1
Introduction to Supramolecular Catalysis

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1.1
Introduction

Much of the inspiration for the design of supramolecular catalytic system arises from the observation and understanding of enzyme catalysis [1–3]. However, synthetic models usually contain only one or few of the features that are present in the biologically enzymatic systems. In contrast, supramolecular enzyme model systems are smaller and structurally simpler than enzymes. The fact that the synthetic systems are simpler than the biological ones does not limit the detail of questions that may be investigated; instead, using these simpler systems it is possible to estimate the relative importance of different factors contributing to catalysis. A further advantage of the use of supramolecular models for studying catalysis is that the compounds can be synthetically manipulated to study a specific property. In the biological realm of catalysis it is a tremendous task to discern a particular factor responsible for the catalytic efficiency of the enzyme.

Supramolecular systems can be considered as new tools of modern physical organic chemistry. The study of catalytic processes using supramolecular model systems aims to explain the observed rate enhancement in terms of structure and mechanism. In some cases, the model systems may even provide a simplified simulation of the action of an enzyme and lead to further understanding of the different mechanism by which enzymes are able to achieve impressive reaction rate accelerations and turnover numbers.

Catalysis is a longstanding proposed application of supramolecular chemistry and the production of supramolecular systems capable of mimicking the catalytic ability of natural enzymes is one of the ultimate goals of self-assembly research. Supramolecular chemists have approached these challenging endeavors from different perspectives. On the one hand, many model systems have been designed that make use of the binding energy to achieve catalysis. Within this approach two types of systems can be differentiated: (a) molecular receptors in which a catalytic site is placed close to a binding site that has been designed to bind selectively the reactant,

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and (b) molecular receptors that promote the reaction of two simultaneously complexed reactants, forming a multimolecular (ternary or higher order) complex, which is held together by weak and reversible interactions.

When two reacting functionalities are brought in close proximity, i.e., by binding to a template/receptor or by inclusion into a molecular vessel, the observed rate acceleration may be a simple effect due to an increase in the effective local concentration [4]. The entropic advantage of an "intramolecular" over an intermolecular reaction can be quantified by measuring the effective molarity $EM = k_{intramol.}/k_{intermol.}$ [3]. The EM value can tell us how catalytic efficiency relates to structure in a system designed to bring functional groups together in close proximity. Although, Page and Jenks have estimated that the entropy changes in solution may have an effective concentration of about 6×10^8 M, and high EMs have been measured for simple cyclization reactions, with rare exceptions the simple approximation of reactants caused by synthetic supramolecular catalytic systems achieve rate accelerations that are tiny by comparison with enzymes ($EM < 10$ M). The low efficiency of this mechanism of catalysis for two-substrate reactions is probably because the molecules of the bimolecular or ternary complexes are not tightly bound – there is residual entropy in the complex due to vibrations. As soon as the molecules become linked in the TS there is still a large loss of entropy not overcome by the binding energy.*

A key feature of enzymes is their ability to bind, and thus stabilize, selectively the transition state and intermediates for a particular reaction. So the problem of catalysis can be defined in terms of the molecular recognition of transition states. We will see below that many supramolecular models often fail to reproduce the turnover ability of enzymes due to inhibition by strongly-bound products. More sophisticated synthetic hosts have been designed to achieve catalysis not only by placing converging binding sites in such a way that reactant molecules are brought together in close proximity (entropy of activation is reduced or partially compensated by the favorable binding energy) but also by stabilization of the intermediate or transition state.† However, even from these more elaborated structures very few efficient supramolecular catalysts have emerged [5]. Sanders has pointed out that it is probably the fear of entropy that has taken supramolecular chemist too far in the direction of rigidity and preorganization. Rigid structures with a slightly mismatch to the TS will not be effective catalysts. Furthermore, the use of large and rigid molecular components in the construction of catalytic supramolecular systems makes it difficult to achieve the sub-ångström adjustments required for perfect TS stabilization. However, to the best of our knowl-

* In enzyme catalysis entropy is probably one of the most important factors. Enzyme reactions take place with substrates that are nanoconfined in the active sites and form a very tight enzyme–substrate complex. The catalytic groups are part of the same molecule as the substrate so there is no loss of transition or rotational entropy in the TS.

† Simply bringing together the reactant groups of the molecules makes productive encounters more probable but the most effective system will be one in which the flexibility of different binding geometries is eliminated and only the transition state like geometry is prescribed. The binding forces for the formation of a bond between two reactants are the intrinsic reactivity of the functional groups and the way the groups are brought together – this second factor is responsible of the efficiency of the catalysis.

edge, this point has not been tested so far, mainly due to the difficult design and synthesis effort required. The construction of self-assembled catalyst in which all recognition motifs, both between the catalyst subunits and between substrate and catalyst, are kinetically labile could provide a feasible approximation to approach the issue of rigidity of the catalytic supramolecular system [6]. The better fit to the transition state accomplished by a flexible supramolecular system is achieved at the expense of a larger loss of vibrational and rotational entropy on going from a not rigid and conformationally unrestricted complex to the fixed geometry of the TS.

Desolvation of the reacting polar groups is also a mechanism by which enzymes achieve rate accelerations. The desolvation of functional groups takes places during the inclusion of the reactants within the catalytic apparatus of the active site. This is another way of looking at the selective stabilization of the TS, in terms of a "specific" solvation of the reactants by the enzyme residues of the active site, which replaces the random solvation by the solvent molecules and the inherent enthalpic and entropic cost associated with their reorganization in the TS.

1.2
Design Approaches to Supramolecular Catalysis

1.2.1
Molecular Receptors that Place a Binding Site Close to a Catalytic Center

Early examples of two-substrate supramolecular catalysis emerge from the work of Bender *et al.*, who studied the hydrolysis of *m-tert*-butylphenyl acetate in the presence of 2-benzimidazoleacetic acid with α-cyclodextrin [7]. Breslow, Knowles and others further extended the use of cyclodextrins as enzyme models. In this regard, Breslow's group synthesized a β-cyclodextrin (cycloheptaamylose) carrying two imidazole groups to model ribonuclease A [8]. More recently, Kim *et al.* have used a series of functionalized β-cyclodextrins with different polyazamacrocycles [9]. The Zn-complexes of these molecules are carboxypeptidase mimics, with the hydrophobic cavity of the cyclodextrin acting as a binding site for the aromatic residue of *p*-nitrophenyl acetate and the Zn(II) metal center complexed by the azamacrocycle being the catalytic site. The doughnut-shaped structure of the cyclodextrins is rather inflexible and it has twelve hydroxyl groups on the top side and six primary hydroxyl groups at the bottom. The torus is slightly more open on the side of the secondary OH groups, but β-cyclodextrins with a cavity diameter of about 7 Å display an efficient binding of the substrate from the side of the primary OH groups. The binding geometry of the complex places the reactive acetate group of the organic substrate close to a nucleophilic water molecule bound to the chelated Zn(II). The reported EMs are in the range 0.2–0.3 M and are based on measurements of $k_{cat} = k_{intra}$ for the decomposition of the productive ternary complex shown in Figure 1.1 and k_{inter} for the reaction of *p*-nitrophenyl acetate and the corresponding Zn(II) complex of the polyazamacrocycle. Two basic assumptions are implicit in the reliability of the calculated EMs: (a) the pK_a and

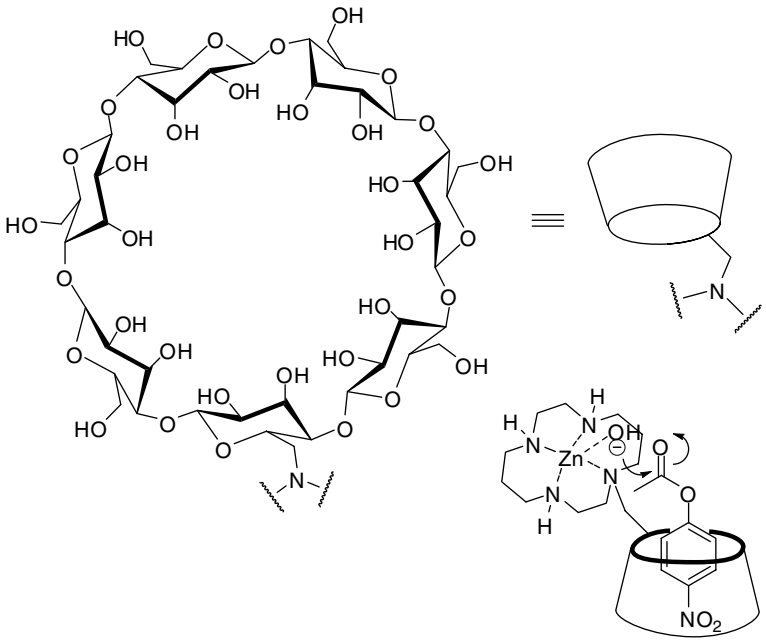


Figure 1.1 Molecular structure of functionalized β-cyclodextrin and the corresponding binary complex with *p*-nitrophenyl acetate.

nucleophilicity of the bound water is unchanged upon linking the macrocycle to the cyclodextrin and (b) the reactivity of the *p*-nitrophenyl acetate does not change on complexation.

