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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-

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

70 **Organic Reactions Catalysed by Supramolecular Hosts**

71 Supramolecular catalysis is hallmarked by the ability of host molecules to stabilize
72 encapsulated reactive species through a number of non-covalent interactions, thereby decreasing
73 the free energy gap between reactant states and transition states. Drawing on multiple stabilizing
74 factors, remarkable catalytic activity has been observed within supramolecular hosts, inviting
75 comparisons to the activity of enzymes. Specifically, supramolecular Brønsted acid catalysis has
76 been enabled via favourable Coulombic and cation-pi interactions within hosts, allowing (for
77 example) Brønsted acid catalysis to take place under usually prohibitive basic, aqueous
78 conditions.[32] This reactivity is demonstrated by an aza-Prins rearrangement, catalysed by the
79 triscatecholate based dodecaanionic host-**1** which has been studied extensively by Raymond,
80 Bergman, Toste, and co-workers. This host effectively stabilizes hydrolytically unstable cationic
81 species, including iminium ions within its core, despite water as solvent,[33] which in the aza-Prins
82 reaction enabled the intramolecular nucleophilic addition of a pendant alkene to an *in-situ*
83 generated iminium ion **(Figure 1a)**.[34] The encapsulated addition complex underwent an unusual
84 1,5-hydride shift, facilitated by the constrictive nature of the interior of host-**1**. The product
85 generated cannot be accessed under conventional acid catalysis in the absence of the host, and
86 demonstrates the role that supramolecular catalysts can play in accessing atypical reaction
87 pathways by an acid catalysed mechanism.

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

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

97 Supramolecular hosts also demonstrate the ability to modulate product selectivity in
98 iminium catalysed reactions. Tiefenbacher and co-workers reported the selective 1,4-reduction of
99 α,β-unsaturated cinnamaldehyde derivatives catalysed by chiral proline derivatives and
100 resorcinarene host-**2** (**Figure 1b**).[36] Host-**2** self-assembles from six equivalents of resorcinarene in
101 organic solvents, and is held together via phenolic hydrogen bonding. The phenolic units of **2** have
102 a lower than expected pKa of 5.5-6 (rather than the typical pKa 10 for phenol) enabling them to
103 function as a built-in source of acid. The polyaromatic nature of the ligands promote acid catalysis
104 via stabilization of cationic intermediate due to favourable cation-pi interactions.[17] In Tiefenbacher
105 and co-workers' report, a proline catalysed 1,4-reduction of α,β-unsaturated aldehydes was
106 subjected to hexamer **2**, and a significant change in the enantiomeric excess (ee) of the product
107 aldehyde was measured. For an *ortho*-methoxy substituted cinnamaldehyde substrate, the **2**-
108 catalyzed reaction yielded the corresponding product with 78% ee (S), compared to 9% ee (S) in
109 the control reaction (69% Δee). The change in the enantioselectivity of the reaction originates from
110 host-**2** blocking the less sterically hindered face of the aldehyde, generating a "mismatched" case
111 with the proline derivatives. This causes the Hantzsch ester to deliver the hydride from the same
112 face into which the proline chiral information projects.[37] Acid catalysis within host-**2** was extended
113 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.

137 In many cases the source of rate acceleration in supramolecular catalysis is poorly
138 understood. To elucidate the effect of host charge, the Raymond, Bergman, and Toste groups
139 reported a two-cage study on the rates of an acid-catalysed Nazarov cyclization.[49] The Nazarov
140 cyclization, which proceeds with up to 10^6-fold rate acceleration in the presence of dodecaanionic
141 host-**1,** was subjected to the octaanionic Si^{IV}-based host-**3** (**Figure 1d**). Host-**1** accelerated the rate
142 680-fold more than host-**3**, due to its superior ability to stabilize the cationic intermediates and
143 transition state of the Nazarov cyclization. For an overall charge-neutral Aza-Cope reaction
144 catalysed by the constricted interior of the hosts, the rate should be independent of host charge
145 because the single positive charge on the reactant does not change during the transformation—and
146 indeed, the rates were found to be within error between hosts **1** and **3**. Despite being isostructural,
147 hosts **1** and **3** exhibit contrasting reactivity due to their difference in charge. In a related study,
148 Gibb and co-workers investigated the effect of charge on the macrocyclization of α, ω thioalkane
149 halides in organic supramolecular capsules.[50] Two related capsules were synthesized: capsule **4,**
150 containing pendant carboxylate anions, and capsule **5**, containing pendant ammonium cations
151 (**Figure 1e**), which both self-assemble in solution to form homodimers that encapsulate
152 hydrophobic molecules. Homodimer **5** catalysed the macrocyclization reaction to completion in a
153 matter of minutes, while in the presence of the anionic homodimer **4**, the reaction required several
154 weeks. This discrepancy in rate originates from stabilization of the thiolate anion (the active
155 nucleophile), by cationic host **5**. These two studies emphasize the importance of charge and
156 electrostatic fields in enabling catalytic pathways within supramolecular hosts.

