Self-Assembled Coordination Cages and Organic Capsules as Catalytic Supramolecular Reaction Vessels

Jeanne L. Bolliger

Abstract Host-guest chemistry has undergone an enormous development since the discovery of cyclodextrins more than 100 years ago which has culminated in the preparation of many artificial host molecules that are not only capable of encapsulating a variety of guests but also of promoting reactions inside their cavities. As the environment dramatically influences the behavior of chemical systems, recent years have seen increased interest in the use of the shielded inner phases of synthetic hosts to stabilize reactive species, shift equilibria, or achieve otherwise unfavorable conformations of guest species. Confinement inside hosts has been used to lower the symmetry of guests, thereby creating new means to control the outcomes of asymmetric reactions in the same way that biological systems make extensive use of tailored microenvironments to promote stereospecific reactions by destabilizing the ground state and stabilizing certain transition state geometries. This chapter will focus on the use of self-assembled coordination cages and organic capsules as homogeneous catalytic supramolecular reaction vessels. Modulation of the cavity environment and binding selectivity is relatively easily achieved because small changes to the geometries of building blocks can lead to much larger changes in the structures and properties of the hollow polyhedral coordination cages formed upon self-assembly. As the reaction medium influences the binding of the reactants and products in subtle but important ways, control over host solubility through host framework charge and substituent effects provides further means to control guest binding strengths, selectivity, and dynamics, and thereby a possible way to overcome product inhibition which is often encountered in supramolecular catalysis. A review will be provided over unusual selectivity observed in reactions carried out in metal-organic capsules as a result of structural constraints. Similarly, rate enhancements in bimolecular reactions due to an increase in effective molarity and

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stabilization of the transition state as well as transformations carried out under unusual conditions—for example, the acid catalyzed hydrolysis of orthoformates under neutral or basic conditions—will be discussed in this chapter. Furthermore, self-assembled coordination cages based on chiral ligands are of particular interest because they provide an asymmetric microenvironment for promoting stereoselective reactions by purely non-covalent interactions. Particular emphasis will be laid on the hydrolysis of organophosphorus species: As an example of the author's work, the catalytic degradation of the insecticide dichlorvos by a $[Fe_4L_6]^{8+}$ cage molecule will be presented, and this report will also include the up-to-date unpublished results obtained from experiments with other organophosphorus insecticides.

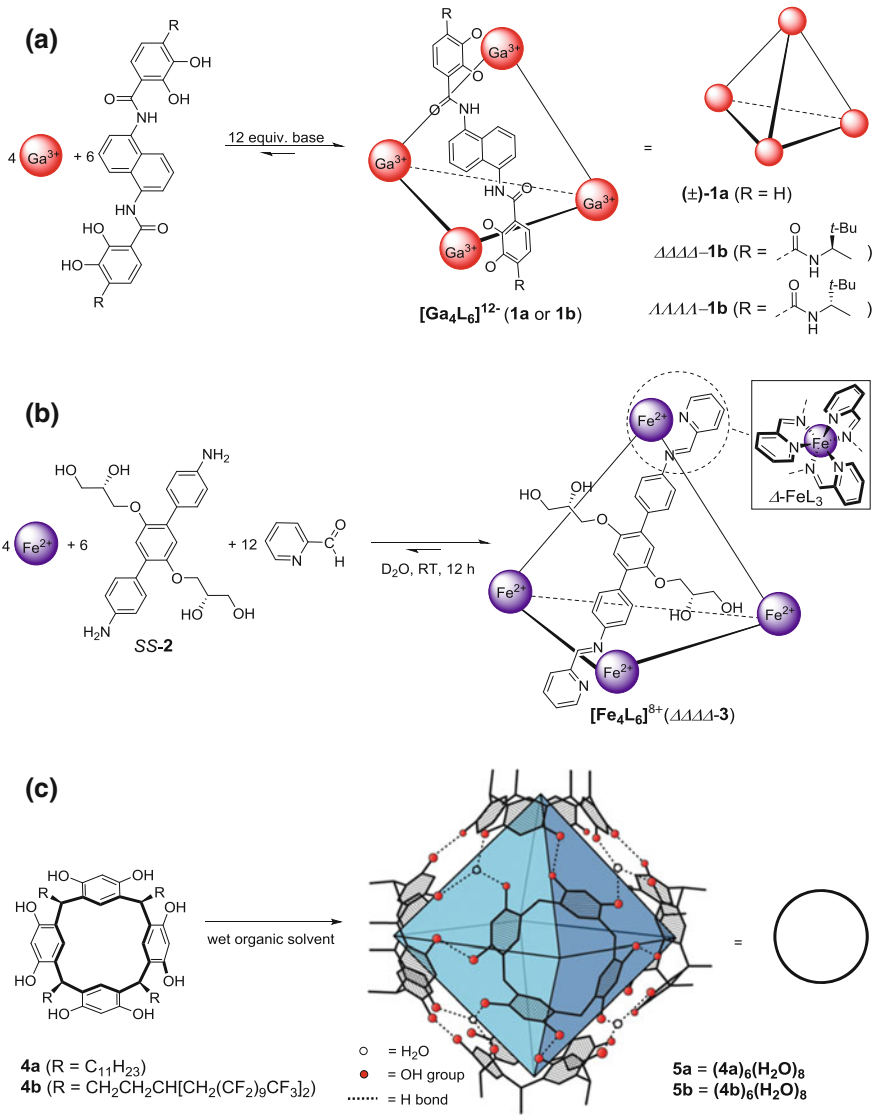
1 Introduction

Supramolecular catalysis has evolved into an extremely broad field ranging from the use of non-covalent interactions as a tool for building and modifying homogenous catalysts to artificial enzyme mimics [1, 2]. This chapter aims to provide a thorough review over a small proportion of this field, namely the use of self-assembled coordination cages and organic capsules as homogeneous catalytic supramolecular reaction vessels [3–6]. These container molecules provide defined hydrophobic cavities which have the potential to mimic binding pockets in enzymes and achieve similar selectivity and catalytic rate enhancements as encountered in biological systems. Self-assembly as a tool for the synthesis of hollow polyhedral coordination cages and organic capsules (see Sect. 2) provides the means for facile modulation of the cavity environment and binding selectivity because small changes to the geometries of building blocks can lead to much larger changes in the structures and properties of the resulting host assemblies. Additionally, small changes to the structures of the host molecules can significantly influence binding constants of both substrates and products as well as the rates achieved in host-guest catalysis. In order to gain a better understanding of the difficulties to overcome when designing host materials for catalytic applications, the thermodynamic and kinetic basics underlying successful host-guest catalysis will be reviewed (see Sect. 3). Eventually, examples of host-guest catalysis will be provided (Sect. 4). Applications of container molecules in catalysis include the promotion of hydrolysis reactions at unusual pH ranges (Sect. 4.1), pre-organization of guest molecules or reactive intermediates leading to regioselective deprotonations (Sect. 4.2), stabilization of cationic transition states in unimolecular and bimolecular reactions (Sect. 4.3 and Sect. 4.4, respectively), and rate enhancements of cycloaddition and condensation reactions (Sect. 4.5). These examples include self-assembled coordination cages based on chiral ligands which are of particular interest as they provide an asymmetric microenvironment for promoting stereoselective reactions by purely non-covalent interactions. Furthermore, encapsulated transition metal complexes will be covered in this review but are limited to non-covalently bound

host-guest systems (Sect. 5). Self-assembled systems containing endohedral functionalities for coordination of metal complexes are beyond the scope of this article and have been reviewed elsewhere [7]. The use of coordination cages in catalytic tandem transformations ranging from preventing transition metal degradation in aqueous solution, over avoiding inhibition of enzymes by compartmentalizing the catalysts, to their use as orthogonal catalysts for stabilizing and converting high-energy intermediates for subsequent catalytic processes is reviewed in the last section of this chapter (Sect. 6).

2 Self-Assembled Coordination Cages and Organic Capsules

Non-covalent host molecules such as self-assembled coordination cages and organic capsules present several advantages over their covalent analogs since they can be prepared in a modular fashion from smaller building blocks. This approach allows facile adaption of the supramolecular assembly to the desired application without the arduous synthesis accompanied with the preparation of larger covalent hosts. Additionally, as self-assembled container molecules are held together by reversible non-covalent interactions, they exhibit a certain flexibility and dynamic behavior which facilitates not only guest encapsulation but also release of the product in catalytic applications. Scheme 1 illustrates the self-assembly of several non-covalent hosts which have been successfully used in catalytic transformations. Self-assembled coordination cages are prepared under thermodynamic reaction conditions from ligands and metal ions, as has been demonstrated by Raymond, Fujita, Ward and many more. Raymond and Bergman's coordination cage in Scheme 1a illustrates how small changes of the ligand structure can be used to form coordination capsules diastereoselectively. While the achiral ligand results in the formation of a racemic mixture of the tetrahedral coordination cages *ΔΔΔΔ*-**1a** and *ΛΛΛΛ*-**1a**, the enantiopure ligands enable the diastereoselective self-assembly of either *ΔΔΔΔ*-**1b** or *ΛΛΛΛ*-**1b**, thus leading to host-assemblies which provide in their cavity an asymmetric microenvironment and can be used for applications in enantioselective host-guest catalysis [8]. In an approach termed subcomponent self-assembly, the Nitschke group has taken advantage of the simultaneous formation of dynamic covalent imine bonds and coordination bonds to prepare coordination cages from even smaller fragments, as for example the coordination capsule *ΔΔΔΔ*-**3** (Scheme 1b) [9]. Since the bis-dicoordinate imine ligands are formed in situ, for example, from the diamine *SS*-**2** by reversible imine bond-formation with 2-pyridinecarboxaldehyde, control over guest binding strengths, selectivity, and dynamics can be exerted easily by subtle changes in the host framework resulting from substituent effects. In *ΔΔΔΔ*-**3**, the 12 glyceryl substituents do not only render this coordination capsule water-soluble but also allow it to form diastereoselectively, presumably by hydrogen bonding of the



Scheme 1 Self-assembled capsules. **a** Example of self-assembled coordination cages; **b** subcomponent self-assembly of coordination cages; **c** hydrogen-bonded organic capsule (adapted from Chem. Commun., 2015, 51, 892–894; Published by The Royal Society of Chemistry)

glyceryl substituents on the faces of the tetrahedral host. Additionally, since these sp^3 hybridized substituents are very flexible, they allow rapid guest exchange and thereby a possible way to overcome product inhibition which is often encountered in supramolecular catalysis.

Next to coordination cages, also hydrogen-bonded organic capsules have been shown to provide binding cavities suitable for host-guest catalysis. Examples are Rebek's dimeric capsule (vide infra) or the hexameric resorcin[4]arene capsule (Scheme 1c), a chiral spherical molecular assembly held together by 60 hydrogen bonds which was initially described by MacGillivray and Atwood [10]. As shown in Scheme 1c, these hexameric hydrogen-bonded organic capsules (e.g. **5a**) form readily in wet organic solvents such as chlororform or benzene from six symmetrically substituted resorcin[4]arene units (e.g., **4a**) and incorporate eight water molecules in the hydrogen-bonded assembly (**5a**=(**4a**)$_6$(H_2O)$_8$).

3 Thermodynamics and Kinetics in Host-Guest Catalysis

3.1 Host-Guest Catalysis Compared to Enzyme Catalysis

Supramolecular chemists aim to copy four key features of enzyme catalysis when attempting to create artificial enzyme mimics. Biological systems make extensive use of tailored microenvironments to promote reactions by destabilizing the ground state and stabilizing certain transition state geometries. In analogy, an ideal self-assembled supramolecular catalyst would provide a (hydrophobic) binding pocket with strong affinity for the substrate, an even stronger stabilization of the transition state or intermediates of the reaction, and weak binding of the product to allow its release and ensure catalytic turnover. Nowadays, the design and synthesis of coordination cages which bind a desired substrate is aided by molecular modeling and generally does not present a problem. The challenges in host-guest catalysis most often are encountered when attempting to stabilize a certain transition state without increasing the affinity of the host for the reaction product. Therefore, while many groups have reported the use of coordination cages and organic capsules as supramolecular reaction flasks to increase the rate of a reaction or achieve unusual reactivity and selectivity [6, 11, 12], only a small proportion of these systems were demonstrated to be truly catalytic.