Recent examples of this kind of methodology can be found, for example, in the work of Rebek *et al.* [10] The catalyst used is a cavitand armed with a Zn salen-type complex (Figure 1.2). The cavitand adopts a vase-like conformation that is stabilized by a seam of hydrogen bonds provided by the six secondary amides. The structure of the catalyst permits a slow dynamic exchange between free and bound guest (reactant) on the ^{1}H NMR time-scale that is controlled by the folding and unfolding of the cavitand.

When the guest used is *p*-nitrophenylcholine carbonate (PNPCC) the Lewis acid zinc(II) activates the well-positioned carbonyl group in the PNPCC@Zn-cavitand towards reactions with external nucleophiles. The energy minimized structure of the PNPCC@Zn-cavitand complex shows that cation–π interactions and C = O···Zn coordination bond occurs simultaneously.

Kinetic studies revealed that the hydrolysis of PNPCC by water present in commercial CH_2Cl_2 buffered with CF_3CO_2H/EtN(i-Pr)$_2$ was catalyzed in the presence of the Zn-cavitand. The hydrolysis of the carbonate is slow under these reaction conditions and only ca. 30% pf PNPCC is decomposed after 5 h. The acceleration of the reaction rate is more than 50-fold when 1 equiv of cavitand is present.

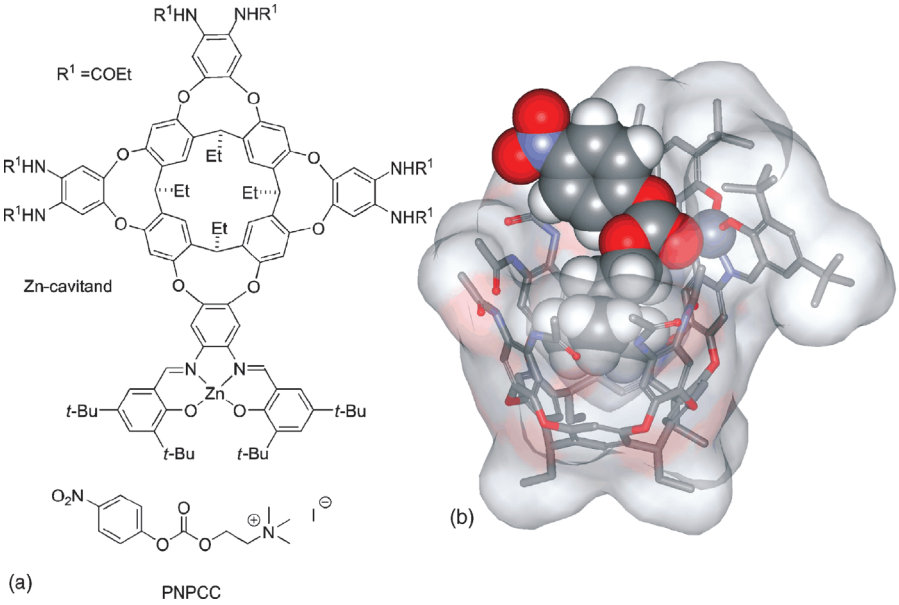


Figure 1.2 (a) Molecular structure of Rebek's Zn-cavitand and *p*-nitrophenylcholine carbonate (PNPCC). (b) CAChe minimized structure of the PNPCC@Zn-cavitand complex.

Another example of a synthetic catalyst capable of orienting the substrate towards the reaction center has been described recently by Crabtree and coworkers (Figure 1.3) [11]. The authors combined molecular recognition through hydrogen bonds and C−H activation to obtain high turnover catalytic regioselective functionalization of sp^3 C−H bonds remote from the −COOH recognition group. The catalyst contains a di-μ-oxo dimanganese catalytic core and two ligands that are based on the covalent connection of a Kemp's triacid unit with a terpy group through a phenylene linker. The Kemp's triacid unit provides a well-known U-turn motif having a −COOH group suitably oriented for the molecular recognition of another −COOH function.

Molecular modeling studies allowed to predict from the proposed geometry of the H-bonded complex with ibuprofen – 2-(4-isobutylphenyl)propionic acid – which C−H (indicated by to arrows) in the substrate would be expected to come closest to the active site and consequently became oxidized. If the oxidation operates via the catalyst–substrate complex predicted by the model complex, then the regioselective product should be the major component of the reaction mixture. When ibuprofen was treated with the catalyst, the selectivity for the regioselective product (97.5 : 2.5) was raised more than 10-fold when compared to the value obtained with a catalyst lacking the −COOH group (77 : 23). Oxidation of an alkyl carboxylic acid using the same catalysts led not only to regioselective oxygenation but also to diastereoselection of a single isomer. With a 0.1% catalyst-to-substrate ratio, a total turnover number of 580 was attained without loss of regioselectivity.

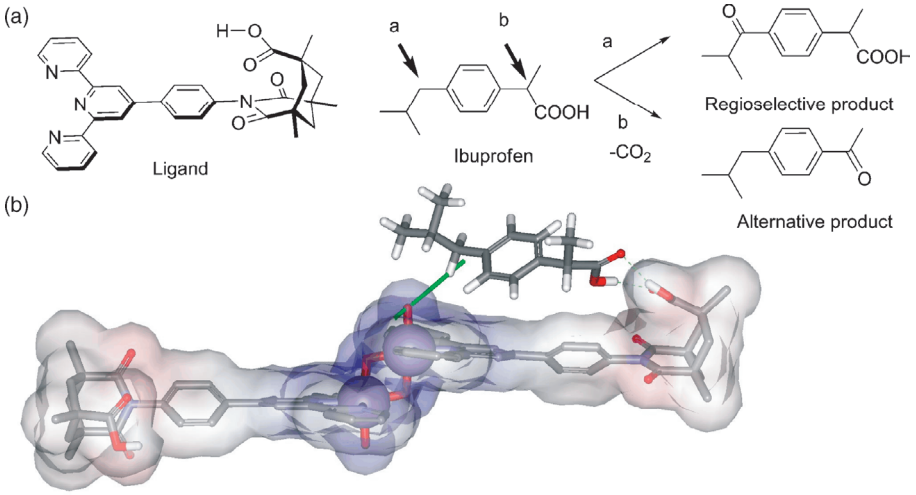


Figure 1.3 (a) Molecular structure of Crabtree's ligand and oxidation products of ibuprofen with the synthetic di-μ-oxo dimanganese catalyst. (b) Molecular model of the supramolecular catalyst (CAChe minimized) docked with ibuprofen.

Wärnmark *et al.* [12] have reported the formation of a dynamic supramolecular catalytic system involving a hydrogen bonding complex between a Mn(III) salen and a Zn(II) porphyrin (Figure 1.4). The salen sub-unit acts as the catalytic center for the catalytic epoxidation of olefins while the Zn-porphyrin component performs as the binding site. The system exhibits low selectivity for pyridine-appended styrene derivatives over phenyl-appended derivatives in a catalytic epoxidation reaction. The

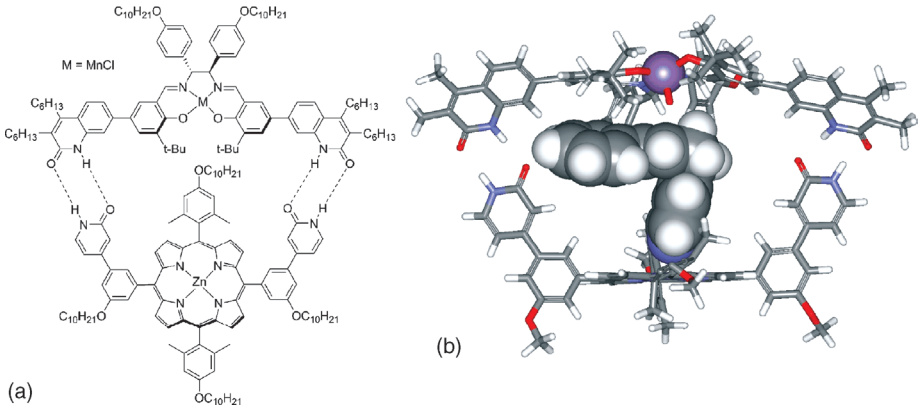


Figure 1.4 (a) Molecular structure of the supramolecular macrocyclic heterodimer catalyst used by Wärnmark *et al.* (b) CAChe minimized 3D representation of a substrate bound inside the hydrogen bonded macrocycle. Long alkyl chains are reduced to a methyl group for clarity. The substrate and the Mn atom (purple) are shown in CPK representation.

authors provide evidence that substrates bound to the supramolecular receptor and the non-bonded substrates are epoxidized by two different catalytic species. They also established the main reasons for the low observed selectivity.