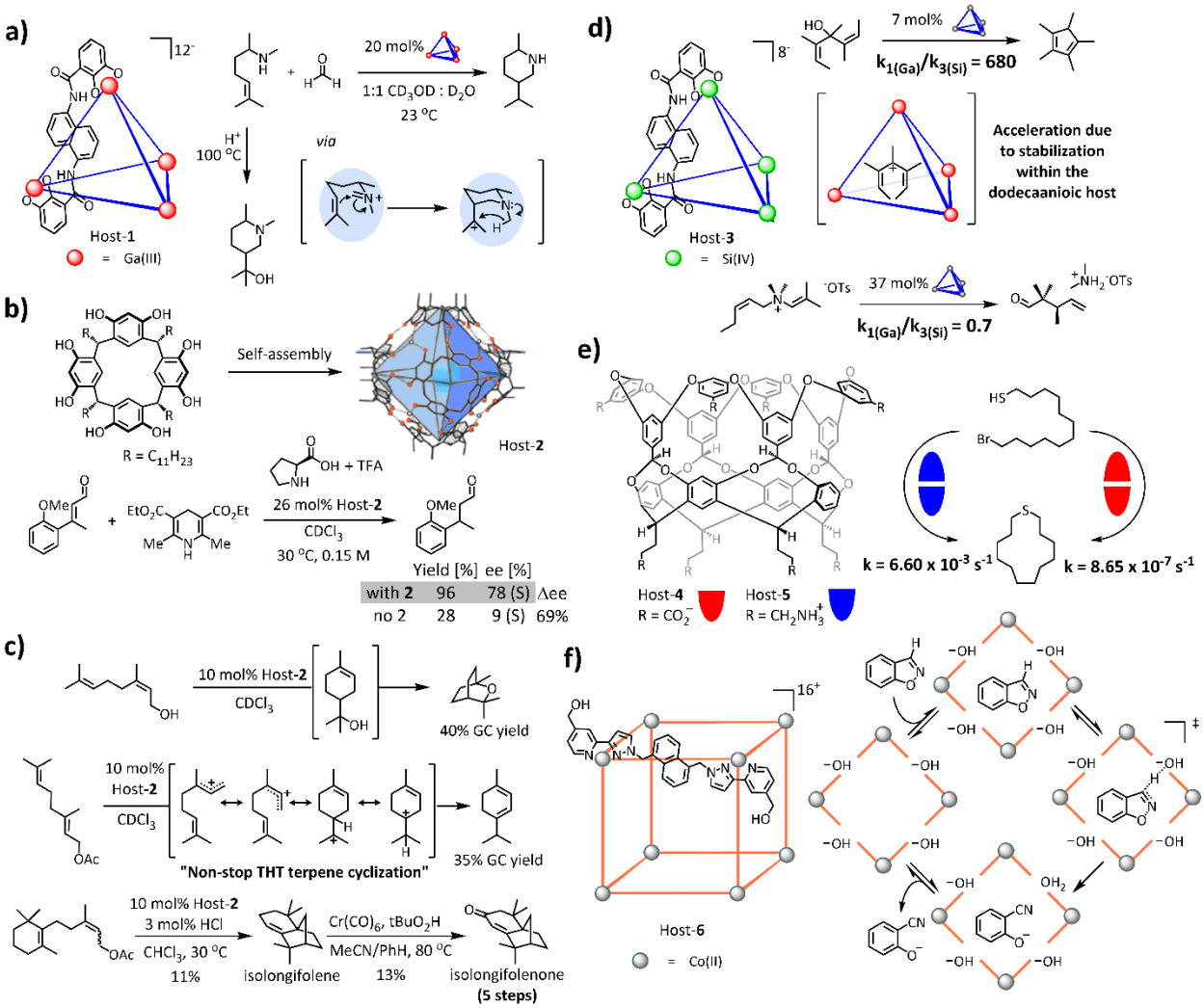

Figure 1: Organic transformations catalysed by supramolecular hosts

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

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

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

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

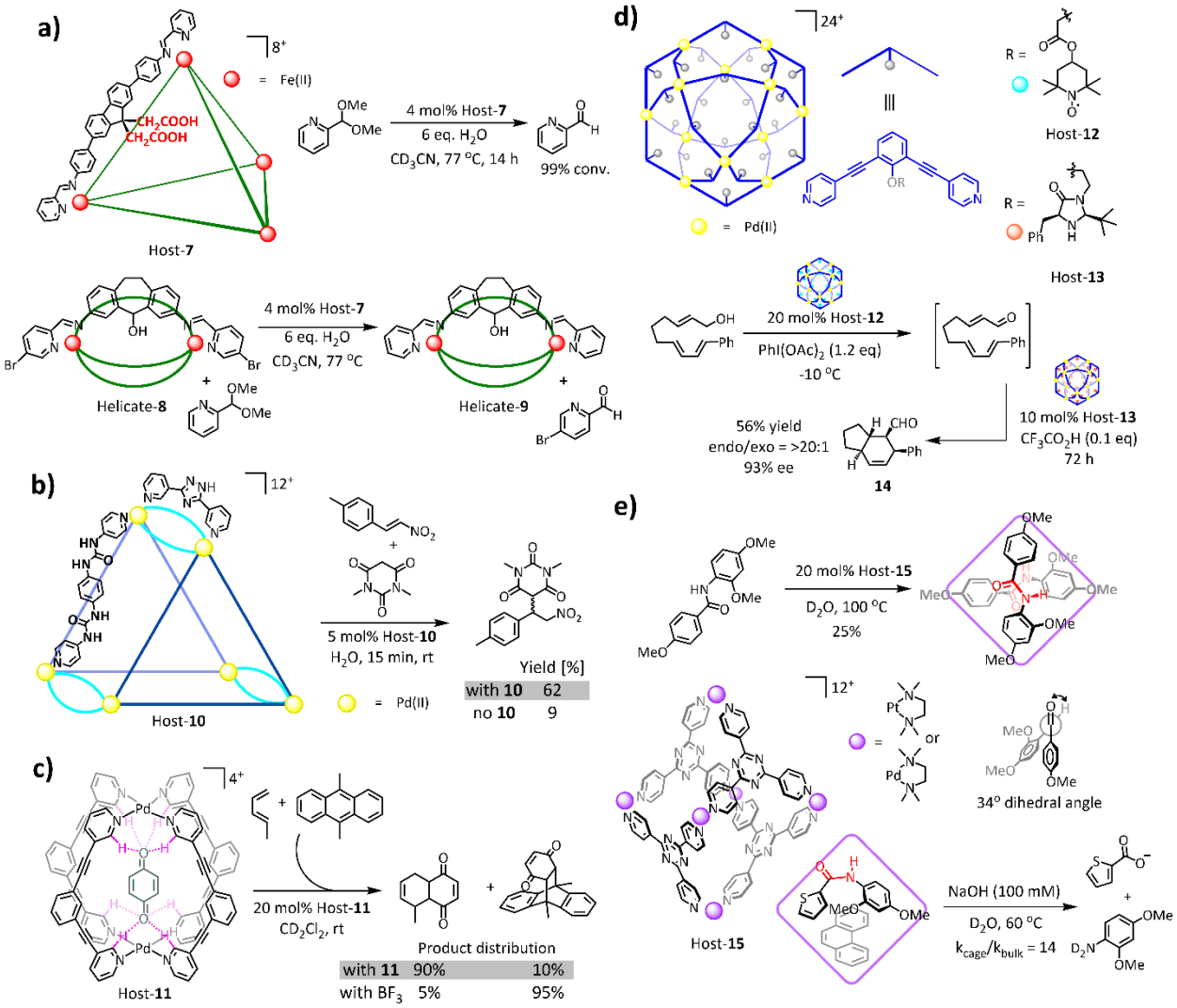

Figure 2: Organic transformations promoted by supramolecular hosts

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.

230 **Organometallic Reactions Catalysed by Supramolecular Hosts**

231 Supramolecular hosts enable novel reactivity for organometallic catalysts in ways
232 otherwise inaccessible by traditional ligand scaffolds, much as proteins can alter the secondary
233 coordination sphere in enzymes. Charged hosts can stabilize oppositely charged reaction
234 intermediates to accelerate or favour a particular reaction pathway, as highlighted by the
235 acceleration of elementary organometallic steps within the anionic tetrahedral host-**1** studied by
236 the Raymond, Bergman and Toste groups (**Figure 1a**).[58] Host-**1** catalysed the reductive
237 elimination of a dimethyl monophosphine Au^{III} iodide (**16**) to form ethane with a 1.9×10^7-fold rate
238 acceleration (**Figure 3a**).[59] This dramatic rate acceleration has been attributed to constrictive
239 binding and stabilization of the positively charged transition state by the anionic host.[60] Similarly,
240 the rate of reductive elimination from an encapsulated Pt^{IV} complex (**17**) was increased 2.6×10^4-
241 fold (**Figure 3a**). Host-**1** has a turnover number (TON) of 312 for the reductive elimination from
242 **16**, but this TON was increased to 947 for related host-**18**, which is made more stable to alkyl
243 halides by chiral amides at its vertices. Host-**18** behaved as a cocatalyst with platinum complex **19**
244 in a dual catalytic mechanism for the sp^3-sp^3 cross coupling of an alkyl tin and alkyl halide,
