state, and upon UV irradiation product **48** was obtained in 79% yield and 38% ee.

Supramolecular hosts can also promote steric control in bimolecular photochemical reactions. Since the early 2000s, Inoue and co-workers have investigated the ability of cyclodextrin hosts to enforce stereo- and enantioselectivity on the photochemical [4+4] cyclodimerization of anthracenes.[96] Cyclodextrins typically favour head-to-tail dimerization of 2-anthracenecarboxylate by encapsulating two anthracenes with their carboxylate groups protruding from either end of the host. Increasingly complex cyclodextrin derivatives have been prepared to mediate this reaction, some bearing substitution at the rims, and others covalently linked to cocatalysts. In recent years, the Yang group has utilized cyclodextrin derivatives to attain high stereo- and regiocontrol over anthracene dimerization. With 0.5 mol% Host-**49**, a **γ**-cyclodextrin tethered to a platinum photosensitizing complex, the syn-head-to-tail cyclodimer **50** was favoured with 31.4% ee and

61% conversion (**Figure 7b**).[97] The attached platinum photosensitizer allowed sensitization with visible light, while anthracene itself only absorbs in the higher energy ultraviolet region. Cyclodextrin hosts can also form 2:2 complexes with anthracene to favour nonclassical "slipped" anthracene dimerization between a central and edge ring. Functionalization of the cyclodextrin's primary alcohol rim with cationic ammonium salts (Host-**51a**/**b**) promotes electrostatic interactions with the carboxylate groups on the anthracenes. As a result, head-to-tail slipped dimers **52** and **53** were preferentially formed in high yield (92-100%) over classical cyclodimers (**Figure 7c**).[98] Additionally, the products were formed with 71% ee for **52** and 45% ee for **53**. Further stereocontrol was achieved with host-**54**, which consists of two β-cyclodextrins tethered together by a sulphide link, and selectively forms anthracene cyclodimer **55** with 100% ee (**Figure 7d**).[99] Selectivity for head-to-tail cycloaddition both with cyclodextrin and in bulk solution was reversed with the use of the bowl-shaped octa-acid cavitand, host-**4** (**Figure 1e**). Host-**4** has a single solvent-exposed opening while cyclodextrin has two, and projects both hydrophilic carboxylate ends in the same direction, promoting the formation of head-to-head cyclodimers **56** and **57** (**Figure 7e**).[100]

In addition to altering the stereochemical outcomes of photochemical transformations, redox-active supramolecular hosts can also function as photosensitizers to access otherwise challenging reactivity. The tris-catecholate tetrahedral host-**1** promoted a redox-neutral photochemical 1,3-rearrangement of allyl-dimethyl-cinnamylammonium derivatives (**58**) within its core via photoinduced electron transfer (PET) from its electron rich ligands (**Figure 7f**).[101] This rearrangement occurred in competition with a background fragmentation reaction, which arises from interception of the cinnamyl cation intermediate with water to give cinnamyl alcohol and dimethyl allyl amine. When the host was blocked by a competitive tetraethylammonium guest, no rearrangement product was observed, and fragmentation was the primary reaction pathway.

Stronger binding affinity of the starting material correlated with more rearrangement product (**59**), and conversely weaker binding affinity resulted in more fragmentation to cinnamyl alcohol and the corresponding amine (**60**). *N*-propyl and *N*-ethyl ammonium derivatives produced 83% and 82% yield of rearrangement products respectively, whereas the weakly bound *N*-*n*-hexyl ammonium produced only fragmentation product. This reaction demonstrates how a host can not only photosensitize a reaction, but also provide access to alternative reaction trajectories through its confined cavity environment.

Fujita and co-workers have also reported a cyclopropane demethylenation photosensitized by a redox-active host (**Figure 7g**).[102] Host-**15** features an electron-deficient triazine ligand, which, upon irradiation, accepts an electron from the excited cyclopropane-containing guest. The resulting cyclopropyl radical cation is then proposed to undergo rapid ring-opening via nucleophilic addition of nitrate, followed by radical fragmentation to yield the olefinic product. An equivalent of the nitrite radical is also generated, which oxidizes the host to reform the nitrate anion. This methodology was applied to achieve selective demethylenation in a dicyclopropanated steroid, providing exclusive generation of the double bond adjacent to the enone (**Figure 7g**). To expand on previous results from Fujita and co-workers on the photo-oxidation of adamantane with host-**15**,[103,104] Dasgupta and co-workers utilized host-**15** in the photo-oxidation of benzyl C–H bonds through host-guest charge transfer.[105] The host pre-organizes the substrate with solvent water molecules to assist with proton-coupled electron transfer, generating a neutral benzylic radical. Under irradiation and pressurized oxygen gas, the generated radical is oxidized to benzaldehyde. The system accommodated a range of toluene derivatives to produce the corresponding benzaldehyde product with >94% yield.