In a somewhat related work, Nolte, Rowan *et al.* [13] described in 2003 a rotaxane complex that mimics the ability of processive enzymes to catalyze multiple rounds of reaction while the polymer substrate stays bound. The catalyst, which consists of a substrate-binding cavity incorporating a manganese(III) porphyrin complex acting as the catalytic center, can oxidize alkenes complexed within the toroid cavity, provided a ligand has been attached to the outer face of the toroid to both activate the porphyrin complex and prevent it from being able to oxidize alkenes outside the cavity.

1.2.2
Molecular Receptors that Promote the Reaction of two Simultaneously Complexed Reactants

The design of supramolecular systems capable of catalyzing bimolecular reactions is challenging: the supramolecular host first needs to recognize the reagents (which requires sufficiently strong binding) and, second, needs to correctly orient the two reagents and bring them together. Kirby [2] has coined the term "matchmakers" to describe synthetic hosts that perform these functions.

If the host has a higher affinity for the product arising from the bimolecular reaction than for the reagents, an additional problem comes into play: inhibition of turnover of the catalyst by the product. Although a host can not be regarded as truly catalytic if this occurs (stoichiometric amounts of host are required to achieve full conversion), the host can still accelerate the rate of the reaction and, interestingly, may even influence the outcome of the reaction.

Sanders and coworkers have designed and prepared a series of cyclic Zn(II) porphyrin trimers that are noteworthy not only because they accelerate the Diels–Alder reaction of a pyridine-substituted diene and a dienophile (Figure 1.5) [14] but because they also influence the stereochemical outcome of the cycloaddition reaction. The cyclic porphyrin oligomers can accommodate the diene and dienophile inside the cavity, thus lowering the activation energy by holding both reagents in close proximity. The larger 2,2,2-porphyrin trimer catalyzes the formation of the thermodynamically more favored *exo*-adduct up to 1000× faster than the formation of the *endo*-isomer. This rate acceleration corresponds to an EM of ca. 20 M, which is quite high for an artificial system. The key effect of the binding process inside the cavity should be recalled at this point, which is capable of reversing the stereochemistry of the reaction and mediating the formation of the unexpected *exo*-product (the *endo*-compound is produced in the absence of catalyst by kinetic control).

The computer generated model in Figure 1.6 shows the perfect fit of the *exo*-adduct inside the 2,2,2-trimer cavity. The smaller 1,1,2-trimer showed a stereoselective bias towards the endo-product at 30 °C; however, this stereoselectivity is lost at higher temperatures (a mixture of both the *endo*- and *exo*-products was observed at 60 °C). The reversal of the stereochemical outcome of the Diels–Alder reaction between the two cyclic dimers (30 °C) appears to lie firstly in a large (500-fold) *endo* acceleration

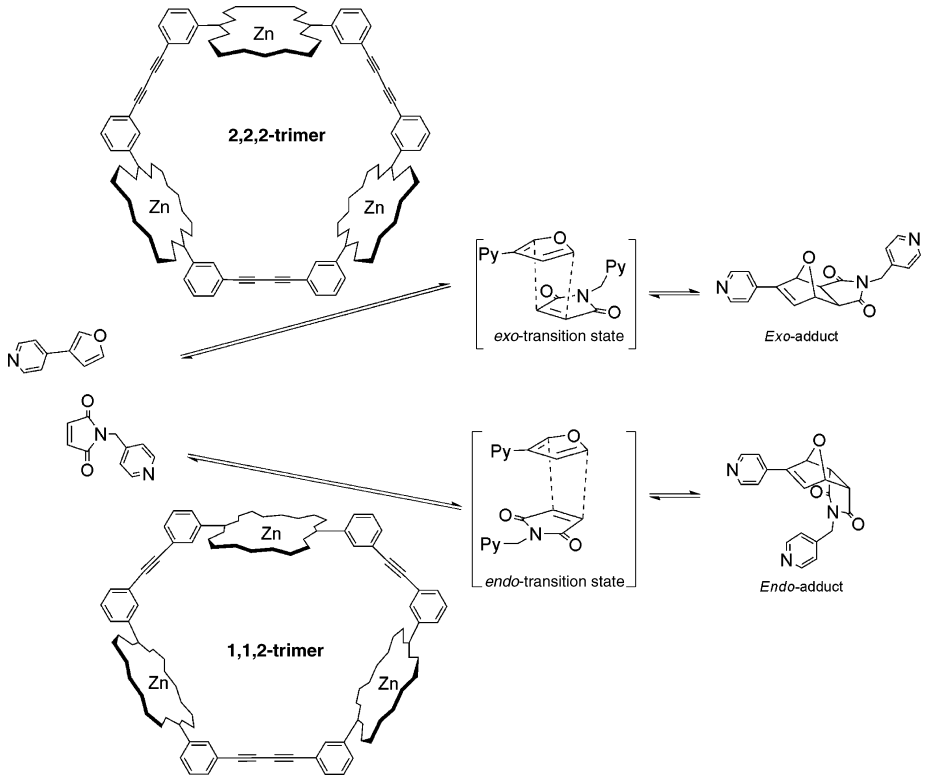


Figure 1.5 Stereochemical outcome of the Diels–Alder reactions under the influence of the 2,2,2- and 1,1,2-trimers.

induced by the smaller 1,1,2-dimer and, secondly, in a lack of complementarity at 30°C of the less flexible 1,1,2-trimer for the *exo*-product. Given its greater flexibility, the 2,2,2-trimer is better suited to accommodate at room temperature the transition state that leads to the *exo*-product.

Sanders and coworkers have extended the use of these cyclic porphyrin systems in the catalysis of acyl-transfer reactions [15] and hetero-Diels–Alder reactions [16].

Kelly and coworkers devised a two binding-site host that accelerates an S_N2 reaction between a primary aliphatic amine and an alkyl bromide [17]. Kelly's host (Figure 1.7) acted as template for the two reactants that were able to form three hydrogen bonds to each aminopyridone from the host. The reactants were the aminomethyl- and bromomethylnaphthyridines indicated in Figure 1.7, which bound strongly ($K > 10^4\,M^{-1}$) to the aminopyridone moieties from the host. A sixfold acceleration of the S_N2 reaction was observed, but turnover could not be demonstrated (the product precipitated from the $CHCl_3$ solution as the HBr salt).

An unavoidable limitation of Kelly's host was that the two binding sites were identical, which allowed non-productive binding of two identical substrates. Kelly therefore designed a new receptor with two different binding motifs that selectively

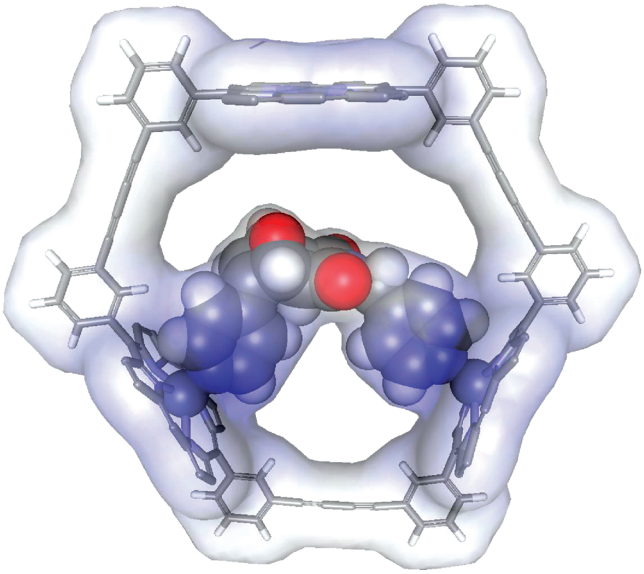


Figure 1.6 CAChe minimized 3D structure of the bound exo-adduct inside the cavity of 2,2,2-trimer (porphyrin substituents omitted for clarity).

recognize each of the two reactants. Furthermore, an additional phenyl group was introduced in the molecule to ensure that the bromide was productively directed towards the amino group. The reaction rate obtained with this variant was twice as high as that obtained with the symmetrical host. These results clearly illustrate the potential of supramolecular catalysis to provide substantial rate accelerations even in reactions with strict stereoelectronic requirements for a linear transition state.

Self-replication offers a direct path to supramolecular catalysis. Rebek *et al.* reported an impressive self-replicating system, which involves the assembly of suitably designed components by hydrogen bonding and π–π-stacking [18]. In the first step, the naphthalene ester and a heterocyclic amine self-assemble under the influence of hydrogen bonding and π–π-stacking interactions. The assembly is preorganized to facilitate the aminolysis of the neighboring ester group (Figure 1.8). The resulting *cis*-amide undergoes isomerization towards the less strained trans-isomer. This compound can then bind the two original reagents to form a ternary complex, which is again preorganized for nucleophilic attack of the ester group to give a dimer. Self-replication is thus elegantly achieved; the only drawback being the high stability of the dimer, which inhibits its role as a template for further self-replication.