245 accelerating the prohibitively slow reductive elimination step of the catalytic cycle (**Figure 3a**).[61]
246 Notably, this represents a unique example in which an organometallic complex shuttles between
247 cooperative catalytic cycles occurring both inside and outside of the host cavity. Host-**1** also
248 accelerates β-hydride elimination from an ethyl dimethyl Pt^{IV} complex to form ethylene, and
249 reductive elimination from an acyl dimethyl Pt^{IV} complex to yield acetone. The scope of this
250 system is limited by the size of the host cavity, which excludes a larger benzyl dimethyl Pt^{IV}
251 complex.

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

262 Supramolecular hosts have also demonstrated the ability to enhance enantioselective
263 transformations induced by single metal catalysts. Notably, Reek and co-workers reported an
264 enantioselective hydroformylation reaction for branched aldehyde products, catalysed by a
265 supramolecular Rh complex.[63] Catalyst-**20** consists of a Rh-ligated chiral phosphoramidite, which
266 is coordinated to a mixed Zn^{II} porphyrin and Pd-based coordination host (**Figure 3c**). **20**⊂Host-
267 **21** provided up to 71% ee and high conversion to the branched product, significantly out-
268 performing the free phosphoramidite Rh catalyst. Cui and co-workers also reported highly
269 enantioselective catalysis with host-**22** (**Figure 3d**)**.** Host-**22** self-assembles from three equivalents
270 of chiral Cr- and Mn-salen based ligands and Zr vertices.[64] This multi-metal host catalysed the
271 tandem epoxidation and nucleophilic ring opening to give product **23** in high conversions and
272 enantioselectivity. While the host did not increase the inherent ee provided by the free Mn-salen
273 catalyst, it led to increased overall conversions. This example thus highlights the ability of
274 supramolecular hosts to stabilize catalysts at lower loadings and increase their TON.