While the examples above require stoichiometric quantities of host, Su and co-workers reported a catalytic photodimerization using host-**61**, which incorporates a RuL_3 photocatalyst into its ligand scaffold.[106] Under blue LED light, host-**61** catalysed dimerization of naphthol derivatives in the presence of oxygen, to yield the corresponding naphthoquinone products (**Figure 7h**). The constricted cavity of the host enforced 1,4-coupling instead of the typically favoured 1,1-coupling to yield BINOL products. When the reaction was run with enantioresolved host-**61**, moderate enantioselectivity was achieved (up to 58% ee), albeit with lower yields.

As shown by these studies, supramolecular hosts assist photochemical reactions in unique ways, by pre-organizing encapsulated substrates to accelerate reaction rate, imposing stereocontrol, improving product selectivity, and in some cases acting as photosensitizers as well.

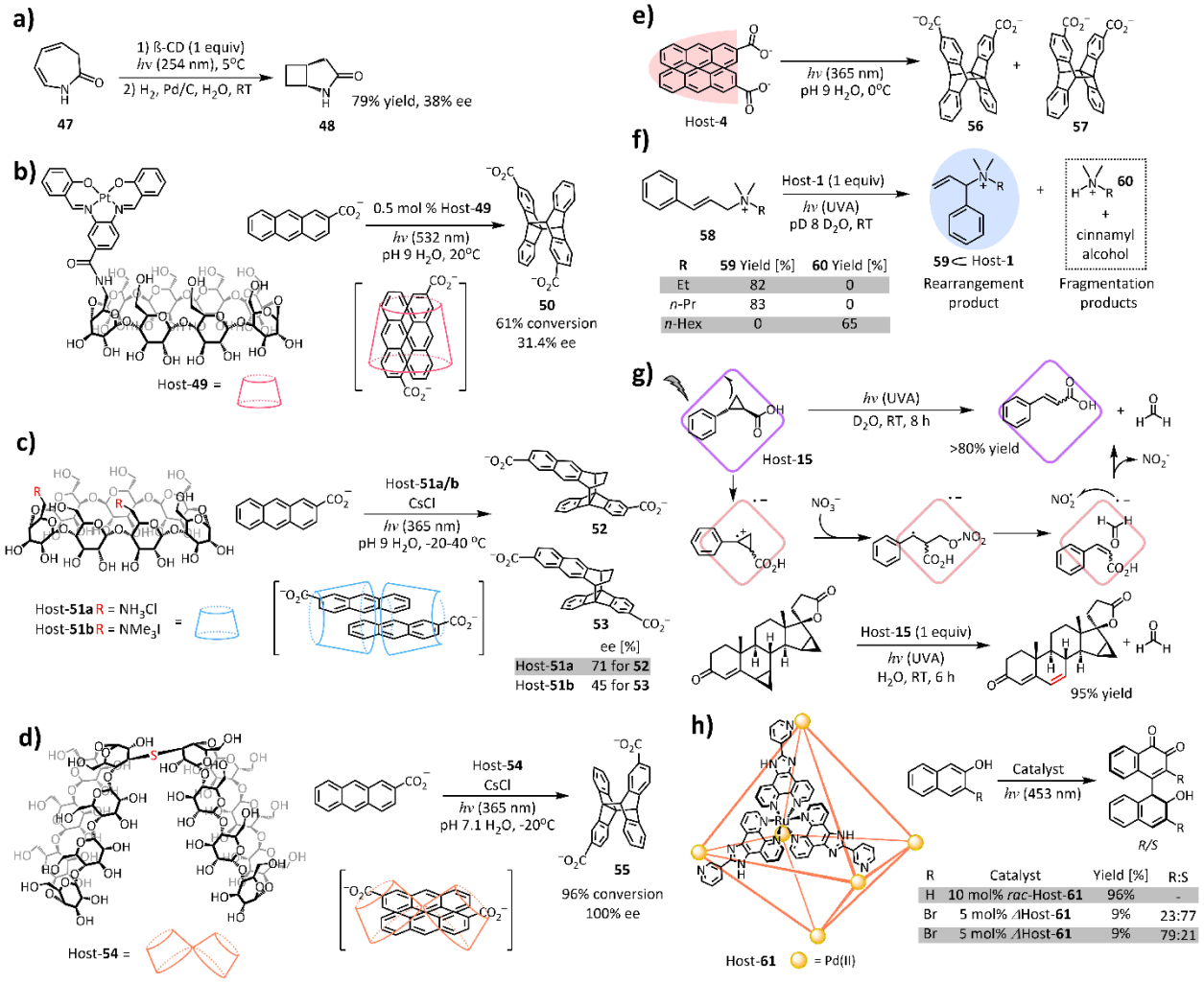

Figure 7: **Photochemical Reactions Aided by Supramolecular Hosts**

a) Electrocyclization catalysed by **β-CD**, followed by Pd/C reduction, reported by Aitken and co-workers. **b)** Left: platinum photosensitizer tethered to **γ**-cyclodextrin. Right: head-to-tail anthracene dimerization catalysed by host-**49. c)** Left: rim-modified β-cyclodextrins hosts **51a/b** Right: slipped anthracene dimerization catalysed by 2:2 β-cyclodextrin:anthracene complexes. **d)** Left: sulphide-linked β-cyclodextrin dimer synthesized by Yang and co-workers. Right: highly enantioselective anthracene dimerization catalysed by host-**54**. **e)** Anthracene dimerization, reported by Ramamurthy and co-workers, catalysed by host-**4**. **f)** 1,3-rearrangement catalysed by host-**1**, and table highlighting the effect of longer chains on the efficiency of rearrangement. **g)** Top: mechanism for demethylenation of cyclopropanes catalysed by host-**15**. Bottom: application of cyclopropane demethylenation to a steroid. **h)** Left: photosensitizing host synthesized by Su and co-workers. Right: naphthol 1,4-dimerization catalysed by host-**61**.

Conclusion

Throughout this review, we have presented advances made at the interface of supramolecular catalysis and a wide range of synthetically relevant fields, including organic, organometallic, and photochemistry. These examples highlight the ability of supramolecular hosts to function as mechanistic probes to deconvolute microenvironment catalysis, and as useful catalysts in challenging organic transformations. Taken together, they also reveal key subsequent directions in which this field can expand.

The shift from proof-of-concept type reactivity to synthetic application is one of the frontiers of supramolecular chemistry, particularly involving asymmetric catalysis and site-selective reactivity. While the development of enantioenriched coordination cages presents a new way of controlling the chiral environment around reactive intermediates and transition states, systematic optimization of the host scaffold remains a major challenge. Fundamental progress directed towards the rational design of chiral host assemblies, including post-assembly modification and templating strategies, is needed for structure activity relationship studies and further development of supramolecular asymmetric methods.[107]