A simplified catalytic cycle for host-guest catalysis employing host H to convert substrate S to product P is displayed in Fig. 1a while Fig. 1c illustrates the relative free energy changes during the catalytic reaction. As generally the case, the catalyst —in this case the coordination cage or organic capsule—lowers the activation energy when compared with the uncatalyzed reaction ($\Delta G^{\ddagger}_{cat} < \Delta G^{\ddagger}$). The first step of the catalytic cycle involves the encapsulation of substrate S which is typically fast and reversible. Depending on the rates of the forward and reverse reaction (k_1 and k_{-1}), the host–guest complex [S⊂H] either is in fast or slow exchange with the empty host H and free substrate S. In order to achieve product formation in the second step, the host H must bind the transition state better than the ground state ($\Delta G^{\circ}_{TS} < \Delta G^{\circ}_{en}$). This rate-limiting step (k_2, also known as k_{cat} in enzymatic catalysis) yields the encapsulated product in form of [P⊂H]. For release of the product

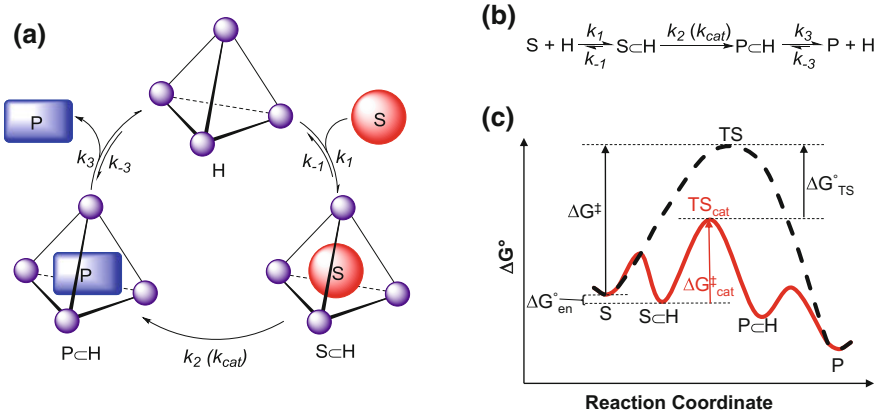


Fig. 1 Host-guest catalysis: same product with and without supramolecular catalyst. **a** Catalytic cycle; **b** rate constants; **c** typical reaction coordinate of the catalyzed reaction versus the uncatalyzed reaction

to take place, k_3 must be large compared to k_{-3}; additionally the product must be more weakly bound than the substrate otherwise product inhibition is likely to occur.

Occasionally, product inhibition does not pose a problem due to steric or electronic interactions resulting in a lower affinity of the product for the host when compared with the starting material [13, 14]. Otherwise, a potential strategy to ensure turnover and thereby closure of the catalytic cycle includes subsequent reactions of the catalytic product upon its release, e.g., the hydrolysis of an iminium cation to an aldehyde which shows significantly lower affinity for its host, thus making the product release irreversible [15]. Furthermore, a change in charge can facilitate catalytic turnover [16].

3.2 New Selectivity Due to Confinement

Encapsulation can significantly alter the properties of the guest which often results in unusual reactivity inside a supramolecular host. As seen in Fig. 2, confinement can lead to a stronger stabilization of an alternative transition state compared to the uncatalyzed reaction and thus explain unusual selectivity observed in the product obtained in cage-catalyzed reactions when compared to the reaction being carried out in bulk solution [17, 18].

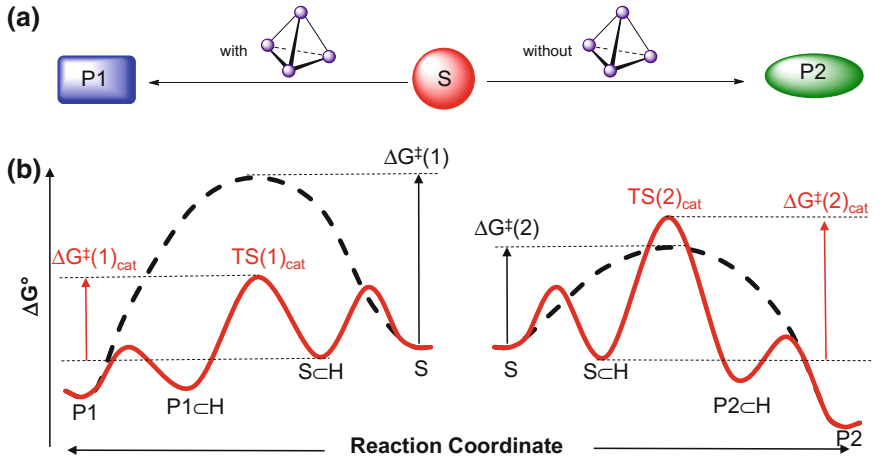


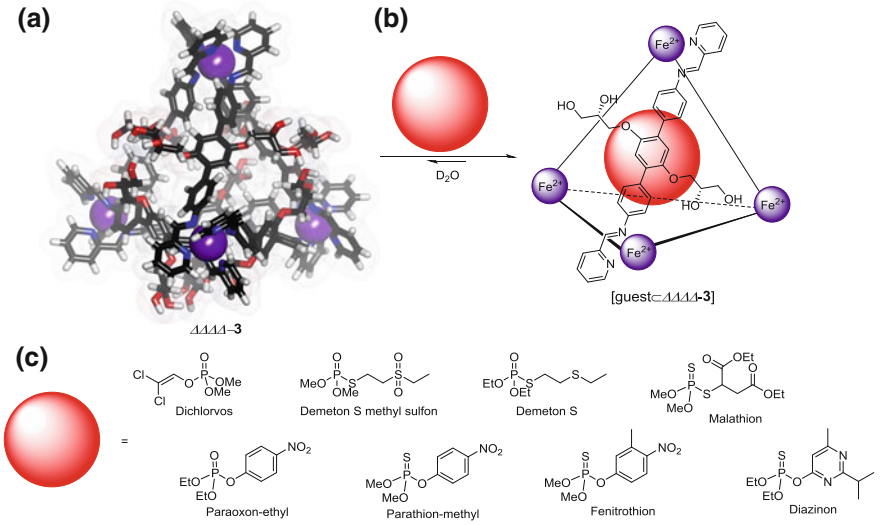
Fig. 2 Encapsulation can lead to new selectivity. **a** Confinement can change the outcome of a reaction; **b** stabilization of a different transition state inside a capsule

4 Host-Guest Catalysis in Self-Assembled Coordination Cages and Organic Capsules

4.1 Catalytic Hydrolysis by Self-Assembled Coordination Cages and Organic Capsules

Hydrolysis reactions can be significantly accelerated in negatively charged coordination cages which show a strong preference for positively charged guests and allow the protonation of encapsulated molecules even in basic media [19]. Likewise, positively charged cage molecules can facilitate hydrolysis by increasing the concentration of hydroxide in its vicinity and/or polarizing heteronuclear bonds of the encapsulated molecule, thus enabling a nucleophilic attack of hydroxide at neutral pH [9].

The author has recently demonstrated this concept in the catalytic hydrolysis of neurotoxic organophosphates by a $[Fe_4L_6]^{8+}$ coordination cage. The positively charged $[Fe_4L_6]^{8+}$ coordination cage *ΔΔΔΔ*-**3** (Scheme 1b) was found to encapsulate in water a wide range of neutral organic and organometallic compounds in its large hydrophobic cavity [9]. Water-soluble guests such as 1-adamantylmethanol were observed to undergo fast exchange on the NMR timescale with free molecules in solution while hydrophobic guests (e.g., dibenzyl) were in slow exchange with their free counterparts. Organophosphorus insecticides are one class of molecules which are encapsulated in *ΔΔΔΔ*-**3** (Scheme 2) and display the same behavior as previously observed with organic guest molecules: water-soluble insecticides (e.g., dichlorvos or demeton S methyl sulfon) were in fast exchange on the NMR timescale with free molecules in solution whereas the hydrophobic insecticides fenitrothion and parathion-methyl showed slow exchange on the NMR timescale.



Scheme 2 Host-guest chemistry of *ΔΔΔΔ*-**3**. **a** Molecular model of *ΔΔΔΔ*-**3**; **b** encapsulation of guests in water; **c** examples of organophosphorus insecticides which are encapsulated

The Nitschke group has recently demonstrated that the organophosphate insecticide and chemical warefare agent (CWA) simulant dichlorvos can not only be encapsulated into *ΔΔΔΔ*-**3** but also that hydrolysis of the toxic compound occurs at an increased rate in the presence of *ΔΔΔΔ*-**3** (Fig. 3) [9, 20]. In the presence of 1 mol% of *ΔΔΔΔ*-**3** an increased rate of hydrolysis was measured at pH 7 at room temperature compared to a reference sample containing only buffer solution. *ΔΔΔΔ*-**3** is acting as a supramolecular catalyst in the hydrolysis of dichlorvos to dimethyl phosphate (DMP) and dichloroacetaldehyde (hydrate) or, alternatively, to dichlorovinylmethyl phosphate (DVMP) and methanol (Fig. 3a). As indicated in Fig. 3b, both pathways are accelerated in the presence of *ΔΔΔΔ*-**3**. Since the hydrolysis products are more water-soluble than the starting material, no product inhibition was observed in the hydrolysis of dichlorvos. The authors suggested as a possible mechanistic explanation for catalytic acceleration that the (reversible) encapsulation of the insecticide by the highly positively charged cage molecule leads to the polarization of the phosphorus-oxygen bonds, thus facilitating a nucleophilic attack at the phosphorus atom and leading to the observed higher rate of hydrolysis in the presence of the cage molecule.

Control reactions carried out in the presence of competing guests (e.g., 1-adamantylmethanol) and inhibiting guests (e.g., dibenzyl) supported the hypothesis that the encapsulation of dichlorvos into *ΔΔΔΔ*-**3** leads to faster hydrolysis. The hydrophobic guest dibenzyl inhibits the catalytic acceleration by forming a strong host–guest complex with *ΔΔΔΔ*-**3**, thereby preventing dichlorvos from binding and resulting in the same rate of reaction as the reference sample. On the other hand, the competing guest 1-adamantylmethanol was seen to slow the

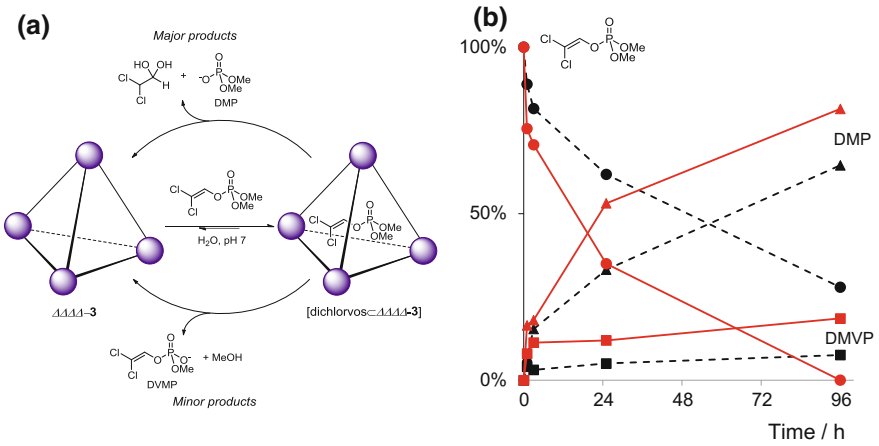
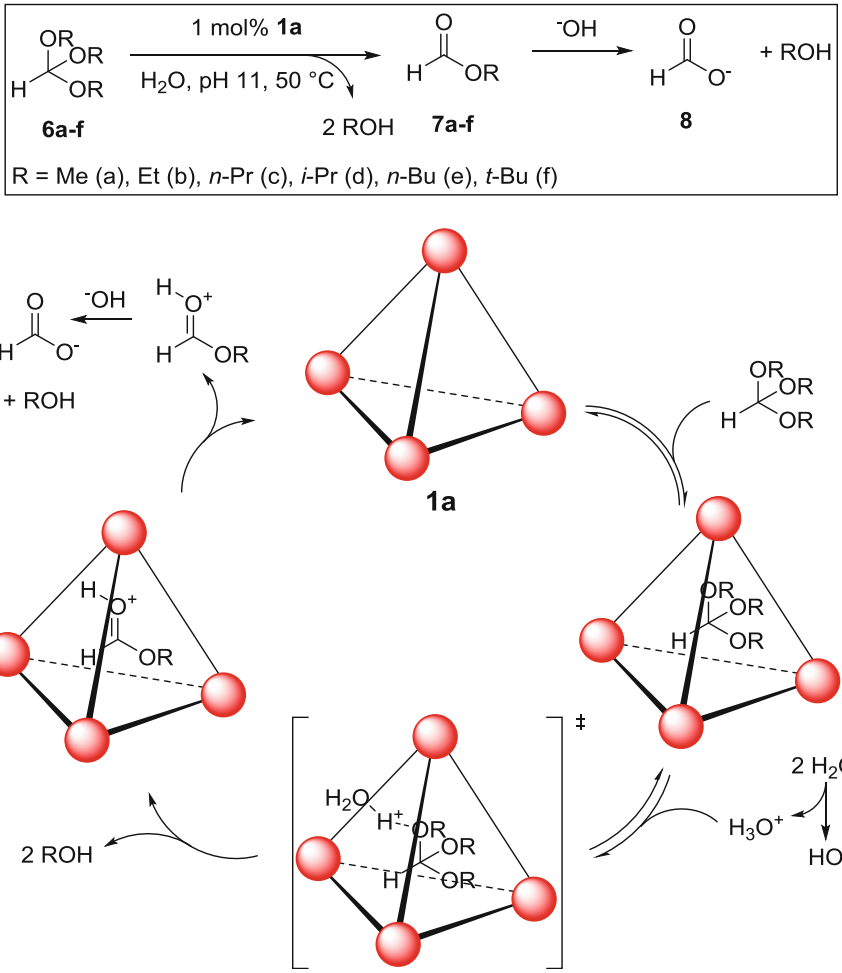


Fig. 3 Hydrolysis of dichlorvos in 0.1 M phosphate buffer at pH 7 and 298 K. **a** Encapsulation of dichlorvos in *ΔΔΔΔ*-**3** and hydrolysis to dimethyl phosphoric acid (DMP, major) and dichlorovinylmethyl phosphoric acid (DVMP, minor); **b** hydrolysis of dichlorvos in 0.1 M phosphate buffer at pH 7 and 298 K followed by NMR: *red line* in the presence of 1 mol% of *ΔΔΔΔ*-**3**, *dashed black line* reference reaction; *red circle* and *black circle* dichlorvos, *red triangle* and *black triangle* dimethyl phosphoric acid (DMP), *red square* and *black square* dichlorovinylmethyl phosphoric acid (DVMP) (Color figure online)

hydrolysis reaction to a rate somewhere between the reference sample and the sample in the presence of pure *ΔΔΔΔ*-**3**. Other control experiments involving the addition of equimolar amounts of subcomponents (12 mol% of 2-formylpyridine, 6 mol% of *SS*-**2**, 4 mol% of $FeSO_4$, or 4 mol% of a mononuclear iron complex formed from 2-formylpyridine and aniline) to the buffered solution at pH 7 showed no acceleration of the rate of hydrolysis of dichlorvos relative to the reference reaction, thus lending further support that the catalytic effect of *ΔΔΔΔ*-**3** can be assigned to encapsulation rather than some structural features present in the subcomponents.