275 In addition to providing rate acceleration to mononuclear catalysts, supramolecular hosts
276 have demonstrated the ability to pre-organize multiple metal catalysts and enhance their catalytic
277 behaviour, as shown by Reek and co-workers. Through hydrogen bonding interactions between
278 host-bound guanidinium moieties and pyridine-bound sulphate moieties, host-**24** can encapsulate
279 up to twelve pyridine-ligated ruthenium complexes (**25**), creating a local ruthenium concentration
280 of up to 0.54M within its cavity—a condition difficult to attain in bulk solution due to solubility
281 and cost considerations (**Figure 3e**).[65] The host-catalyst complex accelerated electrochemical
282 water oxidation by two orders of magnitude through facilitation of the rate-limiting step, dinuclear
283 coupling of molecular oxygen, which was favoured by the increased local concentration of catalyst
284 (**Figure 3e**). Similarly, host-**24** can bind up to twelve copper Xantphos-based catalysts, modified
285 to contain sulphate groups to interact with the host, and accelerate the copper-catalysed cyclization
286 of 4-pentynoic acid.[66] This reaction also involves a rate-limiting dinuclear coupling step, which
287 was accelerated 50-fold despite the low average concentration of catalyst in solution. Additionally,
288 the host increased the turnover number by 2.5-fold compared to the unencapsulated copper catalyst
289 under the same reaction conditions. In a recent study, host-**24** not only pre-organized gold catalyst
290 **26**, but the substrate as well in the intramolecular cyclization of acetylenic acids (**Figure 3e**).[67, 68]
291 Aided by the addition of catalytic base, interactions between the substrate's deprotonated
292 carboxylic acid groups and the host's guanidinium groups led to selective formation of a five-
293 membered ring (**27b**) over a six-membered ring (**27a**), which was favoured in absence of the host.
294 Conversion decreased when the number of encapsulated gold complexes in each host cavity
295 exceeded four, as binding sites for the substrate were blocked, further evidencing the influence of
296 host-induced conformational pre-organization.

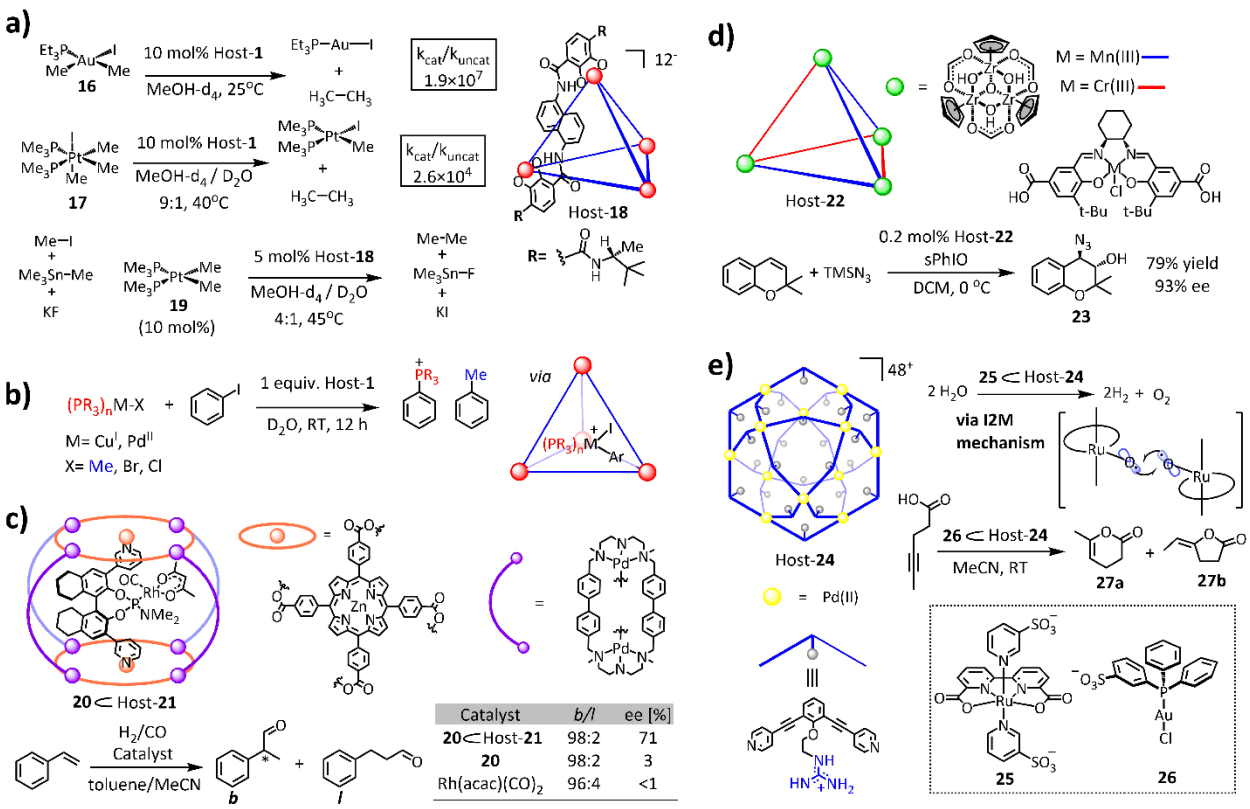

Figure 3: Organometallic transformations promoted supramolecular hosts

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

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

315 The Zhou group also reported a porous coordination cage (host-**29**) that encapsulates metal
316 cations in solution, which were reduced to form neutral metal nanoclusters within its pores.
317 Composite cobalt nanoclusters within host-**29a** showed superior catalytic activity in the hydrolysis
318 of ammonia-borane compared to other first row transition metal nanocluster catalysts (**Figure**
319 **4b**).[70] The negatively charged host-**29a** coordinates and organizes Co^{II} cations into smaller and
320 more uniform particles within its cavity, preventing the detrimental agglomeration of the particles,
321 even after reduction to Co^0. The significance of charge was evidenced by comparison to an overall
322 neutral analogue, host-**29b**, in which the sulphate groups were replaced with tert-butyl groups,
323 leading to instant agglomeration, followed by slower reaction times and slower turnover frequency
324 (**Figure 4b**). Zhou and co-workers also reported encapsulation of Ru^{III} cations in host-**29a** to form
325 uniform Ru^0 nanoclusters with improved catalytic activity in the methanolysis of ammonia
326 borane.[71] These examples highlight the possibilities of cooperation between supramolecular
327 chemistry and metal nanoparticles for small molecule catalysis.