Site-selective supramolecular catalysis is another impactful application that warrants further investigation. The ability of a supramolecular host to maintain high reactivity on a partially encapsulated substrate presents the opportunity to target increasingly complex molecules, as demonstrated in the site-selective hydrogenation reaction by Toste, Raymond, Bergman, and co-workers.[93] We expect to see further applications of this supramolecular strategy in late-stage natural product functionalization and modification of biomolecules such as peptides and proteins.

Although significant progress has been made in the synthetic application of organic and organometallic host-mediated reactions, supramolecular reaction development in photochemistry

and electrochemistry is still a work in progress. Photochemical host-mediated reactivity is largely limited to proof-of-concept transformations such as intramolecular rearrangements, dimerization reactions, and cycloadditions. Initial efforts toward asymmetric and site-selective photochemical reactivity promoted by photoactive hosts show promise for further application-based studies. Light-responsive shape-shifting hosts, such as those developed by Clever and co-workers, may also enable new modes of reactivity as photo-switchable supramolecular catalysts.[108] Host-mediated strategies in electrochemistry have not yet been extensively explored, particularly regarding electrochemically active hosts. Recent reports by Schalley and co-workers indicate the ability of a supramolecular host to alter the redox potential of ferrocene *via* thermodynamic stabilization of ferrocenium upon encapsulation.[109] Lusby and co-workers reported a similar phenomenon, in which encapsulated quinone guests experience a shift in redox potential.[110] These findings suggest the potential of supramolecular hosts to facilitate otherwise challenging electrochemical transformations through selective stabilization of the reduced/oxidized form of the guest.

Finally, the last half-decade has seen major advances in theoretical analyses of supramolecular systems and the reactions that they mediate.[111–115] These calculations have been a long-standing challenge due to the large number of atoms typically associated in a supramolecular system, as well as other parameters such as the number of explicit solvent molecules within the cage. Theoretical calculations can be a useful mechanistic and predictive tool, particularly in real-time collaboration with the corresponding experimental work, and we anticipate a closer interaction between theoretical and supramolecular chemists in the future.

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Author contributions

†M.M., S.M.B., and K.T.X. contributed equally. All authors were involved in surveying the literature and structuring and editing the manuscript.

Competing interests

The authors declare no competing interests.

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