Catalysis has also been induced by encapsulation or inclusion of molecules into cavities of molecular or supramolecular hosts. In both cases, the cavity should be large enough to accommodate concurrently at least two reactants in such a way that the reaction among them is favored (productive geometry). Probably, in these examples, not only the binding energy is used to induce catalysis by reducing or compensating the unfavorable entropy of activation but other specific mechanisms

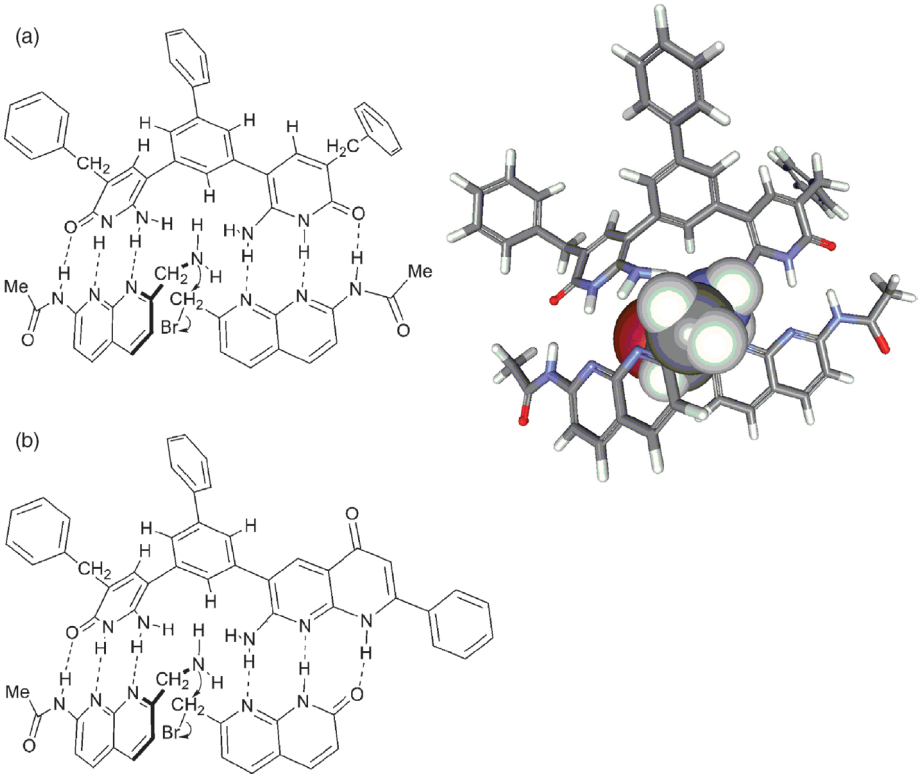


Figure 1.7 Nucleophilic reaction catalyzed by Kelly's hosts; S_N2 reaction in the host with two symmetrical (a) or two asymmetrical (b) hydrogen bonding recognition motifs.

may also come to play. The inner surface of the molecular cage can be complementary to the transition state (TS) and not also to the ground states of the reactants. It is also worth mentioning that, in some cases, when the reactants are encapsulated they become completely isolated from the solvent. This "specific" solvation eliminates the enthalpic and entropic cost of reorganizing the solvent molecules in the TS. Furthermore, the encapsulation or inclusion of the reactants into molecular vessels may produce a two-fold positive contribution to catalysis: (1) by exerting some "strain" to the molecular receptor, i.e., the minimum energy geometry of the vessels is slightly distorted due to the inclusion of the reactants, and (2) by inducing certain "stress" to the included reactants. The "strain" and "stress" energies are expected to be eliminated or reduced upon reaction. The amount of "stress" than can be forced on the included reactants of course depends on the strength of the interactions used to hold together the molecular components that constitute the host. For self-assembled supramolecular nanovessels the interactions are of "noncovalent" nature (usually hydrogen bonds and coordination bonds).

An early study of catalysis induced by inclusion of reactants in molecular vessels derives from the work of Mock *et al.* [19–21]. The authors reported that the

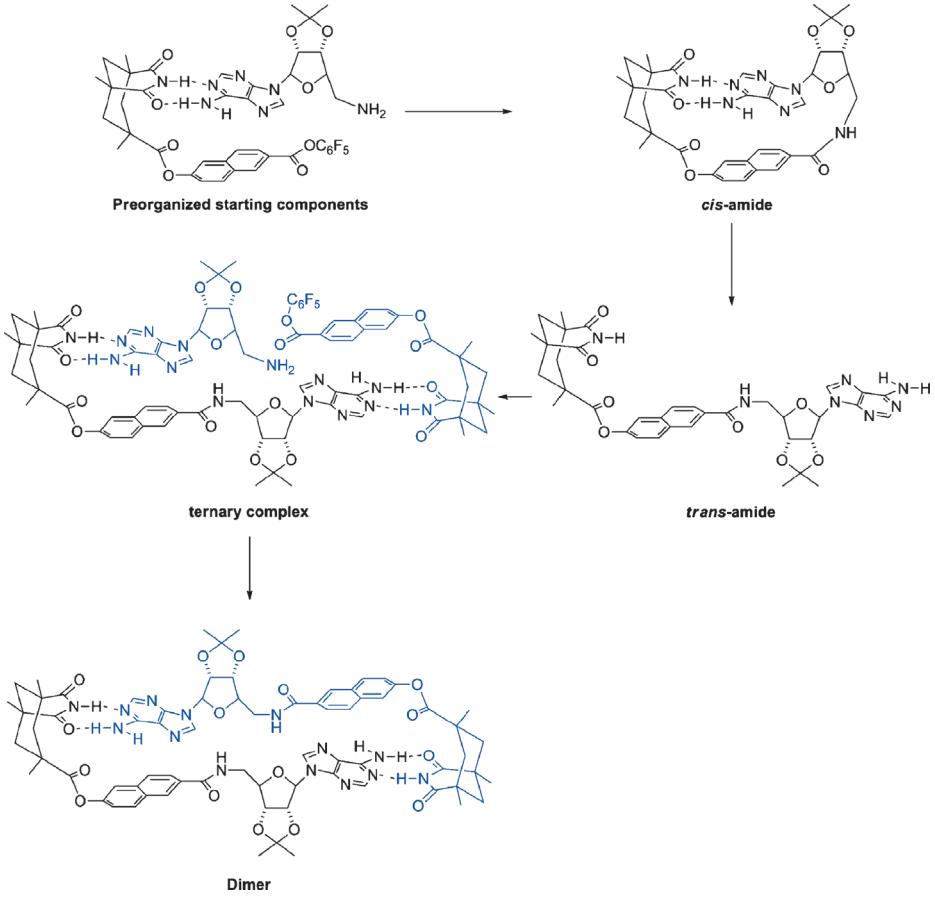


Figure 1.8 Rebek's self-replicating system.

intermolecular 1,3 dipolar cycloaddition between an azide and an alkyne, both of them substituted with an ammonium group, was substantially accelerated (ca. 10^5-fold or EM = 1.6×10^4 M based on Ref. [3]) and became highly regioselective in the presence of cucurbit[6]uril (Figure 1.9). The calculated cavity volume of cucurbit[6]uril (164 $Å^3$) translates into an encapsulated reactant concentration of 10 M. The reaction kinetics also show catalytic saturation behavior, substrate inhibition and slow product release. The presence of a tertiary complex azide-alkyne@cucurbit[6]uril is documented by kinetic analysis. The simultaneous binding of both alkyne and azide (with the NH_3^+ group bound to each set of the carbonyls and with the substituents extended inside the cavity) aligns the reactive groups within the cavity of the host in a productive geometry that catalyzes the exclusive formation of the 1,4-substituted triazole. The authors state that cucurbit[6]uril accomplished catalysis through more than one mechanism. Curcurbit[6]uril not only eliminates or reduces the entropic constrains of the reaction by bringing both reactants together but also its cavity is more adequate for the geometry of the TS cycloaddition than for the bound reactants. Recent

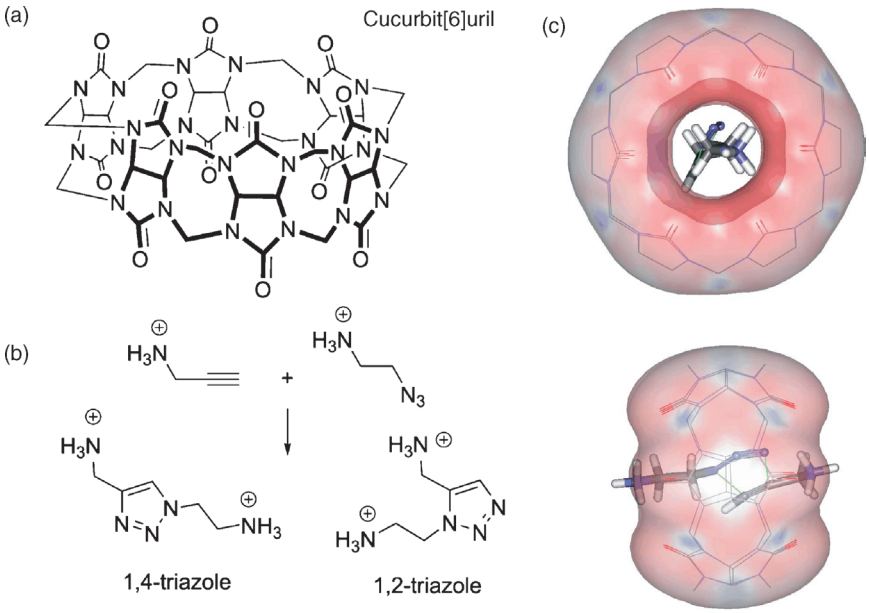


Figure 1.9 (a) Structure of cucurbit[6]uril; (b) 1,3-dipolar cycloaddition; (c) the reaction ternary complex for the formation of the 1,4-triazole.

computational investigations performed on the same system by Maseras and Carlqvist [22] suggest that the main catalytic effect is the elimination of the entropic cost of bringing the reactants together in the ternary complex and turning the addition reaction into a unimolecular one. Maseras and Carlqvist did not find computational evidences for transition state stabilization by the cucurbit[6]uril host.