328 In another instance of supramolecular nanoparticle catalysis, Mukherjee and co-workers
329 reported host-**30a** and host-**30b**, with multiple interior diamine binding sites that aid in the
330 synthesis of Pd^0 nanoparticles. The nanoparticles exhibited improved stability and catalytic
331 performance in the cyanation of aryl halides compared to other common palladium catalysts
332 (**Figure 4c**).[72] Host-**30a** has a significantly smaller cavity than host-**30b**, which led to the
333 formation of smaller Pd nanoparticles. As a result, host-**30a** demonstrated superior catalytic
334 activity, evidencing the influence of supramolecular hosts through modulation of particle size.
335 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.

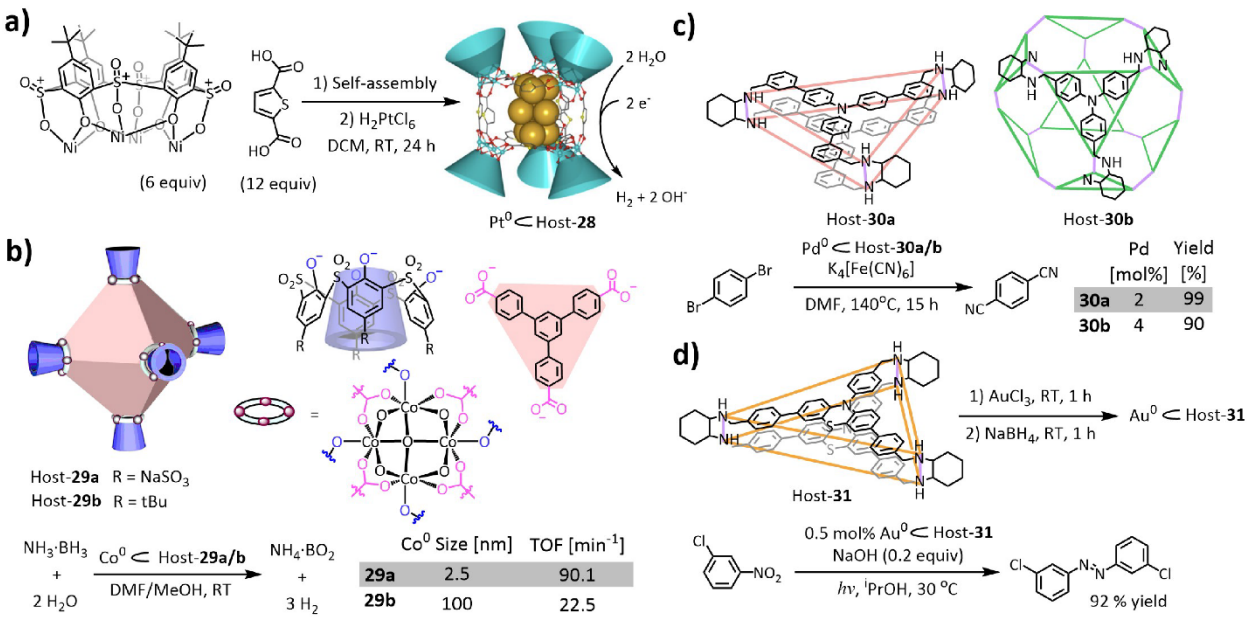

Figure 4: Host mediated metal nanoparticle synthesis and reactivity

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.

356 **Regio- and Site-Selective Reactivity Enabled by Supramolecular Hosts**

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

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

379 intramolecular olefin-metathesis reaction leading to the selective formation of cyclooctene in the
380 presence of Hoveyda-Grubbs-II catalyst.[76] This system was extended to the mono-
381 functionalization reaction of difunctional alkanes by subjecting α, ω-diazide **35** to Staudinger
382 reduction conditions in the presence of stoichiometric quantities of N-methyl urea cavitand, host-
383 **32b**.[77] Remarkably, mono-reduction product **36** was exclusively formed, even with excess
384 phosphine, whereas a mixture of reduction products form in the absence of the host. This
385 selectivity is attributed to a shift in the equilibrium towards conformation **B**/**C** upon mono-
386 reduction, where the amine extrudes from the cavity and the more lipophilic azide is shielded from
387 further reduction. Selective mono-functionalization and macrocyclization was also accomplished
388 successively in a one-pot fashion, as shown by the host-**32a** mediated transformation of diamine
389 **37** to di-lactam **38**.[80]

390 Fujita and co-workers extended this supramolecular "protecting group" approach further
391 by investigating its application to a simple natural product (**Figure 5b**).[81] Previously reported Pd
392 host-**15** (**Figure 2e**) self-assembles from four triazole ligands, forming a highly hydrophobic,
393 octahedral cavity. Geranyllinalool **39** forms a 1:1 inclusion complex with host-**15** under aqueous
394 conditions in which it adopts a U-shaped conformation, evidenced both by ^{1}H-^{1}H NOESY
395 correlation experiments and X-ray crystallography. The terminal prenyl moiety extrudes from the
396 cavity, whereas the two internal trisubstituted double bonds are well-encapsulated. Subjecting
397 host-guest complex **39⊂15** to an aqueous solution of N-bromosuccinimide (NBS) yielded a single
398 product, with exclusive bromination at the exposed prenyl site. Subsequent bromonium ring-
399 opening by NO_3^- counterions formed 14,15-nitratobrominated product **40** in 82% yield. Control
400 experiments in the absence of the cage yielded a mixture of bromination products due to competing
401 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.