Hydrolysis of the other organophosphate insecticides displayed in Scheme 2c either did not take place at all (e.g., fenitrothion is encapsulated in *ΔΔΔΔ*-**3** without being hydrolyzed) or no catalytic turnover occurred due to product inhibition as observed with diazinon.

During the past decade the Raymond and Bergman groups have published several examples of acid catalysis in basic solution employing the negatively charged $[Ga_4L_6]^{12-}$ coordination cage **1a** (Scheme 1a) as catalyst. This supramolecular host relies exclusively on electrostatic and hydrophobic interactions for the thermodynamic stabilization of protonated substrates as observed in the orthoformate hydrolysis promoted by **1a** (Scheme 3) [21, 22]. Orthoformates **6a**–**f** are small enough to undergo reversible encapsulation by **1a** and are readily hydrolyzed in basic solution while tripentyl orthoformate and triphenyl orthoformate are too large to be encapsulated and therefore not hydrolyzed under these



Scheme 3 Acid catalysis in basic solution: orthoformate hydrolysis catalyzed by the negatively charged $[Ga_4L_6]^{12-}$ coordination cage **1a**

reaction conditions. In analogy to enzymes, competitive inhibition is observed in presence of other strongly bound guests, thereby confirming that the cavity of **1a** was the active site for catalysis. The overall reaction mechanism obeys classical enzymatic Michaelis–Menten kinetics including a fast pre-equilibrium step involving the encapsulation of the orthoformate **6a–f** by **1a**, leading to the host–guest complexes [**6a–f**⊂**1a**] which are in equilibrium with the empty host **1a**. Analysis of the rate law indicated that the rate-limiting step involved the proton transfer from protonated water to the encapsulated orthoformate, thus enabling the two successive hydrolysis steps in the cavity which lead to the release of two equivalents of the corresponding alcohol. The resulting protonated formate esters

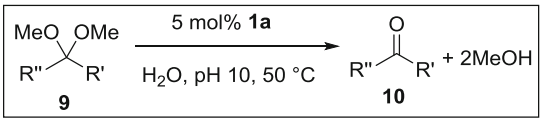
7a–f are released rapidly from **1a** and subsequently hydrolyzed by base in solution to give the third equivalent of alcohol and orthoformate.

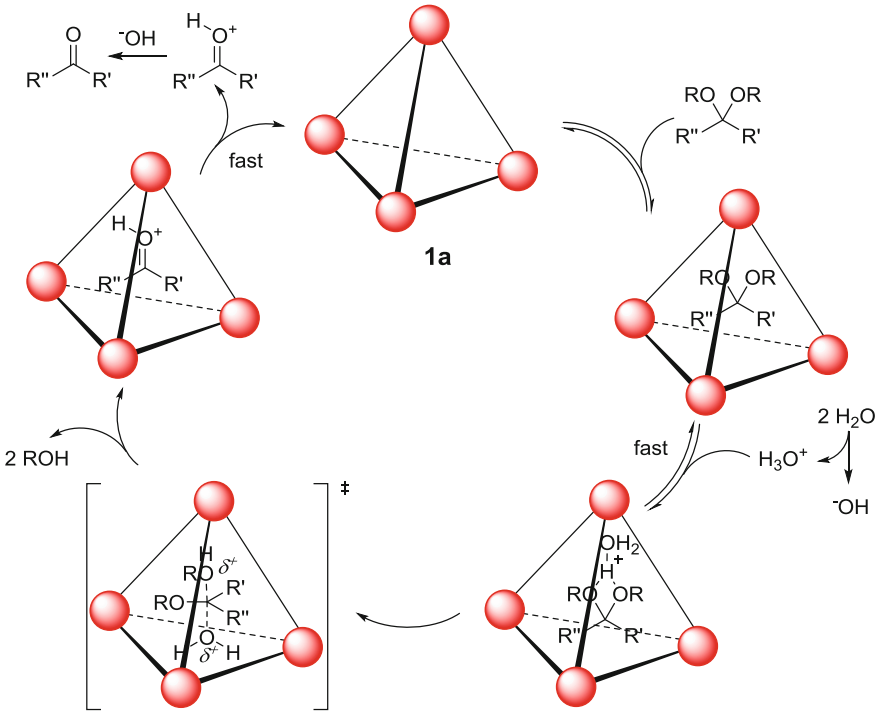
The groups of Raymond and Bergman also investigated the acid catalyzed deprotection of acetals in basic solution inside the supramolecular host **1a** [23, 24]. Acetals are common protecting groups for aldehydes and ketones in organic synthesis due to their high stability under basic conditions. Their deprotection generally is carried out using a Brønsted or Lewis acid in the presence of water. Nevertheless, in the presence of 5 mol% of coordination cage **1a** a variety of smaller dimethoxy alkyl acetals and ketals (**9**) were readily hydrolyzed at pH 10 to the corresponding aldehydes or ketones (**10**) as shown in Scheme 4. Similarly to the above mentioned orthoformate hydrolysis, prospective substrates which are too large to fit into the cavity of **1a** (e.g. 2,2-dimethoxyundecane) do not undergo hydrolytic cleavage under basic conditions and remain unchanged in solution. An in depth analysis of the acid hydrolysis mechanism of acetals by the negatively charged host **1a** revealed that while the mechanism resembled that of orthoformate hydrolysis involving a pre-equilibrium of reversible host–guest complex formation [**9**⊂**1a**] driven by the hydrophobic effect, the subsequent protonation occurred fast, and the rate-limiting step was the attack of water on the protonated substrate (Scheme 4). Following the loss of two equivalents of methanol, the protonated carbonyl product **10** is released and immediately deprotonated in the basic solution. Product inhibition is not a problem since the hydrolysis product **10** is bound less strongly than the starting material **9** and is also generally less soluble in water which allows catalytic turnover and leads to the observed conversions of 87–95% in the presence of 5 mol% **1a**.

The Tiefenbacher group demonstrated that the hexameric resorcin[4]arene capsule **5a** (Scheme 1c) was capable of promoting acetal hydrolysis in wet organic solvents (Scheme 5a). Contrary to the coordination capsules of the Raymond group, this neutral hydrogen-bonded organic capsule is thought to act itself as reasonably strong Brønsted acid with a pK_a between 5.5 and 6 [25]. After protonation of the encapsulated diethyl acetal, the cationic transition state is thought to experience stabilization by cation-π interactions with the aromatic cavity. The rate of hydrolysis strongly depends on the substrate size with smaller diethyl acetals **11a** and **11b** being deprotected significantly faster than the larger acetals **11f** and **11g**, which is consistent with encapsulation being the key to catalytic hydrolysis. Additionally, adding a competing guest such as tetrabutylammonium occupies the catalytic cavity of **5a**, thus reducing the observed hydrolysis rate to the rate of the background reaction (Scheme 5b) which parallels enzymatic catalysis.

4.2 Pre-Organization and Enzyme-Like Deprotonation of Encapsulated Substrates

Enzyme-like pre-organization of reactants inside supramolecular cages can enable reactions at significantly milder conditions due to a higher effective molarity of the

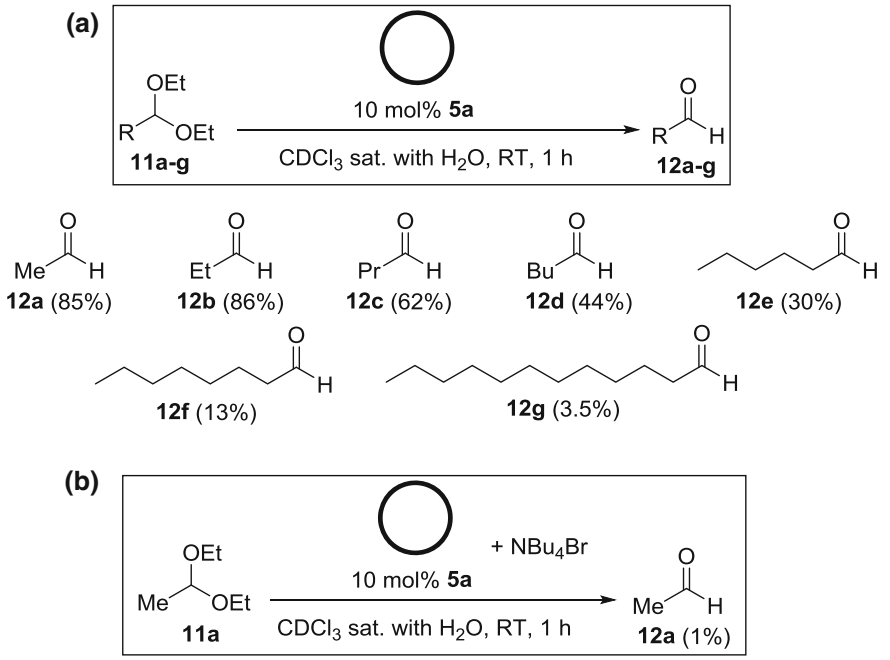




Scheme 4 Proposed mechanism of the acid catalyzed acetal deprotection in basic solution by cage **1a**

reacting molecules and their perfect alignment with respect to the transition state. Additionally, pre-organization can lead to regioselective deprotonation, thus allowing the (kinetic) formation of reaction products not observed in bulk solution.

The efficient catalysis of the Kemp elimination of benzisoxazole **14** with hydroxide to form 2-cyanophenolate **15** inside the cavity of the water-soluble $[Co_8L_{12}]^{16+}$ cage **13** (Fig. 4) has been assigned to enzyme-like pre-organization of the reactants [16]. As **13** binds neutral substrates strongly, benzisoxazole is readily encapsulated and forms a host–guest complex ([**14**⊂**13**]) where the CH bond is pointing towards the apertures on the faces of the cubic cage **13**. Additionally, ion pairing of the highly charged supramolecular host **13** with hydroxide leads to a high local concentration of partially desolvated hydroxide ions around the cavity. Due to the ideally situated hydrophobic guest molecule, deprotonation of the CH bond occurs at a pH as low as 8.5 (Fig. 4c) compared to a pH of 14 required in bulk



Scheme 5 Acid catalyzed acetal deprotection inside hexameric resorcin[4]arene capsule **5a**. **a** Size dependent rates of hydrolysis of various diethyl acetals; **b** cationic species, e.g. tetrabutylammonium salts, are inhibitors due to their encapsulation in **5a**

solution (Fig. 4b). Since **13** binds neutral guests much more strongly than either cationic or anionic molecules, the hydrophilic 2-cyanophenolate **15** is readily released, thus enabling catalytic turnover.

Similarly, enzyme-like control over the regioselectivity of carbocation deprotonation inside the coordination cage **1a** has been shown to lead to the kinetically favored products of the Nazarov cyclization rather than the most thermodynamically stable compounds [18]. This acid catalyzed reaction of pentadienols **16a–c** results under thermodynamic reaction conditions in bulk solution in the formation of cyclopentadiene **18** via a diallylic carbocation intermediate which undergoes a conrotatory electrocyclic ring closure as predicted by the Woodward-Hoffmann rules [26]. As previously seen in the orthoformate and acetal hydrolysis reactions [19], **1a** can act as an acid catalyst under neutral conditions which in the case of the Nazarov cyclization promotes the formation of the cyclized allyl cation and stabilizes this reactive intermediate inside the cavity of the negatively charged supramolecular host **1a** [27]. The cage-catalyzed Nazarov cyclization of pentadienols **16a** and **16b** leads to the formation of the kinetic product dihydrofulvene **17** as a result of the regioselective deprotonation of the intermediary *trans*-cyclopentadienyl cation by water through the apertures on the faces of the tetrahedral $[Ga_4L_6]^{12-}$ coordination cage **1a** (Scheme 6a). **16c** forms the *cis*-cyclopentadienyl cation which is deprotonated to give **18** (Scheme 6b).