Rebek has reported a new synthetic molecular vessel that can accelerate a 1,3-dipolar cycloaddition between an alkyne and an azide (Figure 1.10) [23]. The catalytic molecular capsule is formed by dimerization of two resorcinarene derivative subunits. The capsule has a roughly cylindrical cavity capable of accommodating two different aromatic guests. The orientation of the encapsulated guests is constrained to edge to edge approaches, and only the peripheral substituents make contacts. This arrangement seems to be appropriate for catalyzing the reaction between peripheral substituents of substrates anchored in the capsule by their respective aromatic groups. In particular, the cycloaddition under study involves phenylacetylene and phenyl azide. These compounds react very slowly to give equal amounts of the two regioisomers in the absence of the capsule ($k_{out} = 4.3 \times 10^{-9}\,M^{-1}\,s^{-1}$, $v = 1.3 \times 10^{-15}\,M\,s^{-1}$). In the presence of the capsule only the 1,4-isomer is formed. Control experiments have shown that only the 1,4-isomer is encapsulated. The local concentration of each reactant inside the capsule is 3.7 M (capsule volume $\approx 450\,Å^3$). Consequently, the rate inside the capsule due to just an increase of the effective local concentration, and assuming that the productive geometry can be achieved, would be $v \sim 6 \times 10^{-8}\,M\,s^{-1} = k_{out}\,[alkyne]_{in}[azide]_{in}$, a value larger than the initial rate observed ($v = 1.3 \times 10^{-9}$

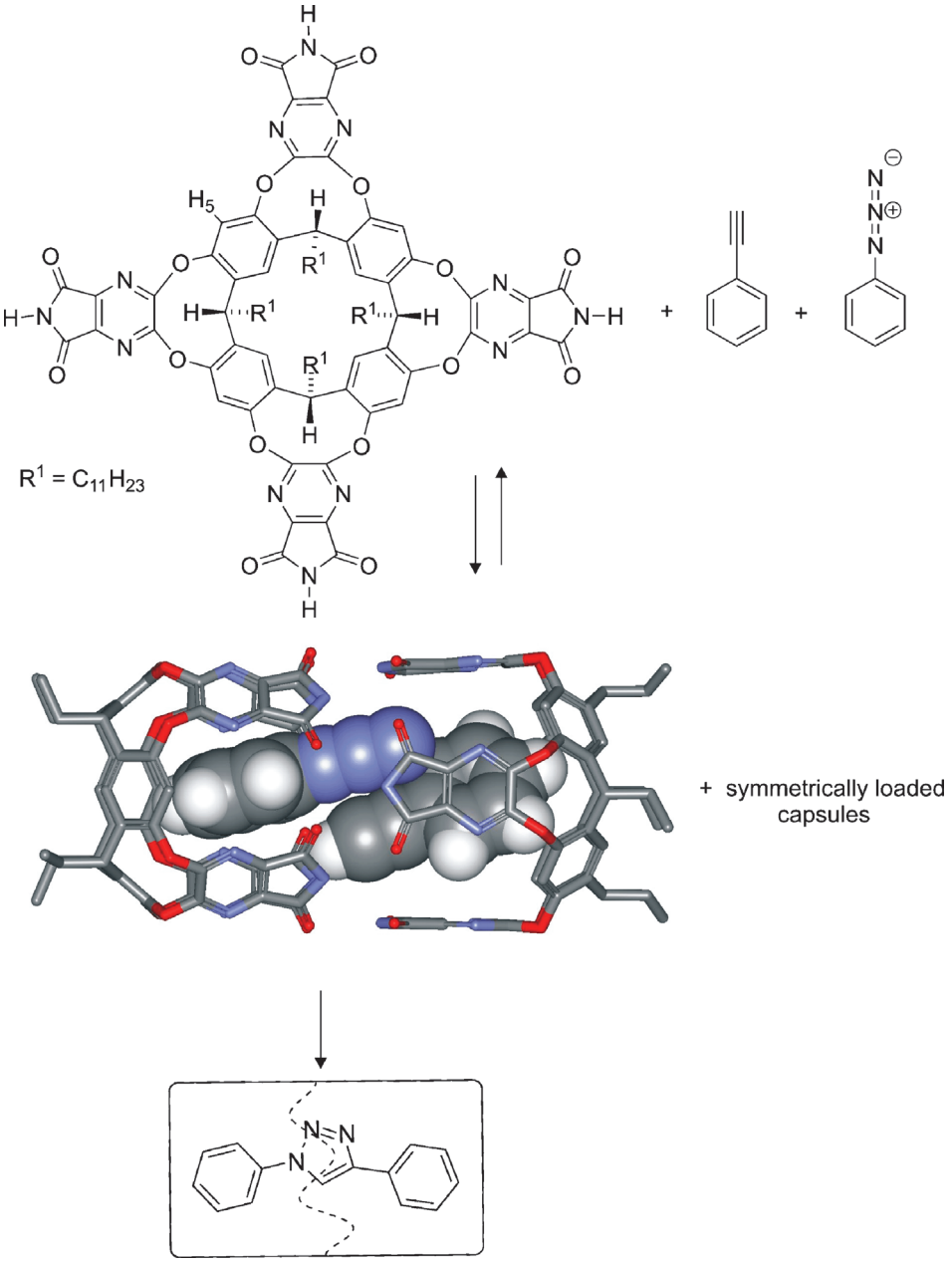


Figure 1.10 Representation of Rebek's capsule for the acceleration of a 1,3-dipolar cycloaddition between an alkyne and an azide.

$M\,s^{-1}$). The reaction rate outside the capsule at the concentrations used for the experiment should be $v = k_{out}[alkyne][azide] = 4.3 \times 10^{-9}\,M^{-1}\,s^{-1} \times 0.05\,M \times 0.025\,M = 5.4 \times 10^{-12}\,M\,s^{-1}$. Thus, a rate acceleration of some 240 times can be estimated for the reaction taken place inside the capsule (EM = 120 M value taken from Ref. [3]). Probably, the reactants in the capsule are not positioned in the ideal geometry to achieve the TS and there are no reasons to believe that the TS is bound better than reactants. The most striking result of this work is the direct observation of the Michaelis complex, which simplifies the kinetic analysis. Unfortunately, the product is the best guest in the system and gradually the capsule is filled with it and the reaction is slowed by product inhibition.

In the latter two examples the EM values calculated from rate data are higher than the actual concentration of encapsulated reactants. This result indicates a favorable directional correlation of functionalities in the complex, but it is apparent that Rebek's capsule is less efficient than cucurbit[6]uril in promoting the productive geometry or stabilizing the TS. The molecular capsules not only concentrate reactants but also increase the time that the reacting function reside within critical distance (productive geometry) – both factors are determinant in achieving effective catalysis [24].

In striking contrast with these two previous examples of 1,3-dipolar cycloaddition catalyzed by encapsulation, the EMs calculated for particular examples of Diels–Alder reactions catalyzed by Rebek's softball [25] or by Sanders' [26] cyclophane, which was selected from a dynamic combinatorial library (DCL), are lower than the actual reactant concentration calculated from the volumes of the molecular cavities. Probably, the Diels–Alder reactions have more stringent orientational requirements than the 1,3-dipolar cycloaddition. The reactants of the Diels–Alder reactions, when encapsulated or included, spend a significant amount of time in ternary complexes displaying a non-productive mutual orientation.