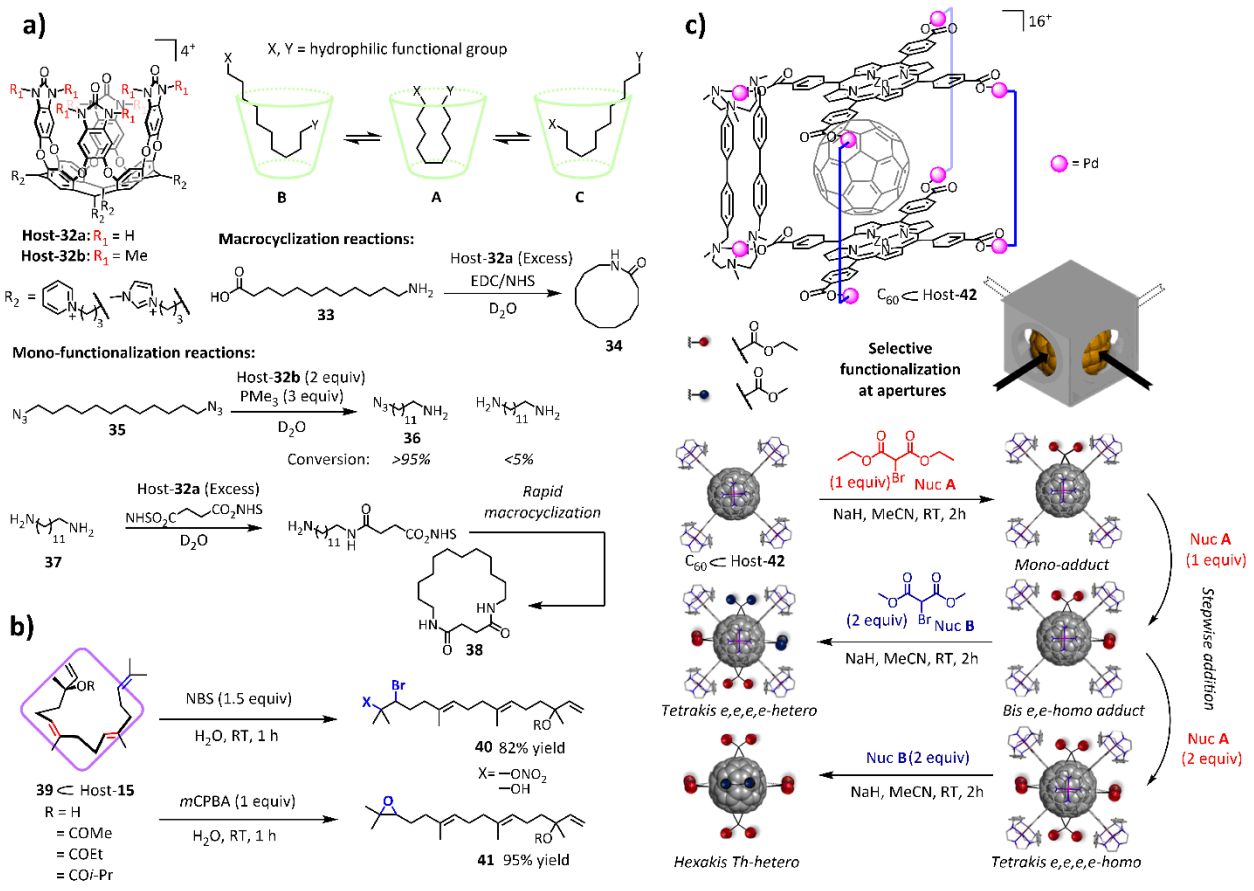

Figure 5. Regio- and site-selective reactivity rendered by stoichiometric amounts of supramolecular hosts

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

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

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

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

457 While previous examples involved multi-component syntheses of novel supramolecular
458 hosts, Sollogoub and co-workers demonstrated regioselective reactivity using covalent *N*-
459 heterocyclic carbene (NHC)-capped α-cyclodextrin host-**45a** and β-cyclodextrin host-**45b** (**Figure**
460 **6c**).[90] NHC coordination to $Cu^{I}Cl$ creates an active encapsulated catalyst for the borylation of
461 phenylalkynes.[91] Subjecting substituted and unsubstituted terminal and internal phenylalkynes to
462 host-**45a**-mediated borylation conditions resulted in excellent selectivity for the linear products,
463 yielding *b/l* ratios as low as 0.02. In contrast, the larger host-**45b** catalysed the formation of the
464 branched product as the major isomer under otherwise identical conditions. NMR studies of the
465 reaction intermediates revealed that the selectivity-determining *syn*-borylcupration step occurs
466 within the host cavity. DFT analyses suggested that the smaller cavity size of **45a** enforces an
467 orthogonal, horizontal approach of the acetylene, whereas **45b** promotes a vertical approach, in
468 which the alkyne projects directly into the larger cavity.

469 In another example by Sollogoub and co-workers, host-**45a/b** were utilized in the
470 regioselective hydrosilylation of conjugated enones (**Figure 6c**).[92] The generation and stabilization
471 of a distinct, monomeric Cu-H species within the host cavity enabled asymmetric reduction of
472 acetophenone in good yields and enantiomeric excess using phenylsilane as the reductant.
473 Furthermore, host-**45a** was selective for the 1,2-reduction product for benzylideneacetone
474 derivatives, whereas the larger host-**45b** generated the 1,4-reduction product. This example again
475 demonstrates the ability of the two cyclodextrin-based ligands to stabilize and select for different
476 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.