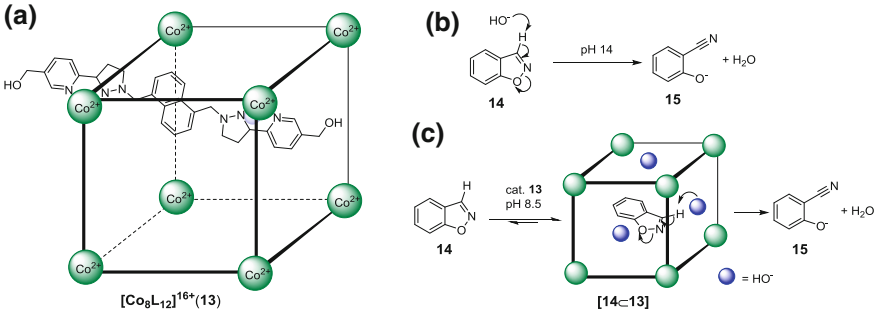
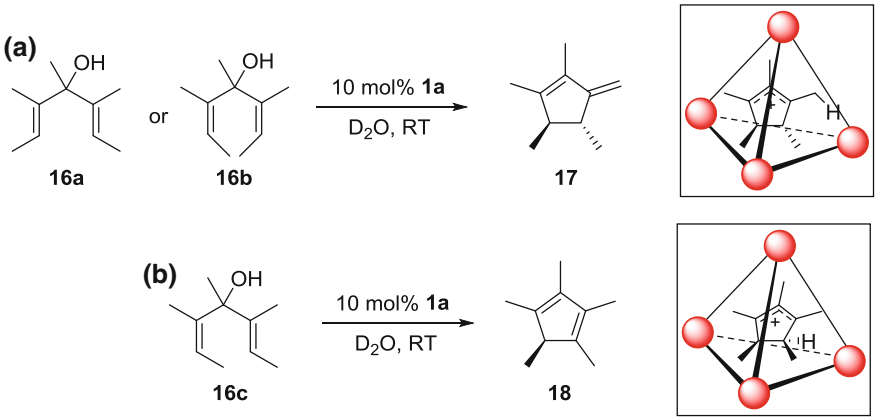


Fig. 4 Kemp elimination catalyzed by **13**. **a** A water-soluble cubic $[Co_8L_{12}]^{16+}$ coordination cage **13**; **b** Kemp elimination under strongly basic conditions; **c** Kemp elimination inside the supramolecular catalyst. **13** occurs at significantly lower pH



Scheme 6 Nazarov cyclization promoted by **1a** leads to the kinetic product by regioselective deprotonation of the intermediary carbocation stabilized by **1a** (*insets*)

4.3 *Host-Guest Catalysis Involving Stabilization of Cationic Transition States in Unimolecular Rearrangement and Cyclization Reactions*

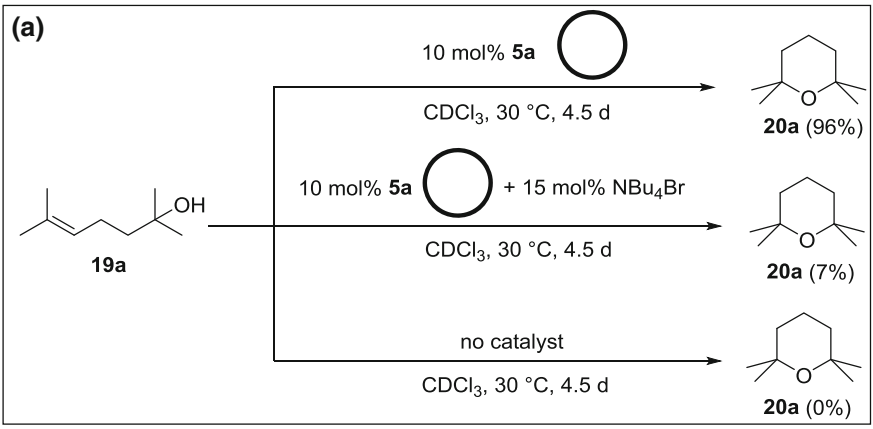
When carried out in bulk solution, reactions involving highly reactive cationic intermediates often undergo undesired side reactions. Stabilizing these intermediates by non-covalent interactions and reducing their accessibility for nucleophilic attack by solvent molecules is expected to lead to more selective reactions. Catalysis of reactions proceeding via cationic transition states can therefore be expected to proceed more selectively and at a higher rate inside supramolecular assemblies which allow the stabilization of cationic intermediates and transition

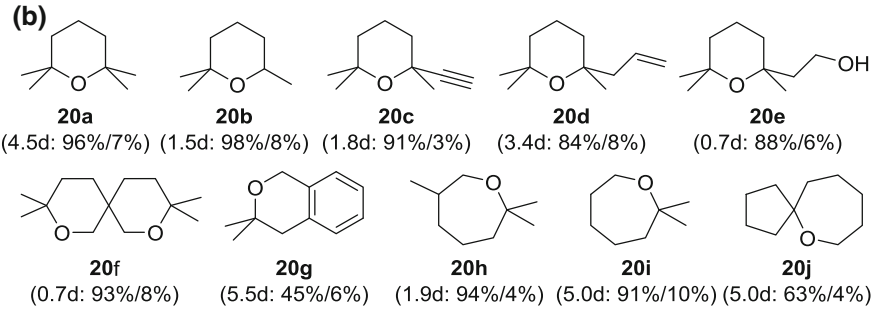
states by cation-π and cation dipole interactions, assuming product inhibition does not occur [4].

Aromatic supramolecular capsules, such as the hydrogen-bonded resorcin[4]arene hexamer **5a**, possess a hydrophobic cavity with a high affinity for positively charged species (e.g., ammonium cations) due to extensive cation-π interactions between the host and guest molecules. Taking advantage of the ability of **5a** to act as a Brønsted acid as well as stabilizing the resulting cationic transition state, the Tiefenbacher group demonstrated that the intramolecular hydroalkoxylation of the unsaturated alcohol **19a** to the corresponding cyclic ether **20a** could be carried out in 96% yield in the presence of 10 mol% of capsule **5a** (Scheme 7a) [28]. Adding a competing guest to a **5a**-catalyzed reaction, such as the strongly bound tetrabutylammonium cation, significantly reduced the observed yield (7%), while performing the reaction without **5a** gave no product at all, thus confirming that the reaction takes place inside the self-assembled enzyme-like organic capsule. Various differently substituted tetrahydopyranes and oxepanes were formed in moderate to excellent yield, giving the desired Markovnikov products as shown in Scheme 7b.

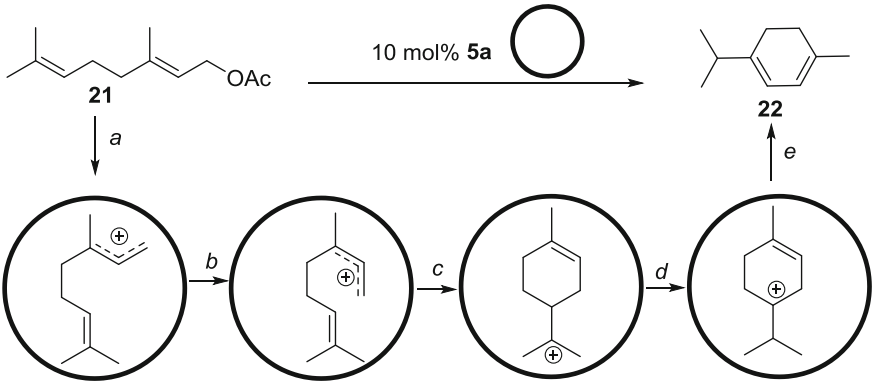
The same group also reported a biomimetic tail-to-head terpene cyclization catalyzed inside the cavity of the self-assembled capsule **5a** which is proposed to proceed via a series of cationic intermediates (Scheme 8) [29]. In analogy to the hydrophobic binding pocket of terpene cyclase, the hydrophobic cavity of the resorcin[4]arene hexamer **5a** is capable of stabilizing the allylic cation formed upon encapsulation of geranyl acetate **21** by cation-π interactions with the aromatic host (Scheme 8a). The catalytic cascade involves an isomerization step from the *transoid* to the *cisoid* cation (Scheme 8b), followed by a cation-olefin cyclization (Scheme 8c). A subsequent Wagner-Meerwein 1,2-H-shift (Scheme 8d) and selective deprotonation (Scheme 8e) leads to α-terpinene in good selectivity.

In a related monoterpene-like cyclization based on the Prins cyclization, the groups of Raymond, Bergman, and Toste explored the use of various racemic, homochiral, and enantiopure $[Ga_4L_6]^{12-}$ coordination cages as supramolecular catalysts [8, 30, 31]. As already seen above, in water the negatively charged host **1a** readily encapsulates cationic molecules (e.g., ammonium ions) or neutral compounds which undergo protonation inside the hydrophobic cavity of the coordination capsule and thereafter are stabilized by strong cation-π interactions between the charged guest and the naphthalene units of the cage. Thorough investigation of the proton-mediated Prins cyclization of the unsaturated aldehyde **23** to form preferably the *trans*-cyclization product **24** has led to the proposed catalytic cycle shown in Scheme 9. Although under the aqueous reaction conditions the aldehyde **23** is in equilibrium with its hydrate, only **23** is reversibly encapsulated by the coordination cage (K_1). This encapsulation is believed to be driven by the hydrophobic effect as it results in the release of bound solvent from **A**. Due to the confined space, the encapsulated substrate adopts a chair-like conformation (**B**), which is activated by protonation of the carbonyl group (K_2) for the intramolecular nucleophilic attack of the ideally situated alkene. The stabilized cationic intermediate in **C** is then irreversibly converted to the encapsulated alcohol **24** in **E** either stepwise via the cyclic carbocation in **D**, followed by rapid deprotonation (k_1, k_2) or

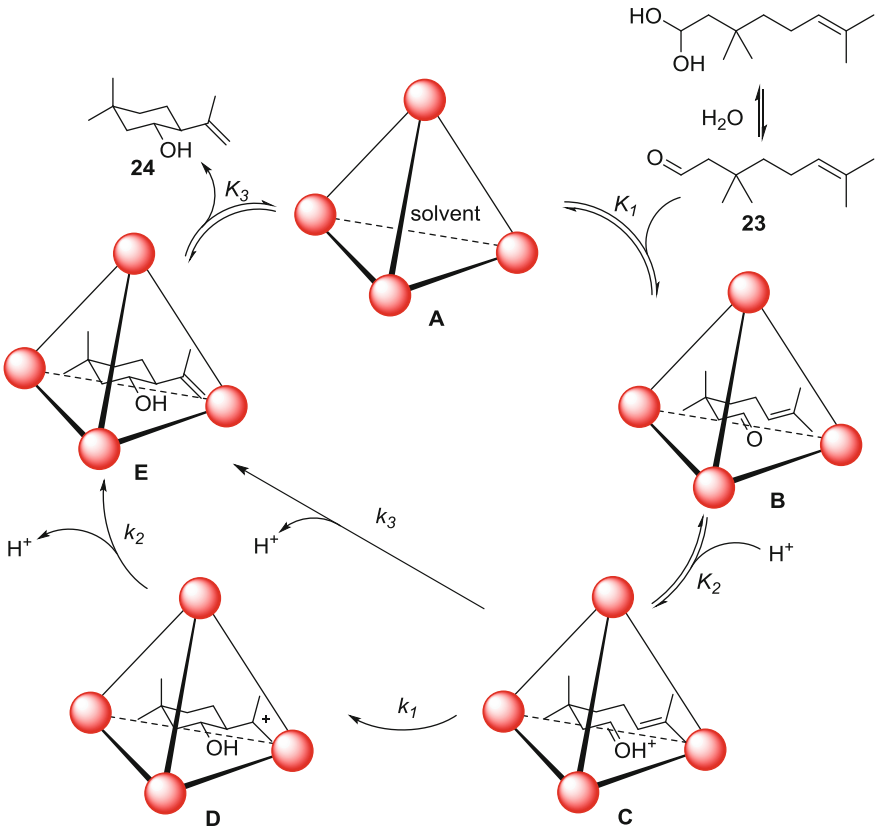




Scheme 7 Intramolecular hydroxyalkylation catalyzed inside **5a**. **a** Catalytic reaction and control experiments; **b** scope of the intramolecular hydroxylation (time: yield with 10 mol% of **5a** without/with 15 mol% NBu_4Br)



Scheme 8 Terpene cyclization catalyzed inside the cavity of the hexameric resorcin[4]arene capsule **5a**. The formation of α-terpinene **22** from geranyl acetate **21** is proposed to proceed via cationic intermediates (*a*–*e*)



Scheme 9 Proposed mechanism of $[Ga_4L_6]^{12-}$ coordination cage catalyzed Prins cyclization. Both stepwise (k_1, k_2) or concerted mechanisms (k_3) are plausible

in a concerted fashion (k_3) and released from the supramolecular host (K_3). No product inhibition was observed in this case which the authors attribute to the higher solvation of the released alcoholic product **24** compared to the aldehyde **23**.