Fujita *et al*. [27]. have used a self-assembled octahedral $[M_6L_4]$ (M = {Pd^{II}(TMEDA)}, L = tris-(3pyridyl)triazine) cage to catalyze and impose geometry constrains onto the Diels–Alder reaction of anthracene and maleimide to give an unexpected regioselectivity (Figure 1.11). As commented above, in the two previous examples of 1,3-dipolar additions, the geometric requirements of the interior of the molecular capsules control the most favorable arrangement of the reacting groups, producing a change of the reaction selectivity observed in solution. In Fujita's example, the two reactants, *N*-cyclohexylmaleimide and several anthracene derivatives, adopt a fixed orientation within the capsule in a way that the cycloaddition can only take place with the 1,4-positions of the anthracene molecule. The Diels–Alder reaction of anthracene in the absence of the capsule yields and adduct bridging the center ring (9,10-positions) of the anthracene framework as a consequence of the high localization of π-electron density at that site. Also, when sterically less demanding *N*-propylmaleimide was used, only the 9,10-adduct was formed. In the presence of the M_6L_4 capsule the yield of the reaction after 5 hours at 80°C was 98% and only the *syn*-1,4-adduct was detected. In contrast, in the absence of the capsule the reaction gave only the conventional 9,10-adduct in 44% yield. However, the reaction using this capsule is not catalytic as the product is bound better.

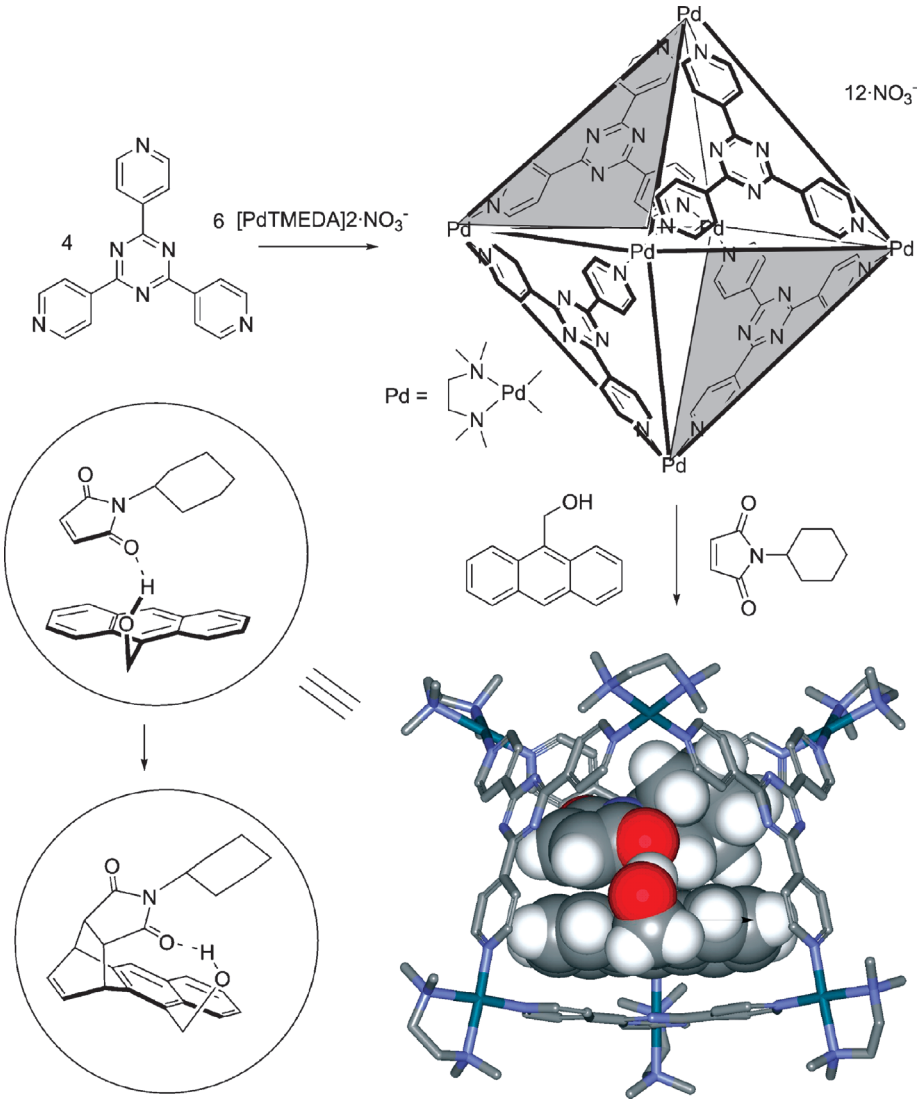


Figure 1.11 Fujita's self-assembled coordination cage, which is prepared by simple mixing of an exo-tridentate organic ligand and end-capped Pd(II) ion in a 4 : 6 ratio. Cache optimized structure of the ternary complex anthracene-maleimide@metallocage. Molecular structure of the syn-isomer of the 1,4-Diels–Alder adduct.

Raymond *et al.* [28] have employed a cavity-containing tetrahedral metal ligand assembly (M_4L_6) as a catalytic host for several reactions, e.g., the 3-aza-Cope rearrangement of allyl enammonium cations (Figure 1.12). Unstable organic species can also be stabilized within the same capsule [29]. The self-assembled cage preferentially hosts cationic guest over neutral ones as the cage is negatively charged.

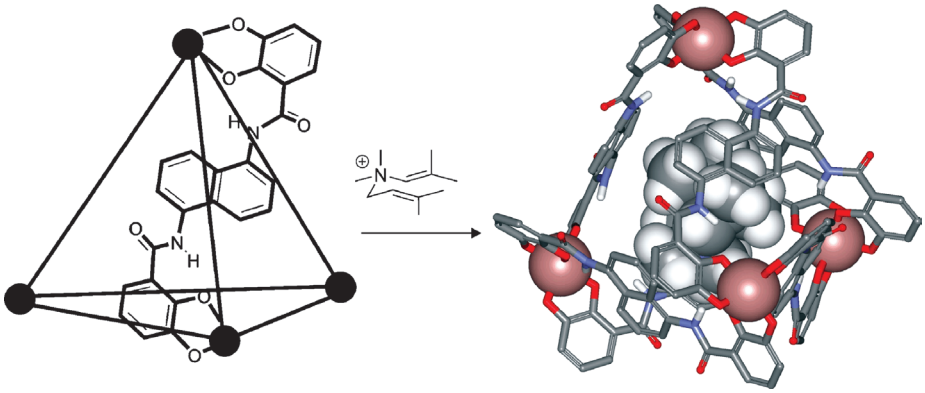


Figure 1.12 Schematic representation of the M_4L_6 cage and molecular structure of an enammonium substrate for the 3-aza Cope reaction. CAChe model of the M_4L_6 supramolecular assembly, encapsulating the enammonium substrate.

Upon binding the rates of rearrangement are accelerated for all substrates studied. The measured activation parameters of the reactions reveal that the supramolecular host can reduce both the entropic and the enthalpic barriers for the rearrangement. The capsule acts as a true catalyst, since release and hydrolysis facilitates turnover.

1.2.3 Preparation of the Catalyst Backbone via Supramolecular Interactions

In the earliest examples of supramolecular catalysis, a full arsenal of noncovalent interactions (electrostatic, hydrogen bonding, π–π stacking, and van der Waals interactions, hydrophobic and solvatophobic effects) and other reversible interactions, such as metal–ligand interactions, was employed to generate chemical assemblies between the reagent(s) and the catalytic system. By virtue of this supramolecular assembly, the reagents are more readily transformed into the final products (rate acceleration) or can even undergo reactions that are otherwise unfavored. All of the representative examples shown so far in this introduction demonstrate how supramolecular interactions have been involved in the directing and/or facilitating the catalytic event.

A completely different approach to achieve catalysis using supramolecular strategies has been developed in recent years. Noncovalent interactions normally lead to the rapid formation of bonds in an effective, reversible and strikingly apparently simple way. Chemists have exploited these features and have elegantly used reversible interactions (noncovalent effects and metal–ligand chemistry) to generate the backbones of a myriad supramolecular catalysts by bringing together the starting building blocks. These molecules contain the functional groups required for desired catalysis, and the motifs required for the assembly process of the supramolecular catalyst, via noncovalent and metal–ligand interactions. Furthermore, this novel methodology has enabled synthesis of libraries of structurally diverse

supramolecular ligands with unprecedented ease compared to the use of standard covalent chemistry. The design and synthesis of chiral supramolecular catalysts appear to be very straightforward with this strategy, as the chiral components of the starting building blocks are simply incorporated into the supramolecular catalysts within the assembly process. Early examples in this field emerge from the pioneering work of Breit and coworkers [30] (Chapter 2), who reported the *in situ* generation of a library of bidentate ligands from the tautomeric 2-pyridone/2-hydroxypyridine pair. The dimerization of the tautomeric pair is governed by hydrogen bonding and is strongly favored in aprotic solvents. In addition, when the monomers contain a phosphorus donor group (PPh_2 in Figure 1.13), which can coordinate to a metal centre, the formation of the bidentate ligand is favored through chelation. This approach was used to prepare suitable catalysts for the rhodium-catalyzed