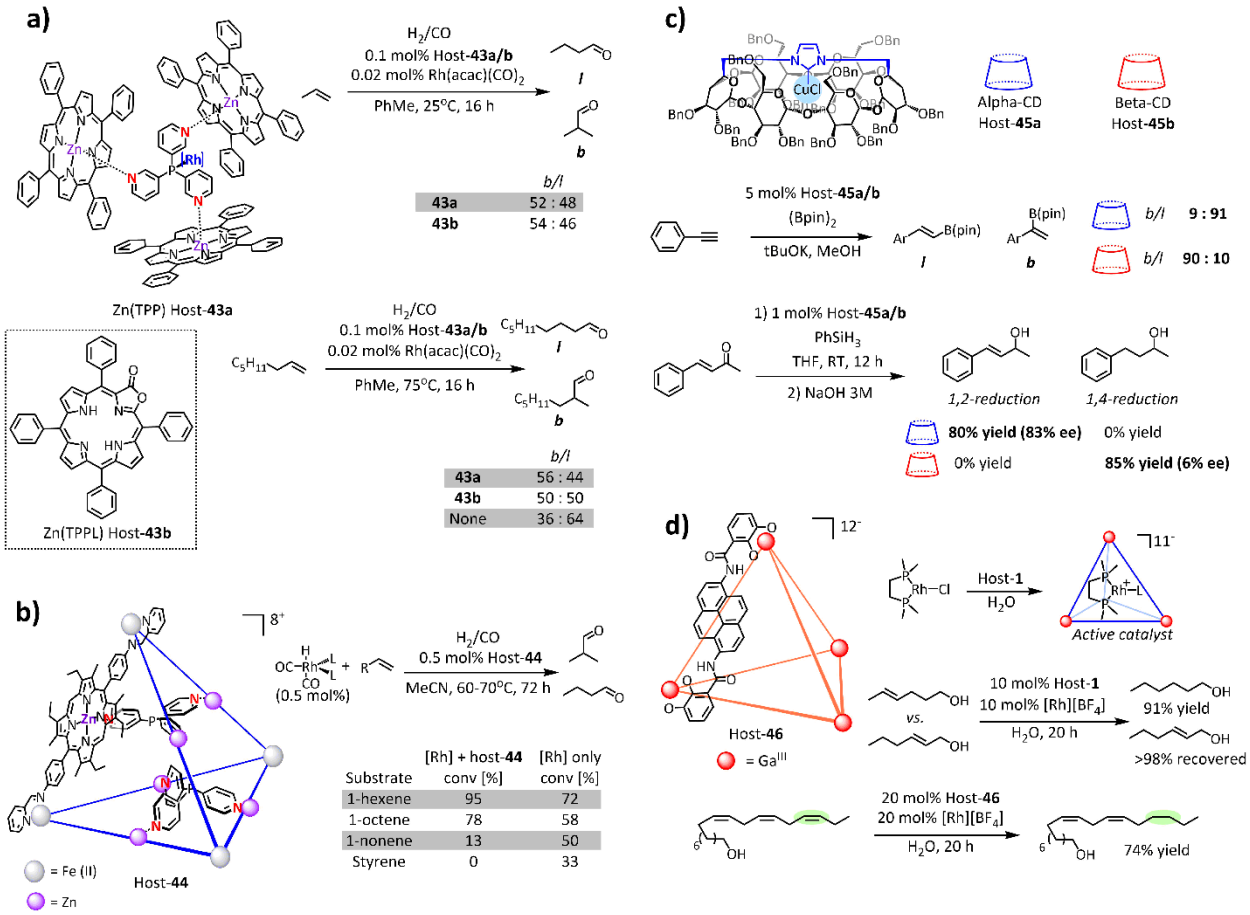

Figure 6. Regio- and site-selective reactivity catalysed by supramolecular hosts

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.

508 **Photochemical Reactivity Enabled by Supramolecular Hosts**

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

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

531 61% conversion (**Figure 7b**).[97] The attached platinum photosensitizer allowed sensitization with
532 visible light, while anthracene itself only absorbs in the higher energy ultraviolet region.
533 Cyclodextrin hosts can also form 2:2 complexes with anthracene to favour nonclassical "slipped"
534 anthracene dimerization between a central and edge ring. Functionalization of the cyclodextrin's
535 primary alcohol rim with cationic ammonium salts (Host-**51a**/**b**) promotes electrostatic
536 interactions with the carboxylate groups on the anthracenes. As a result, head-to-tail slipped dimers
537 **52** and **53** were preferentially formed in high yield (92-100%) over classical cyclodimers (**Figure**
538 **7c**).[98] Additionally, the products were formed with 71% ee for **52** and 45% ee for **53**. Further
539 stereocontrol was achieved with host-**54**, which consists of two β-cyclodextrins tethered together
540 by a sulphide link, and selectively forms anthracene cyclodimer **55** with 100% ee (**Figure 7d**).[99]
541 Selectivity for head-to-tail cycloaddition both with cyclodextrin and in bulk solution was reversed
542 with the use of the bowl-shaped octa-acid cavitand, host-**4** (**Figure 1e**). Host-**4** has a single solvent-
543 exposed opening while cyclodextrin has two, and projects both hydrophilic carboxylate ends in
544 the same direction, promoting the formation of head-to-head cyclodimers **56** and **57** (**Figure 7e**).[100]

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

554 Stronger binding affinity of the starting material correlated with more rearrangement product (**59**),
555 and conversely weaker binding affinity resulted in more fragmentation to cinnamyl alcohol and
556 the corresponding amine (**60**). *N*-propyl and *N*-ethyl ammonium derivatives produced 83% and
557 82% yield of rearrangement products respectively, whereas the weakly bound *N*-*n*-hexyl
558 ammonium produced only fragmentation product. This reaction demonstrates how a host can not
559 only photosensitize a reaction, but also provide access to alternative reaction trajectories through
560 its confined cavity environment.