Since the coordination cage **1a** is chiral and exists in solution as a racemic mixture of homochiral cages (*ΔΔΔΔ*-**1a** and *ΛΛΛΛ*-**1a**), the authors pursued the preparation of the related enantiopure $[Ga_4L_6]^{12-}$ cages *ΔΔΔΔ*-**1b** and *ΛΛΛΛ*-**1b** (see Scheme 1b) which self-assemble diastereoselectively due to their enantiopure ligands. Similarly, the larger pyrene-based coordination cages **25a**, *ΔΔΔΔ*-**25b** and *ΛΛΛΛ*-**25c** (Fig. 5) have been prepared as catalysts to promote enantioselective reactions inside these chiral assemblies.

As could be demonstrated in the Prins cyclization of **23** catalyzed by a racemic mixture of homochiral cage **1a** (Schemes 9 and 10), the *trans*-isomer **24** (and its enantiomer) was obtained in high yield while the formation of the *cis*-isomer **26** was disfavored in the cage-catalyzed reaction. Employing the enantiopure *ΔΔΔΔ*-**1b** capsule did not change the diastereomeric ratio notably; however, one of the

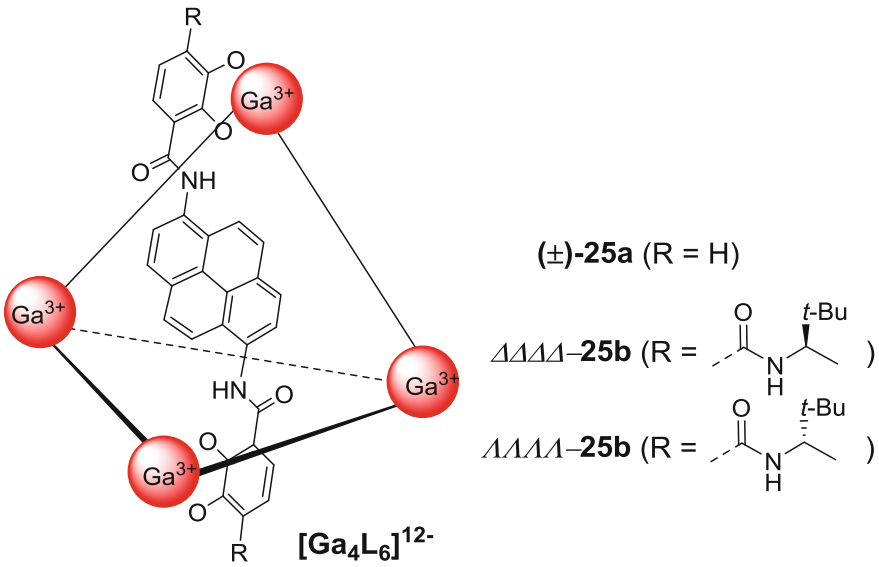
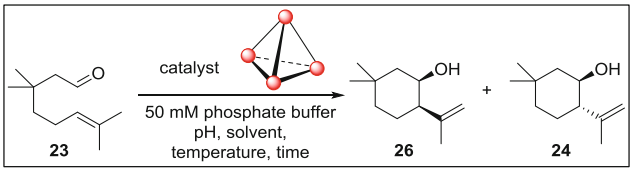


Fig. 5 Extended $[Ga_4L_6]^{12-}$ coordination cages. Diastereoselective self-assembly from enantiopure ligands gives *ΔΔΔΔ*-**25b** or *ΛΛΛΛ*-**25b**, respectively

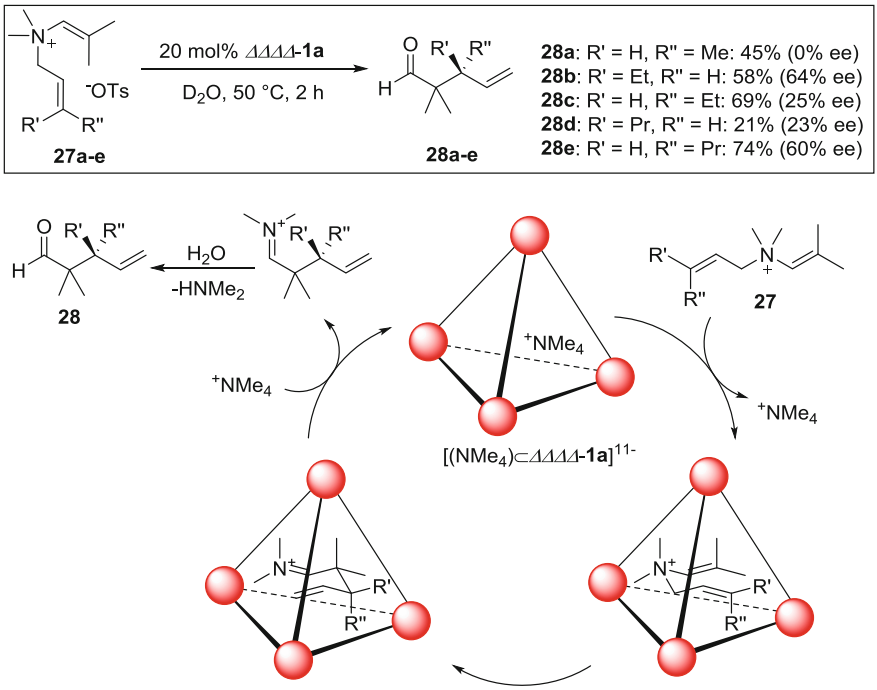


catalyst	mol%	temp/°C	pH (50 mM phosphate buffer in)	time/h	%conv.	% 26	% 24
(±)-**1a**	10	60	pH 7.50 (water)	28	91	14	86
ΔΔΔΔ-**1b**	2.5	25	pH 8.00 (water/methanol 1:1)	50	92	12	88 (61%ee)
ΛΛΛΛ-**25b**	2	40	pH 8.00 (water/methanol 1:1)	16	93	2	98 (33% ee)

Scheme 10 $[Ga_4L_6]^{12-}$ coordination cages as catalysts for the enantioselective Prins cyclization

trans-isomers was obtained in 61% ee. Changing to the larger coordination cage *ΛΛΛΛ*-**25b** led exclusively to the *trans*-isomer, albeit in the case of **24** with loss in enantioselectivity.

As one of the first unimolecular rearrangement reactions catalyzed by **1a** involving cationic species, the aza-Cope rearrangement of allylenammonium and propargylenammonium substrates was published collaboratively by the groups of Raymond and Bergman [15, 32–34]. Aza-Cope rearrangements involving allylenammonium substrates **27** have been carried out both in presence of a racemic mixture of homochiral cages **1a**[32] as well as in presence of enantiopure *ΔΔΔΔ*-**1a**



Scheme 11 Aza-Cope rearrangement of allylenammonium substrates **27a–e** catalyzed by the enantiopure $[Ga_4L_6]^{12-}$ coordination cage *ΔΔΔΔ*-**1a**

obtained by resolution from (±)-**1a** (Scheme 11) [34]. The observed enantioselectivities of up to 64% ee for the aldehyde products **28a–e** of the aza-Cope rearrangement reactions vary strongly with subtle changes in size and shape of the prochiral substrates **27a–e** when carried out with 20 mol% of *ΔΔΔΔ*-**1a** as catalyst. As indicated in the catalytic cycle in Scheme 11, these cage-catalyzed [3]-sigmatropic rearrangements proceed via a chair-like transition state which is enforced upon encapsulation of the substrate. The resulting iminium ion is readily hydrolyzed in solution to the corresponding aldehyde which is not encapsulated in the host and therefore does not inhibit the catalytic turnover.

4.4 *Bimolecular Reactions Involving Nucleophilic Attack on Capsule-Stabilized Cationic Transition States and Intermediates*

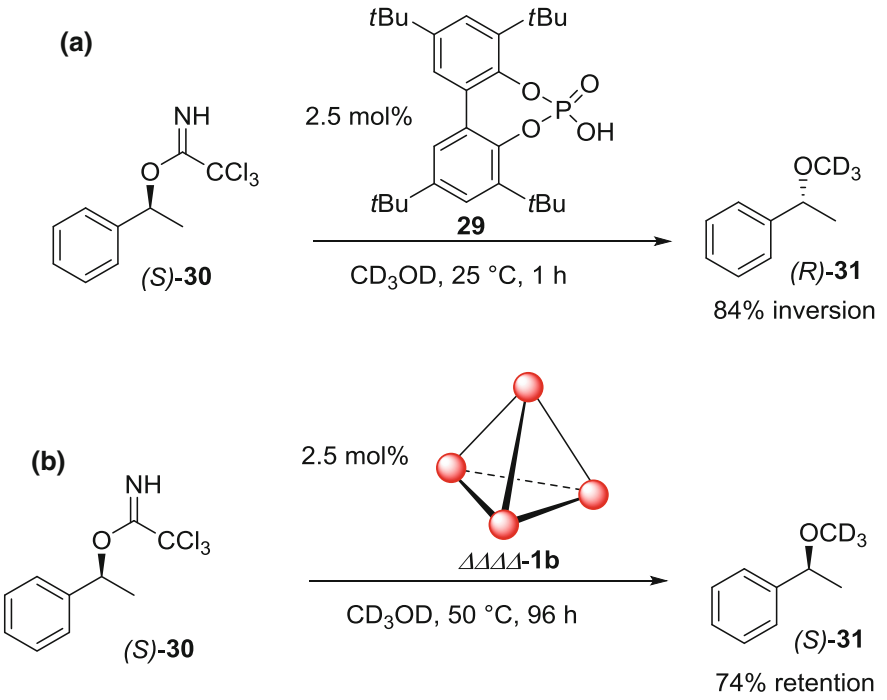
Bimolecular reactions inside the confined space of supramolecular assemblies include solvolysis and hydration reactions and can be promoted by activating, for example, the electrophilic substrate by protonation which facilitates the subsequent nucleophilic attack of the reaction partner.

In an exceptional case of nucleophilic substitution at sp^3 carbons, the groups of Raymond, Bergman, and Toste observed overall retention of absolute stereochemistry in reactions catalyzed by the water-soluble hosts **1a**, *ΔΔΔΔ*-**1b**, and *ΛΛΛΛ*-**1b** [17]. In contrast, nucleophilic substitutions at saturated carbon centers generally proceed via an S_N1 or an S_N2 pathway which dictates their stereochemical outcome: S_N1 reactions lead to racemized products while S_N2 reactions yield products with inversion of stereochemistry. This includes the phosphoric acid (**29**) catalyzed solvolysis of the secondary benzylic compound (*S*)-**30** which proceeds in bulk solution via an S_N2 mechanism to give (*R*)-**31** with 84% inversion of stereochemistry (Scheme 12a). The nucleophilic substitution reaction on the benzylic substrate (*S*)-**30** inside cage *ΔΔΔΔ*-**1b** proceeds with unprecedented 74% retention of stereochemistry found for the product (*R*)-**31** (Scheme 12b). As these $[Ga_4L_6]^{12-}$ cages are known to decrease the pK_a of encapsulated guests, protonation of the acid activated trichloroacetamide leaving group in (S)-**30** occurs upon encapsulation, followed by the loss of the leaving group. The authors proposed that the cavity of the host can stabilize the developing positively charged intermediate in the transition state through cation-π interactions with the naphthalene walls of the cage, thus blocking the back side of the carbocation from nucleophilic attack. This complexation also limits planarization and the stabilized carbocation is trapped by a nucleophile (in this case the solvent) faster than rotation can occur, resulting in the observed retention of stereochemistry.

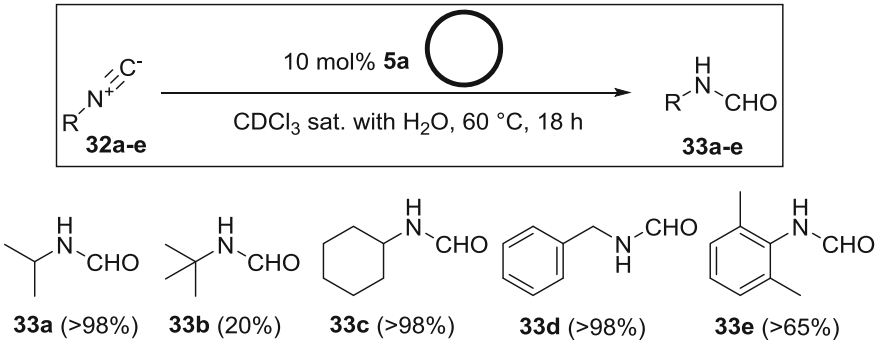
Similarly, efficient isonitrile hydration takes place through encapsulation and activation by protonation within the hexameric resorcin[4]arene capsule **5a** (Scheme 13) [35]. No hydration takes place in bulk solution but neutral isonitriles **32a–e** are readily encapsulated and converted in the presence of water to the corresponding *N*-formylamides **33a–e** inside the organic capsule **5a**. Although the mechanism was not investigated experimentally, the catalytic reaction was proposed to proceed via protonation of the carbenic carbon atom followed by nucleophilic addition of water. Catalytic hydration was strongly dependent on size and electronic properties of isonitriles **32a–e** which gave the corresponding *N*-formylamides **33a–e** in variable yields.

4.5 Bimolecular Reactions Catalyzed by Coordination Cages and Organic Capsules

Bimolecular reactions catalyzed by self-assembled hosts either can proceed via encapsulation and activation of one of the substrates or by co-encapsulating two different molecules which react in the confines of the cavity with each other. Product inhibition is an often encountered obstacle; nevertheless, careful selection of reactants, host assemblies or reaction conditions have led to multiple examples of host-guest catalysis.