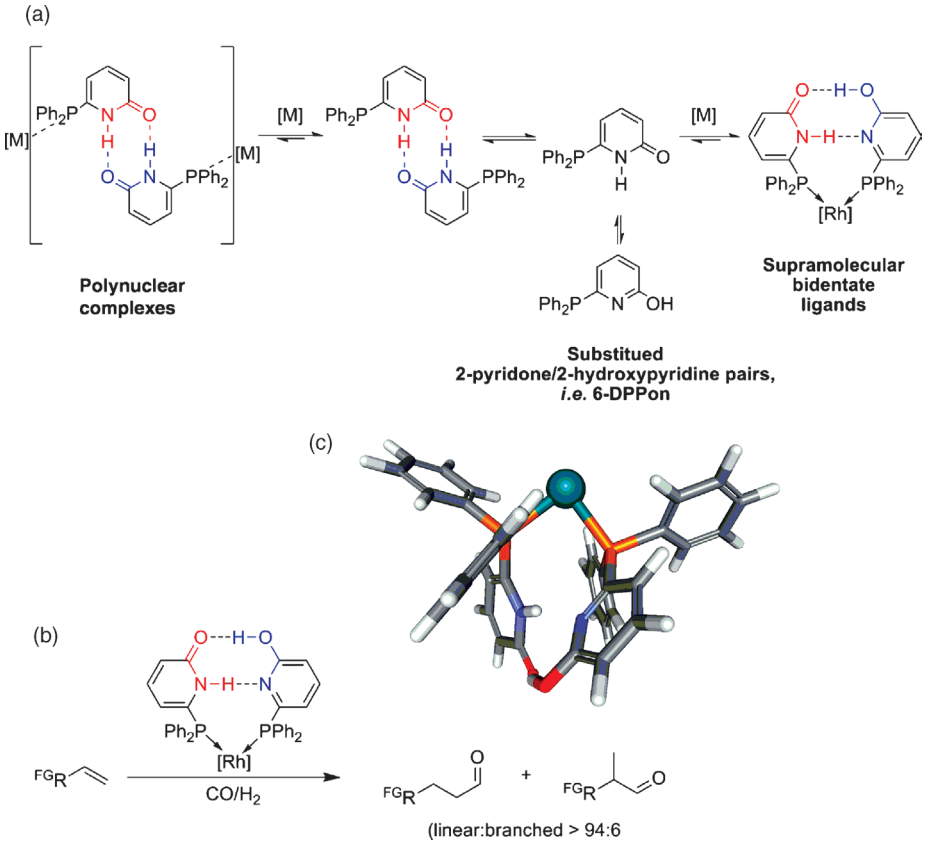


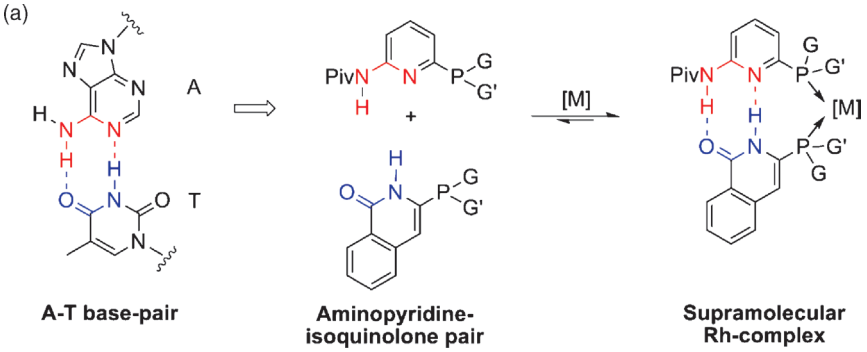
Figure 1.13 Generation of rhodium-based supramolecular catalysts by assembly of pyridine/hydroxypyridine pairs: (a) Self-assembly modes of pyridine-based phosphines. (b) Alkene hydroformylation with supramolecular rhodium-diphosphine catalysts; (c) CAChe minimized 3D structure of the rhodium-diphosphine complex (other ligands from the metal omitted for clarity).

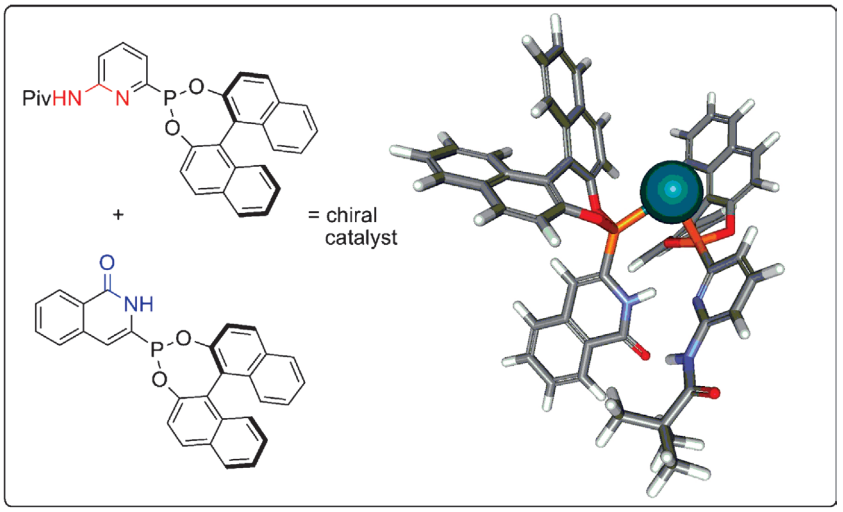
hydroformylation of various structurally diverse terminal olefins, including arenes, alcohols, aldehydes, acetals, amides, esters, ethers and carbamates. The catalyst itself was generated by self-assembly of the pyridone and hydroxypyridine tautomers of 6-(diphenyl-phosphino)pyridine-2(1*H*)-one (6-DPPon), and a rhodium precursor. Notably, the reactions were generally carried out at room temperature and under ambient pressure to afford the linear aldehydes in good yields and with high regioselectivities [31,32]. Bear in mind that the catalytic properties of the metal center have been tuned by the use of ditopic ligands with a molecular skeleton based on supramolecular interactions. Studies on the complexing of 6-DPPon with different metals and ligands revealed that the catalytically less active polynuclear complexes is also formed, depending on the co-ligands and the complexing conditions [33].

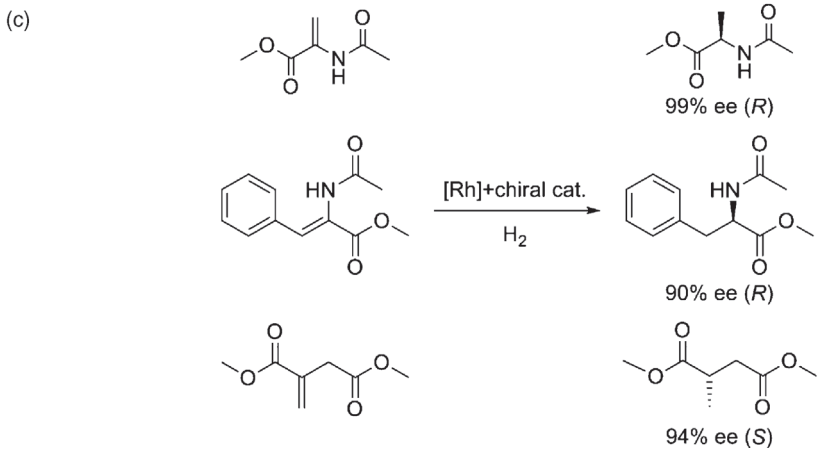
The development of new, highly active chiral catalysts is an ever challenging area of research. Breit and coworkers have expanded their aforementioned supramolecular strategy to the preparation of asymmetric chiral bis-phosphorus substituted derivatives (Figure 1.14) [34]. They have also reported the generation of a library of heterodimeric chelating ligands based on the adenine-thymine (A-T) base pair, which serves in biological systems for a high precision self-assembly of complementary species by hydrogen bonding [35,36]. The preliminary pyridine/hydroxypyridine tautomers used are not amenable to the preparation of defined heterodimeric systems, since the mixing of two differently substituted pyridones would lead to statistical mixtures of homo- and heterodimeric dimers. Therefore, aminopyridine and isoquinolone moieties, which were substituted with several phosphorus-containing functional groups, were used as adenine and thymine analogues in an attempt to utilize a precise self-assembly strategy. As Breit and coworkers aimed to develop chiral supramolecular bidentate ligands for asymmetric catalysis, the adenine and thymine-like building blocks incorporated chiral phosphino or phosphonite groups. Hence, the assembled heterodimers could be described as chiral chelating bis-phosphorus substituted derivatives (Figure 1.14). Rhodium complexes derived from this supramolecular species were studied in the asymmetric hydrogenation of functionalized olefins. The bisphosphonite based on the BINOL-substituted aminopyridine and isoquinolone (Figure 1.14) yielded remarkably high enantiomeric excesses (up to 99%) in the hydrogenation of substituted acrylic acid derivatives. To further investigate the substrate scope of the newly prepared catalyst, cinnamic and itaconic acid derivatives were also hydrogenated, with enantiomeric excesses of 90% and 94% obtained, respectively.