561 Fujita and co-workers have also reported a cyclopropane demethylenation photosensitized
562 by a redox-active host (**Figure 7g**).[102] Host-**15** features an electron-deficient triazine ligand, which,
563 upon irradiation, accepts an electron from the excited cyclopropane-containing guest. The resulting
564 cyclopropyl radical cation is then proposed to undergo rapid ring-opening via nucleophilic addition
565 of nitrate, followed by radical fragmentation to yield the olefinic product. An equivalent of the
566 nitrite radical is also generated, which oxidizes the host to reform the nitrate anion. This
567 methodology was applied to achieve selective demethylenation in a dicyclopropanated steroid,
568 providing exclusive generation of the double bond adjacent to the enone (**Figure 7g**). To expand
569 on previous results from Fujita and co-workers on the photo-oxidation of adamantane with host-
570 **15**,[103,104] Dasgupta and co-workers utilized host-**15** in the photo-oxidation of benzyl C–H bonds
571 through host-guest charge transfer.[105] The host pre-organizes the substrate with solvent water
572 molecules to assist with proton-coupled electron transfer, generating a neutral benzylic radical.
573 Under irradiation and pressurized oxygen gas, the generated radical is oxidized to benzaldehyde.
574 The system accommodated a range of toluene derivatives to produce the corresponding
575 benzaldehyde product with >94% yield.

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

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

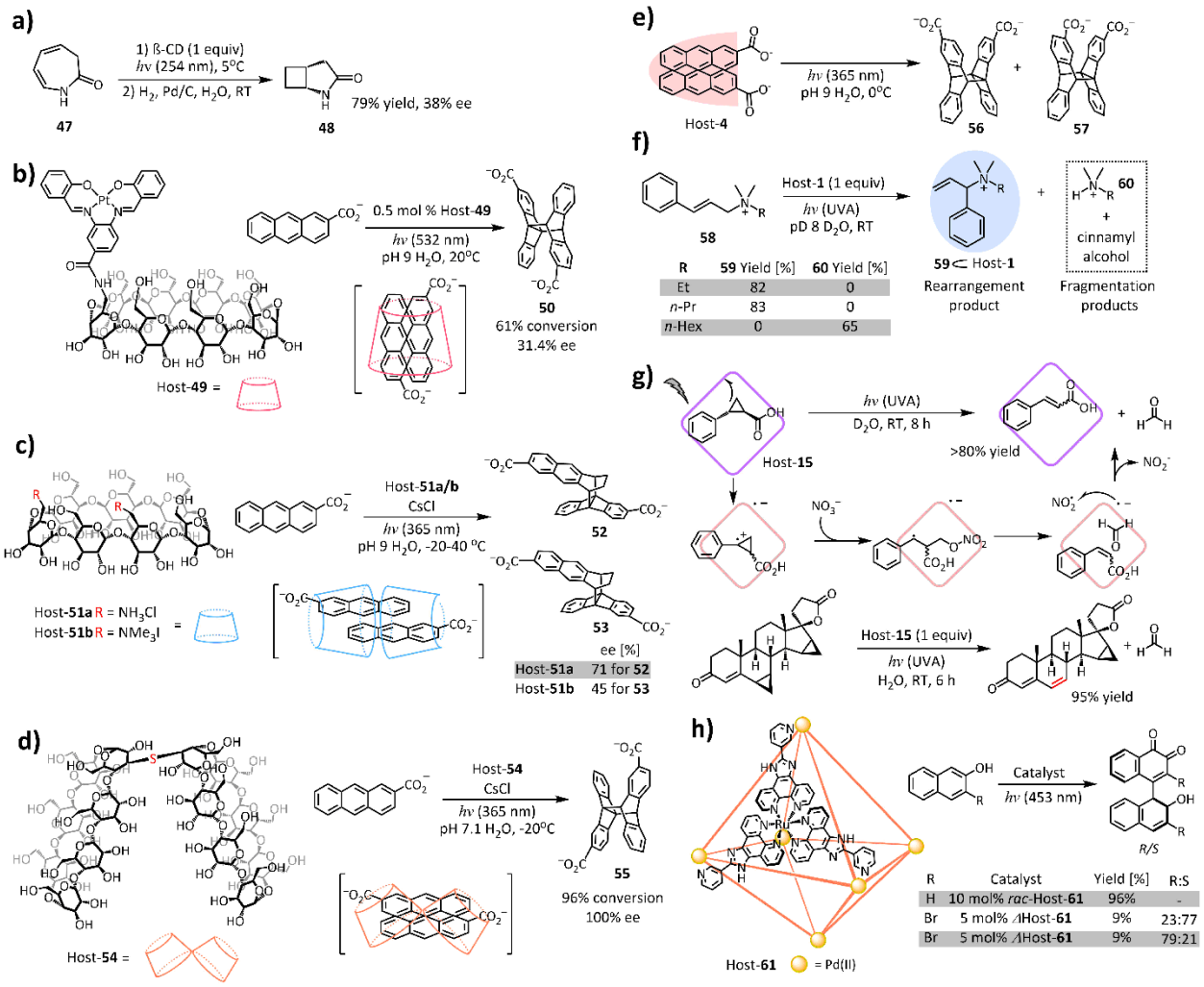

Figure 7: **Photochemical Reactions Aided by Supramolecular Hosts**

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**.

601 **Conclusion**

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

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

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

622 Although significant progress has been made in the synthetic application of organic and
623 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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