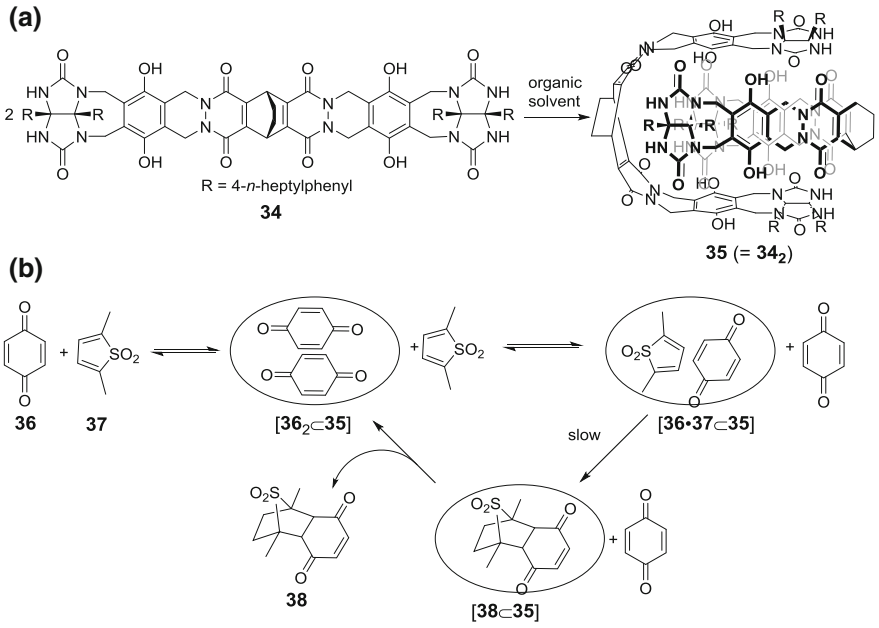


Scheme 12 Nucleophilic substitution and its stereochemical outcome. **a** The phosphoric acid catalyzed nucleophilic substitution in bulk solution leads to inversion of configuration as expected for an S_N2 reaction; **b** in contrast, the cage-catalyzed nucleophilic substitution reaction on a secondary benzylic carbon center gives the product with overall retention of the absolute configuration



Scheme 13 Isonitrile hydration promoted by the hexameric resorcin[4]arene capsule **5a**

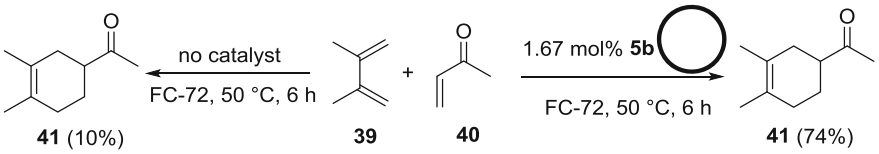
One of the first examples of catalytic hydrogen-bonded self-assembled molecular capsules was published by Rebek: dimerization of **34** in organic solvents leads to the "hydroxy softball" **35** which is held together by 16 hydrogen bonds



Scheme 14 **a** Dimerization of **34** in organic solvent results in the hydrogen-bonded capsule **35**. **b** A Diels-Alder reaction promoted by capsule **35**

(Scheme 14a). In a first example, this group observed a rate acceleration in the Diels-Alder reaction between *p*-quinone **36** and cyclohexadiene inside the organic capsule **35**, but this system suffered from product inhibition due to the high affinity of the Diels–Alder adduct for **35** [36]. Successful catalysis of the Diels–Alder reaction by the dimeric capsule **35** was subsequently achieved between **36** and the thiophene oxide derivative **37** [13]. The authors proposed a catalytic cycle (Scheme 14b) where the resting state of the capsule contains two molecules of *p*-quinone [**36**$_2$⊂**35**] which is in equilibrium with [**36**·**37**⊂**35**] containing the two co-complexed reactants. The rate-limiting cycloaddition takes place within the confines of the organic capsule, followed by a comparably fast displacement of the endo-adduct **38** from the complex [**38**⊂**35**] by two equivalents of quinone, thus completing the catalytic cycle.

Shimidzu and coworkers demonstrated the application and recycling of catalytic hydrogen-bonded organic capsules bearing fluorinated substituents which selectively dissolved in the fluorous layer of a biphasic system [37]. Due to the fluorophobic effect, the fluorinated version of the hexameric resorcin[4]arene capsule (**5b**) was observed to significantly accelerate the formation of the Diels-Alder adducts such as **41** from various dienes (e.g., **39**) and dienophiles (e.g., methyl acrylate **40**) when carried out in a fluorous biphasic system in comparison to the reactions carried out in the absence of **5b** (Scheme 15). Encapsulation was shown to increase the endo/exo ratio, particularly with larger substrates where only the



Scheme 15 Diels–Alder reaction promoted by the fluorinated capsule **5b**

endo product was formed. Furthermore, the authors demonstrated that **5b** could be recycled and reused for catalysis with no decrease in activity after five consecutive runs.

Fujita and coworkers reported the use of aqueous organopalladium cages **42** and **43a** (Fig. 6) as supramolecular reaction vessels for the Diels–Alder cycloaddition of anthracenes and maleimides (Scheme 16) [14]. The bowl-shaped host **42** efficiently catalyzes the Diels–Alder reaction between anthracene derivative **44** and maleimide **45** to yield **46** quantitatively (Scheme 16a). The catalytic cycle is thought to involve binding of the anthracene derivative which can stack onto the triazine ligands of the host, gaining stabilization from aromatic-aromatic or charge-transfer interactions. Likewise, maleimide encapsulation is favored due to stacking interactions and the reactant-like transition state experiences similar stabilization. However, upon formation of the adduct **46** most of these favorable aromatic stacking interactions are lost due to the bending of the former anthracene molecule which closes the catalytic cycle by release of **46** and encapsulation of a new pair of substrates. While this reaction is catalytic and does not suffer from product inhibition, the regioselectivity (addition at the 9,10-position of the anthracene) does not differ from reactions carried out in bulk solution. Although the Diels-Alder reaction carried out inside the octahedral coordination cage **43a** requires a stoichiometric amount of the

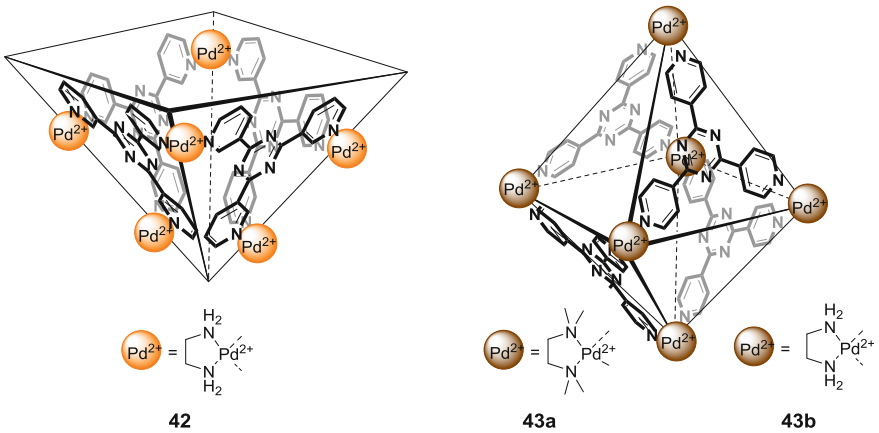
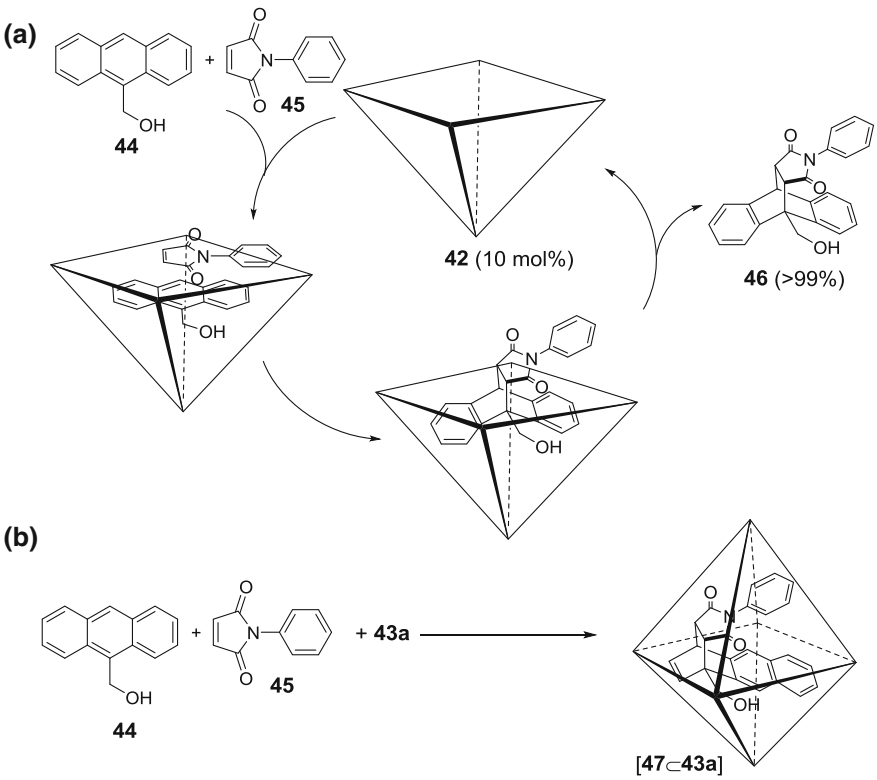


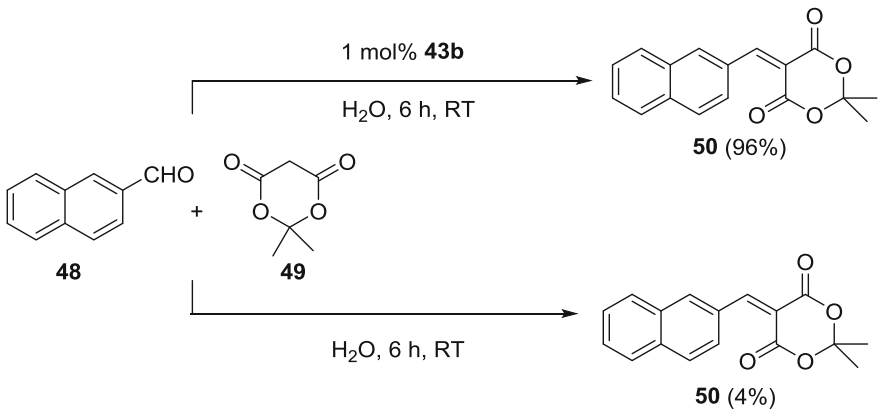
Fig. 6 Water-soluble organopalladium cages assembled from *cis*-end-capped Pd(II) salts and triazine-based tridentate ligands. **42** resembles an open basket while the palladium atoms in **43a** and **43b** are arranged in an octahedral fashion



Scheme 16 **a** Diels–Alder reaction catalyzed by **42** proceeds with normal selectivity; **b** inside **43a** the DA reaction leads to an unusual product but is not catalytic (product inhibition)

organopalladium host, its unusual regioselectivity is worth mentioning (Scheme 16b). This palladium capsule forms rapidly and exclusively the desired host–guest complex [(**44**·**45**)⊂**35**] with the co-encapsulated substrates being held in a very defined position due to the restricted space in the interior of the capsule. The proximity of the dienophile **45** to the terminal aromatic ring of the anthracene in **44** leads to the exclusive formation of the 1,4-adduct **47** instead of usual the 9,10-adduct **46**. Additionally, only the exo-selective syn-adduct is formed within the confines of the cavity of **43a**. Unfortunately, the naphthalene ring of **47** forms strong π–π stacking interactions with the triazine ligand of **43a** which prevents catalytic turnover.

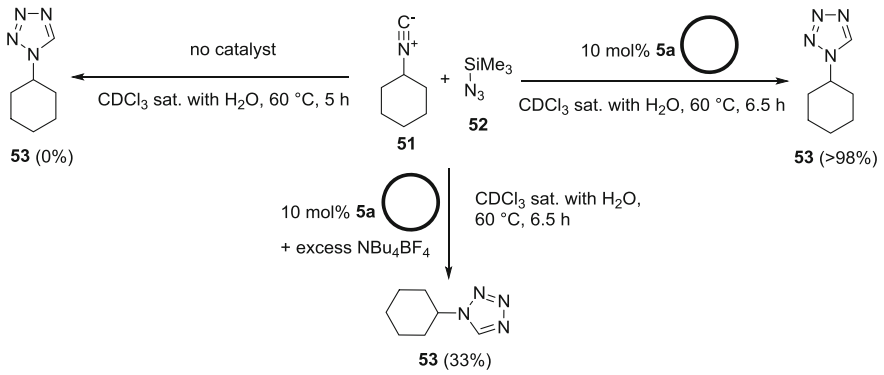
The cage-catalyzed Knoevenagel condensation between aldehyde **48** and Meldrum's acid **49** under neutral conditions in water was efficiently catalyzed by the previously problematic octahedral cage **43b** (Scheme 17) while the bowl-shaped organopalladium host **42** proved to be a poor catalyst, yielding the condensation product **50** even with stoichiometric quantities of **42** only in 17% yield [38]. The reaction catalyzed by **43b** involves the encapsulation of up to four equivalents of the aromatic aldehyde in the hydrophobic cavity of **43b**. Meldrum's



Scheme 17 Knoevenagel condensation under neutral conditions in water. **a** Catalyzed by the octahedral organopalladium capsule **43b**; **b** background reaction in the absence of cage

acid **49** is not encapsulated due to its high water-solubility and is under the reaction conditions in equilibrium with its enolate. Electrostatic interaction between the positively charged coordination cage and the monoanionic enolate is proposed to lead to the nucleophilic attack of the enolate on the encapsulated aldehyde which is facilitated by stabilization of the formed oxyanion intermediate by the cationic cage environment. Dehydration of this intermediate is possible inside the hydrophobic cavity of the coordination cage despite the aqueous solvent and leads to the desired condensation product **50**. As **50** is too large for the host it is spontaneously released, thereby allowing another molecule of substrate to undergo a catalytic Knoevenagel condensation inside **43b**.

As previous studies have shown, isonitriles are good guests for the organic capsule **5a** which presumably catalyzes the isonitrile hydration by protonation [35]. In the case of the catalytic preparation of substituted 1*H*-tetrazoles from isonitriles and TMS-azide there is no evidence for a protonation step being involved in the catalytic cycle [39]. Nevertheless, activation of the reaction between **51** and **52** clearly occurs by encapsulation into **5a** which leads to complete conversion to the desired 1*H*-tetrazole **53**, possibly assisted by the electron-rich interior surface of the cavity rather than hydrogen bonding with the hydroxyl groups of the separate resorcin[4]arene components. Control experiments in the presence of the capsule and the competing guest tetrabutylammonium significantly reduces the yield of **53** while reactions carried out in the absence of **5a** yielded no product at all (Scheme 18).

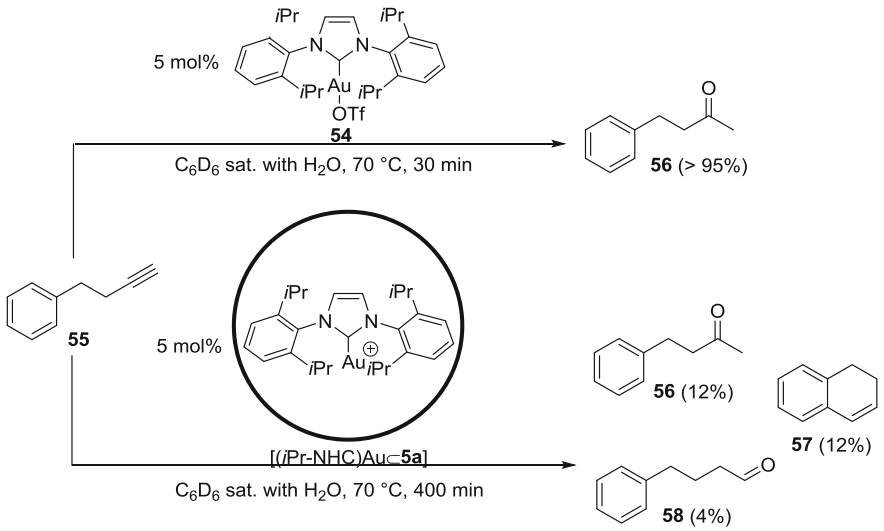


Scheme 18 1*H*-tetrazole formation promoted by hydrogen-bonded capsule **5a**

5 Encapsulated Metal Complexes

Confinement has been shown to be a viable method to modulate the activity and selectivity of transition metal catalysts. Metalloenzymes demonstrate beautifully how not only the directly coordinated ligands but also the second coordination sphere—in this case the binding pocket of the prosthetic group—play a crucial role in catalyzing highly selective reactions. Transition metals in confined spaces include covalently bound metal catalysts (see Chapter "Endohedral Functionalization of Molecular Cavities for Catalysis in Confined Spaces"), confined species obtained by the template-ligand approach, and metal complexes which are encapsulated into coordination cages and self-assembled organic capsules [7]. Encapsulation of metal catalysts has not only been employed to alter their reactivity and selectivity but also was found to enable their use under otherwise incompatible reaction conditions by preventing their degradation (vide infra).

The chemo- and regioselectivity of alkyne hydration is found to change upon encapsulation of the gold catalyst within the hexameric resorcin[4]arene host **5a** [40]. While the hydration of the terminal alkyne **55** catalyzed by the free (*i*-Pr-NHC)Au(OTf) complex **54** quantitatively yielded the expected Markovnikov adduct **56** (Scheme 19a) or formed selectively the 1,2-dihydronaphthalene **57** under anhydrous conditions, the cationic host–guest complex [(*i*-Pr-NHC)Au⊂**5a**]$^+$ was observed to lead to a different product distribution (Scheme 19b). Equimolar amounts of the Markovnikov product **56** and its dehydration product **57** were accompanied by the formation of a small amount of the anti-Markovnikov-adduct **58**. The origin the cyclic dehydration product and the linear aldehyde are not entirely clear although the hydrophobic interior of capsule **5a** is assumed to prevent efficient nucleophilic attack of water, thus changing the chemoselectivity of the reaction, while the shape of the cavity may further facilitate both intramolecular reaction leading to **57** and the nucleophilic attack on the terminal alkyne carbon giving **58** by enforcing a favorable geometry of the encapsulated gold-activated

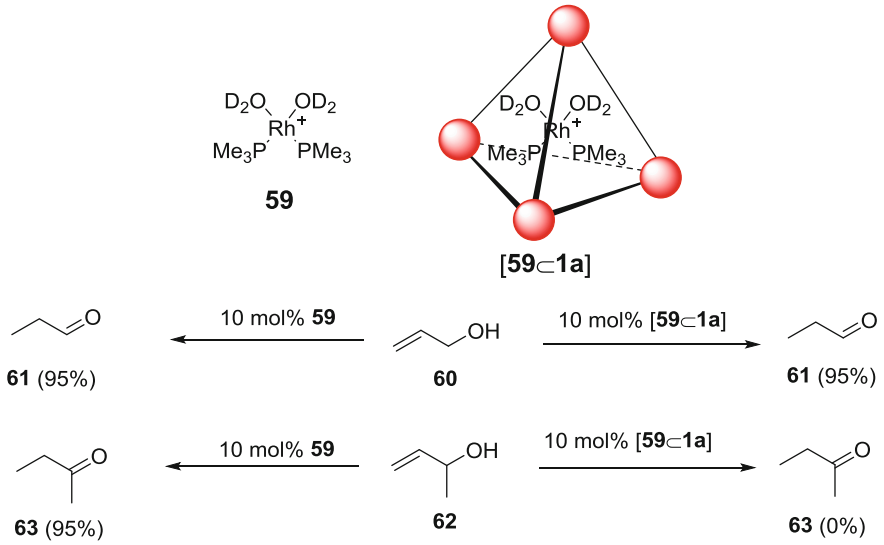


Scheme 19 Gold catalysis in hydrogen-bonded capsule

substrate. Investigation of the substrate selectivity in the alkyne hydration demonstrated a clear size-dependence for reactions mediated by the host–guest complex [(*i*-Pr-NHC)Au⊂**5a**]$^{+}$ with smaller 4-R-phenylacetelyenes reacting faster that larger substrates (for R=H, Me, *t*-Bu the relative rates were found to be 1.6/1.3/1.0) [41]. Reactions rates carried out in the presence of the free (*i*-Pr-NHC) Au(OTf) **54** complex were observed to proceed faster with more electron-rich alkynes (for R=H, Me, *t*-Bu the relative rates were found to be 1.0/1.4/1.5), thus showing a reversed order compared to the encapsulated gold catalyst.

High substrate specificity has been reported by the groups of Bergman and Raymond in the rhodium catalyzed allylic alcohol isomerization upon encapsulation of rhodium catalysts in the coordination cage **1a** [42]. The cationic hydrated bisphosphine rhodium(I) complex **59** does not distinguish in bulk solution between the allyl alcohols **60** and **62** and yields the corresponding isomerization products **61** and **62** quantitatively whereas the encapsulated catalyst [**59**⊂**1a**] isomerized **60** in quantitative yields to the aldehyde **61** but showed no reactivity in the isomerization of **62** (Scheme 20).

In a similar allylic alcohol isomerization, the water-sensitive ruthenium(II) catalyst was protected from decomposition by encapsulation into the self-assembled $[Ga_4L_6]^{12-}$ cage **1a** which permitted its use in aqueous solution (vide infra) [43]. Likewise, encapsulation of a gold catalyst led to an enhancement in catalytic activity in the hydroxyalkylation of allenes and furthermore increased its lifetime under the reaction conditions [44].



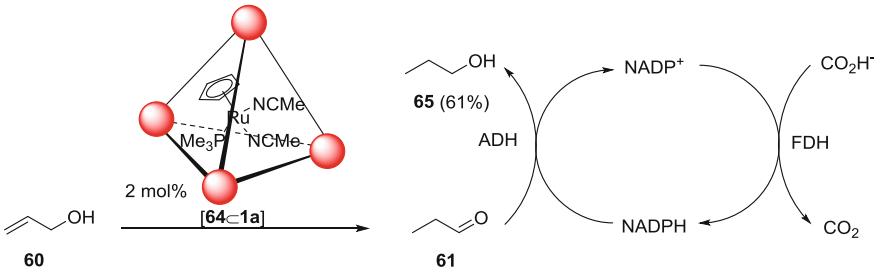
Scheme 20 Rh catalysis inside the coordination cage **1a** exhibits highly size and shape selective reactivity

6 Orthogonal Tandem Catalytic Reactions Using Self-assembled Coordination Cages

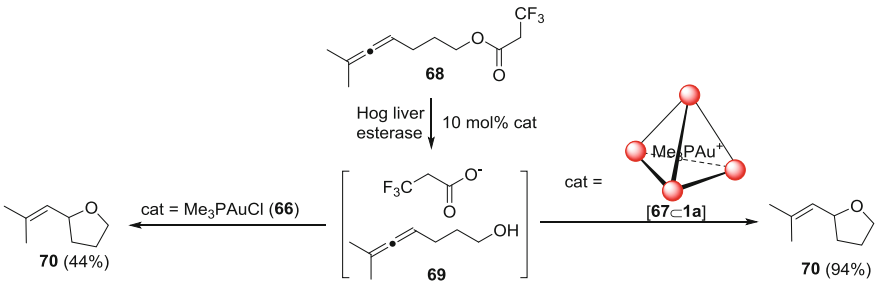
Tandem catalysis and catalytic cascade reactions allow the synthesis of complex structures while avoiding the isolation of any intermediate products. Orthogonal tandem catalysis describes one-pot reactions in which sequential catalytic processes occur through two or more distinct catalytic cycles [45]. The main challenge is to ensure orthogonal reactivity of all components and catalysts in this multistep process in order to obtain the desired product in good yield. Compartmentalization has been used to address catalyst incompatibilities by imposing physical barriers to avoid their direct contact, thus allowing the tandem reactions to be carried out in one pot.

Raymond, Bergman, and Toste recently demonstrated that a supramolecular approach allowed combining otherwise incompatible transition metal catalysts with enzymes by encapsulating the metal complexes into a $[Ga_4L_6]^{12-}$ coordination cage [46]. Protecting a ruthenium(II) complex inside a supramolecular host prevents its degradation in aqueous media and enables the transition metal catalyzed allylic isomerization of **60** to the aldehyde **61** under bioorthogonal conditions [43], which allows the following enzymatic reduction by alcohol dehydrogenase (ADH) to 1-propanol **65** to be carried out in the same pot without necessitating the isolation of the intermediate product (Scheme 21).

In a second example of a procedure combining enzymatic and transition metal catalysis the authors reported that encapsulation of the gold(I) catalyst was required



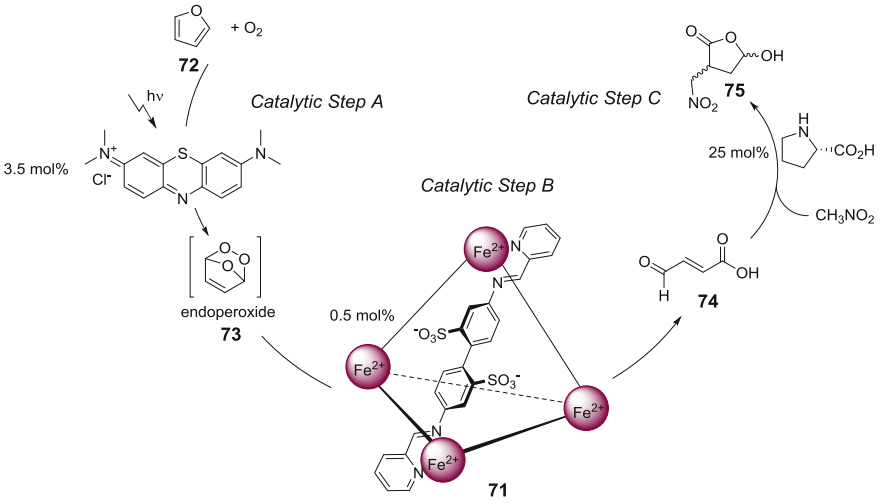
Scheme 21 A catalytic tandem reaction incorporating transition metal catalysis and enzymatic catalysis: the product of the ruthenium catalyzed allyl alcohol isomerization, **61**, is efficiently reduced by alcohol dehydrogenase (ADH) and formate dehydrogenase (FDH)



Scheme 22 A catalytic tandem reaction employing the enzyme hog liver esterase to generate in situ the hydroxy allene **69** which is transformed to the cyclic ether **70** by a gold catalyst

to achieve high yields in the sequential enzymatic ester hydrolysis of **68** to **69**, followed by the gold-catalyzed intramolecular hydroxyalkylation (Scheme 22) [44, 46]. Mechanistic investigations revealed that hog liver esterase is inhibited by the free gold catalyst which limits the yield of the intermediate product **69**, thus leading to low overall yield of **70** after the subsequent gold-catalyzed intramolecular hydroxyalkylation. Encapsulation (compartmentalization) of the gold complex prevents its inhibiting effect on the esterase and thereby allows quantitative conversion of the allene ester **68** to the tetrahydrofuran derivative **70** over two steps.

In a self-organizing chemical assembly line, the Nitschke group showed recently that coordination cages could not only be used as catalysts in multistep one-pot syntheses but also self-assembled in situ from its subcomponents [47]. The reported example consists of three noninterfering catalytic steps A, B, and C which transform furan (**72**) into 5-hydroxy-3-(nitromethyl)dihydrofuran-2(*3H*)-one **75** (Scheme 23). In the photooxidation cycle (A) singlet oxygen ($^1O_2$) is generated via absorption of visible light by the sensitizer methylene blue and undergoes a hetero-Diels-Alder reaction with furan **72** to give the high-energy intermediate **73**, an endoperoxide. The self-assembled coordination cage **71** encapsulates in the



Scheme 23 One-pot conversion of furan **72** to 5-hydroxy-3-(nitromethyl)dihydrofuran-2(*3H*)-one **75** by three sequential catalytic steps: Photocatalysis (A), host-guest catalysis (B), and organocatalysis (C)

second catalytic cycle (B) selectively the endoperoxide **73** and transforms it into its linear isomer fumaraldehydic acid **74**. The L-proline catalyzed 1,4-addition of nitromethane to **74** followed by cyclization leads in the organocatalytic cycle (C) to the final product **75**.

References

1. Raynal M, Ballester P, Vidal-Ferran A, van Leeuwen PWNM (2014) Supramolecular catalysis. Part 1: non-covalent interactions as a tool for building and modifying homogeneous catalysts. Chem Soc Rev 43:1660–1733. doi:10.1039/C3CS60027K
2. Raynal M, Ballester P, Vidal-Ferran A, van Leeuwen PWNM (2014) Supramolecular catalysis. Part 2: artificial enzyme mimics. Chem Soc Rev 43:1734–1787. doi:10.1039/C3CS60037H
3. Brown CJ, Toste FD, Bergman RG, Raymond KN (2015) Supramolecular catalysis in metal-ligand cluster hosts. Chem Rev 115:3012–3035. doi:10.1021/cr4001226
4. Catti L, Zhang Q, Tiefenbacher K (2016) Self-assembled supramolecular structures as catalysts for reactions involving cationic transition states. Synthesis 48:313–328. doi:10.1055/s-0035-1560362
5. Gangemi CMA, Pappalardo A, Sfrazzetto GT (2015) Applications of supramolecular capsules derived from resorcin[4]arenes, calix[n]arenes and metallo-ligands: from biology to catalysis. RSC Adv 5:51919–51933. doi:10.1039/C5RA09364C
6. Vardhan H, Verpoort F (2015) Metal-organic polyhedra: catalysis and reactive intermediates. Adv Synth Catal 357:1351–1368. doi:10.1002/adsc.201400778
7. Leenders SHAM, Gramage-Doria R, de Bruin B, Reek JNH (2014) Transition metal catalysis in confined spaces. Chem Soc Rev 44:433–448. doi:10.1039/C4CS00192C

8. Zhao C, Sun Q-F, Hart-Cooper WM et al (2013) Chiral amide directed assembly of a diastereo- and enantiopure supramolecular host and its application to enantioselective catalysis of neutral substrates. J Am Chem Soc 135:18802–18805. doi:10.1021/ja411631v
9. Bolliger JL, Belenguer AM, Nitschke JR (2013) Enantiopure water-soluble [Fe4L6] cages: host-guest chemistry and catalytic activity. Angew Chem Int Ed 52:7958–7962. doi:10.1002/anie.201302136
10. MacGillivray LR, Atwood JL (1997) A chiral spherical molecular assembly held together by 60 hydrogen bonds. Nature 389:469–472. doi:10.1038/38985
11. Koblenz TS, Wassenaar J, Reek JNH (2008) Reactivity within a confined self-assembled nanospace. Chem Soc Rev 37:247–262. doi:10.1039/B614961H
12. van der Vlugt JI, Koblenz TS, Wassenaar J, Reek JNH (2010) Chemistry in self-assembled nanoreactors. In: Brinker UH, Mieusset J-L (eds) Mol. Encapsulation, Wiley, pp 145–174
13. Kang J, Santamaría J, Hilmersson G, Rebek J (1998) Self-assembled molecular capsule catalyzes a Diels–Alder reaction. J Am Chem Soc 120:7389–7390. doi:10.1021/ja980927n
14. Yoshizawa M, Tamura M, Fujita M (2006) Diels-Alder in aqueous molecular hosts: unusual regioselectivity and efficient catalysis. Science 312:251–254. doi:10.1126/science.1124985
15. Hastings CJ, Fiedler D, Bergman RG, Raymond KN (2008) Aza cope rearrangement of propargyl enammonium cations catalyzed by a self-assembled "nanozyme". J Am Chem Soc 130:10977–10983. doi:10.1021/ja8013055
16. Cullen W, Misuraca MC, Hunter CA et al (2016) Highly efficient catalysis of the Kemp elimination in the cavity of a cubic coordination cage. Nat Chem 8:231–236. doi:10.1038/nchem.2452
17. Zhao C, Toste FD, Raymond KN, Bergman RG (2014) Nucleophilic substitution catalyzed by a supramolecular cavity proceeds with retention of absolute stereochemistry. J Am Chem Soc 136:14409–14412. doi:10.1021/ja508799p
18. Hastings CJ, Backlund MP, Bergman RG, Raymond KN (2011) Enzyme-like control of carbocation deprotonation regioselectivity in supramolecular catalysis of the Nazarov cyclization. Angew Chem Int Ed 50:10570–10573. doi:10.1002/anie.201105325
19. Pluth MD, Bergman RG, Raymond KN (2009) Proton-mediated chemistry and catalysis in a self-assembled supramolecular host. Acc Chem Res 42:1650–1659. doi:10.1021/ar900118t
20. Bolliger JL (2014) [Fe4L6]8+ cages: encapsulation and catalytic degradation of an insecticide. Chim Int J Chem 68:204–207. doi:10.2533/chimia.2014.204
21. Pluth MD, Bergman RG, Raymond KN (2007) Acid catalysis in basic solution: a supramolecular host promotes orthoformate hydrolysis. Science 316:85–88. doi:10.1126/science.1138748
22. Pluth MD, Bergman RG, Raymond KN (2008) Supramolecular catalysis of orthoformate hydrolysis in basic solution: an enzyme-like mechanism. J Am Chem Soc 130:11423–11429. doi:10.1021/ja802839v
23. Pluth MD, Bergman RG, Raymond KN (2007) Catalytic deprotection of acetals in basic solution with a self-assembled supramolecular "nanozyme". Angew Chem Int Ed 46:8587–8589. doi:10.1002/anie.200703371
24. Pluth MD, Bergman RG, Raymond KN (2009) The acid hydrolysis mechanism of acetals catalyzed by a supramolecular assembly in basic solution. J Org Chem 74:58–63. doi:10.1021/jo802131v
25. Zhang Q, Tiefenbacher K (2013) Hexameric resorcinarene capsule is a brønsted acid: investigation and application to synthesis and catalysis. J Am Chem Soc 135:16213–16219. doi:10.1021/ja4080375
26. Woodward RB, Hoffmann R (1969) The conservation of orbital symmetry. Angew Chem Int Ed Engl 8:781–853. doi:10.1002/anie.196907811
27. Hastings CJ, Pluth MD, Bergman RG, Raymond KN (2010) Enzymelike catalysis of the Nazarov cyclization by supramolecular encapsulation. J Am Chem Soc 132:6938–6940. doi:10.1021/ja102633e

28. Catti L, Tiefenbacher K (2015) Intramolecular hydroalkoxylation catalyzed inside a self-assembled cavity of an enzyme-like host structure. Chem Commun 51:892–894. doi:10.1039/C4CC08211G
29. Zhang Q, Tiefenbacher K (2015) Terpene cyclization catalysed inside a self-assembled cavity. Nat Chem 7:197–202. doi:10.1038/nchem.2181
30. Hart-Cooper WM, Zhao C, Triano RM et al (2015) The effect of host structure on the selectivity and mechanism of supramolecular catalysis of Prins cyclizations. Chem Sci 6:1383–1393. doi:10.1039/C4SC02735C
31. Hart-Cooper WM, Clary KN, Toste FD et al (2012) Selective monoterpene-like cyclization reactions achieved by water exclusion from reactive intermediates in a supramolecular catalyst. J Am Chem Soc 134:17873–17876. doi:10.1021/ja308254k
32. Fiedler D, Bergman RG, Raymond KN (2004) Supramolecular Catalysis of a unimolecular transformation: Aza-Cope rearrangement within a self-assembled host. Angew Chem Int Ed 43:6748–6751. doi:10.1002/anie.200461776
33. Fiedler D, van Halbeek H, Bergman RG, Raymond KN (2006) Supramolecular catalysis of unimolecular rearrangements: substrate scope and mechanistic insights. J Am Chem Soc 128:10240–10252. doi:10.1021/ja062329b
34. Brown CJ, Bergman RG, Raymond KN (2009) Enantioselective catalysis of the Aza-Cope rearrangement by a chiral supramolecular assembly. J Am Chem Soc 131:17530–17531. doi:10.1021/ja906386w
35. Bianchini G, Sorella GL, Canever N et al (2013) Efficient isonitrile hydration through encapsulation within a hexameric self-assembled capsule and selective inhibition by a photo-controllable competitive guest. Chem Commun 49:5322–5324. doi:10.1039/C3CC42233J
36. Kang J, Rebek J (1997) Acceleration of a Diels-Alder reaction by a self-assembled molecular capsule. Nature 385:50–52. doi:10.1038/385050a0
37. Shimizu S, Usui A, Sugai M et al (2013) Hexameric capsule of a resorcinarene bearing fluorous feet as a self-assembled nanoreactor: a Diels-Alder reaction in a fluorous biphasic system. Eur J Org Chem 2013:4734–4737. doi:10.1002/ejoc.201300652
38. Murase T, Nishijima Y, Fujita M (2012) Cage-catalyzed Knoevenagel condensation under neutral conditions in water. J Am Chem Soc 134:162–164. doi:10.1021/ja210068f
39. Giust S, La Sorella G, Sperni L et al (2015) Supramolecular catalysis in the synthesis of substituted 1 H-Tetrazoles from isonitriles by a self-assembled hexameric capsule. Asian J Org Chem 4:217–220. doi:10.1002/ajoc.201402229
40. Cavarzan A, Scarso A, Sgarbossa P et al (2011) Supramolecular control on chemo- and regioselectivity via encapsulation of (NHC)-Au catalyst within a hexameric self-assembled host. J Am Chem Soc 133:2848–2851. doi:10.1021/ja111106x
41. Cavarzan A, Reek JNH, Trentin F et al (2013) Substrate selectivity in the alkyne hydration mediated by NHC–Au(I) controlled by encapsulation of the catalyst within a hydrogen bonded hexameric host. Catal Sci Technol 3:2898–2901. doi:10.1039/C3CY00300K
42. Leung DH, Bergman RG, Raymond KN (2007) Highly selective supramolecular catalyzed allylic alcohol isomerization. J Am Chem Soc 129:2746–2747. doi:10.1021/ja068688o
43. Brown CJ, Miller GM, Johnson MW et al (2011) High-turnover supramolecular catalysis by a protected ruthenium(II) complex in aqueous solution. J Am Chem Soc 133:11964–11966. doi:10.1021/ja205257x
44. Wang ZJ, Brown CJ, Bergman RG et al (2011) Hydroalkoxylation catalyzed by a gold(I) complex encapsulated in a supramolecular host. J Am Chem Soc 133:7358–7360. doi:10.1021/ja202055v
45. Lohr TL, Marks TJ (2015) Orthogonal tandem catalysis. Nat Chem 7:477–482. doi:10.1038/nchem.2262
46. Wang ZJ, Clary KN, Bergman RG et al (2013) A supramolecular approach to combining enzymatic and transition metal catalysis. Nat Chem 5:100–103. doi:10.1038/nchem.1531
47. Salles AG, Zarra S, Turner RM, Nitschke JR (2013) A self-organizing chemical assembly line. J Am Chem Soc 135:19143–19146. doi:10.1021/ja412235e

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