The advancements in supramolecular catalysis are not limited to transitions-metal catalyzed reactions. Clarke and coworkers recently reported the preparation of a library of organocatalysts and their application in the asymmetric Michael addition of ketones to nitroalkenes [37]. They proposed use of a supramolecular catalyst formed

Figure 1.14 Generation of supramolecular catalysts for asymmetric hydrogenation: (a) Assembly of heterodimeric chelating ligands. (b) Structure of the optimal rhodium-diphosphonite complex for asymmetric hydrogenation (other ligands from the metal center omitted for clarity). (c) Enantioselective hydrogenation of functionalized alkenes.


(a)
A
T
[M]
A-T base-pair
Aminopyridine-isoquinolone pair
Supramolecular Rh-complex


(b)
= chiral catalyst


(c)
[Rh]+chiral cat.
H2
99% ee (R)
90% ee (R)
94% ee (S)

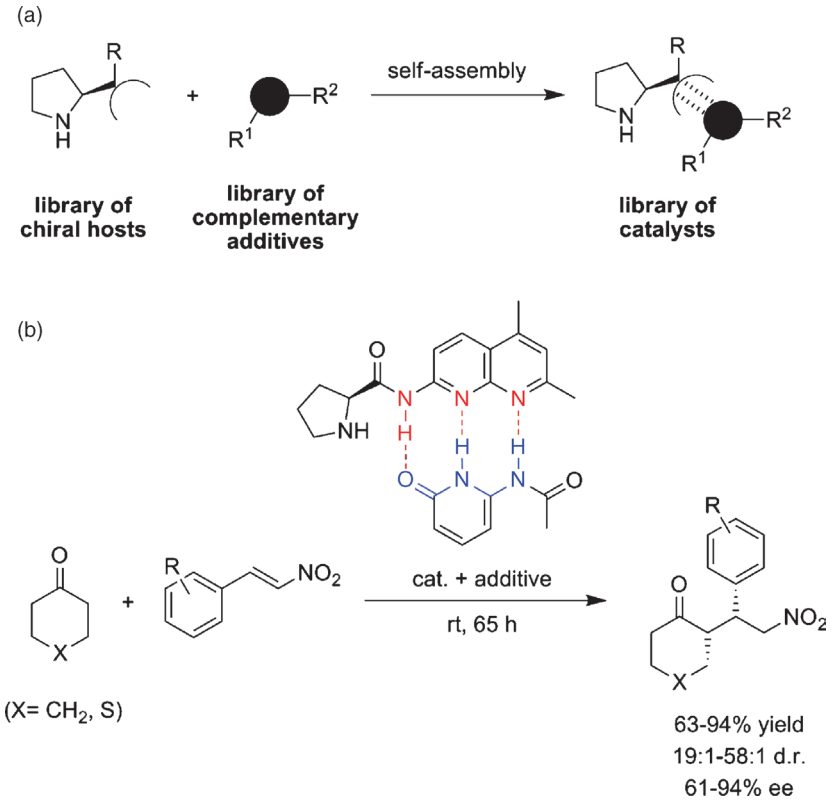


Figure 1.15 Supramolecular catalysts for organocatalysis: (a) Route to catalyst libraries; (b) asymmetric nitro-Michael reaction.

by complementary hydrogen bonding between a first unit, containing a proline fragment responsible for enantioselective catalysis, and a second, hydrogen bonding-complementary, unit bearing an achiral additive to influence the steric environment at the catalytic site (Figure 1.15).

Since amidonaphthyridines and pyridinones were known to be highly complementary recognition motifs, and were also easily accessible, they were chosen as the complementary units to achieve precise self-assembly by hydrogen bonding. It was observed that any catalyst arising from the combination of a chiral and an achiral fragment was more effective than the simple proline catalyst – a general enhancement in the diastereoselectivity and enantioselectivity of the reaction was observed when an additive was used. The catalyst/additive combination indicated in Figure 1.15 turned out to be best suited for the Michael reaction between six-membered cyclic ketones and several nitroalkenes.

Hydrogen bonding is not the only supramolecular strategy for efficiently generating the catalyst backbone by assembly of suitable constituent blocks: metal-directed self-assembly has also been employed. Reek, van Leeuwen and coworkers (Chapter 8)

have exploited the use of a nitrogen donor group that binds to Zn(II)-porphyrins to construct a library of chiral supramolecular phosphorus-containing bidentate ligands for asymmetric catalysis [38]. Takacs and coworkers (Chapter 9) have prepared libraries of chiral bidentate *P,P*-ligands via metal-directed self-assembly, and used them in asymmetric allylation and hydrogenation reactions [39]. Their route to the supramolecular catalysts was based upon the self-assembly of two bisoxazoline-containing units around a zinc(II) center to form a tetrahedral $(box)_2Zn$ complex. The final complex contained a second set of ligating groups equipped to bind a second metal to form a catalytic site. All of these examples of supramolecular catalysts formed via metal–ligand interactions will be discussed in more detail in other chapters of this book. Rather than designing two complementary constituent blocks that are capable of assembling with each other, Reek, van Leeuwen and coworkers reported in their pioneering work from 2003 [40] a very elegant strategy to generate supramolecular catalysts in which the constituent units of the final entity are assembled around a template molecule. The supramolecular bisphosphite indicated in Figure 1.16 was generated by the binding of two pyridine-phosphite units onto a bis-Zn(II) porphyrin template. The preferential binding affinity of Zn(II)-porphyrins for nitrogen donor atoms rather than phosphorus groups was crucial and allowed generation of a supramolecular catalyst with two free phosphite groups that could be further utilized in rhodium-catalyzed transformations. The supramolecular rhodium-complexes indicated in Figure 1.16 were studied in the hydroformylation of 1-octene and styrene. With 1-octene, the supramolecular complex showed slightly

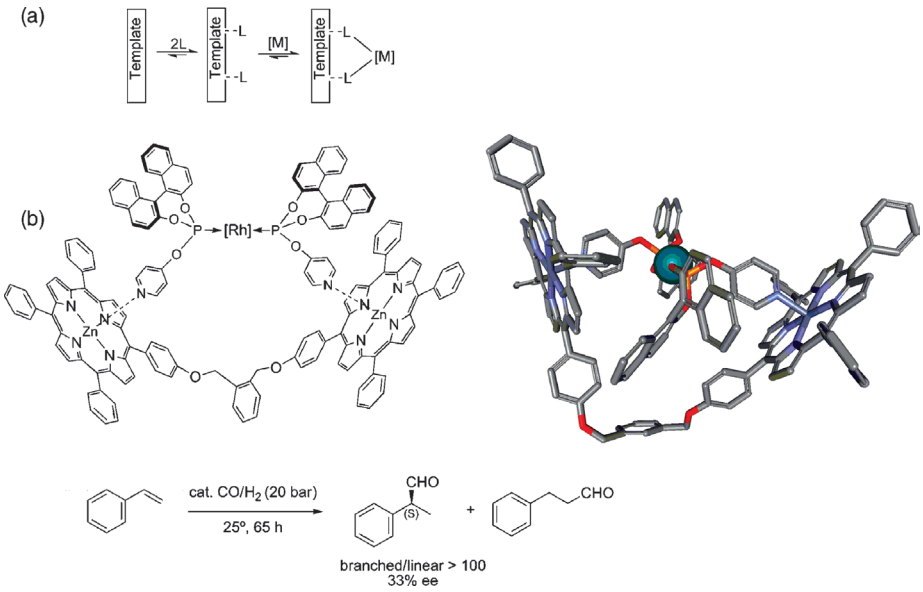


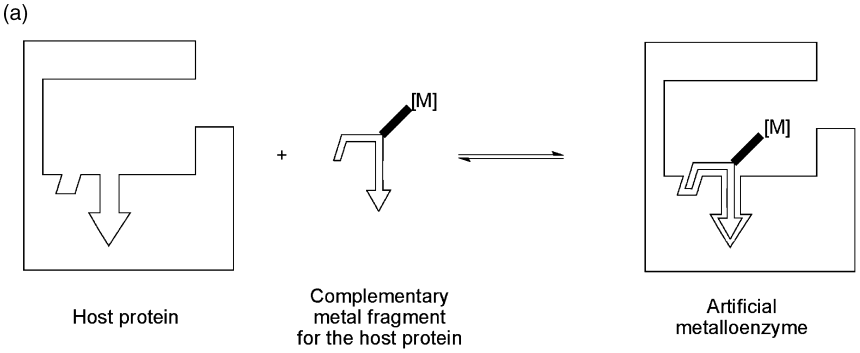
Figure 1.16 Transition metal Rh-catalysts formed by self-assembly: (a) Schematic representation of the self-assembly process. (b) Hydroformylation of styrene with supramolecular Rh-catalysts.

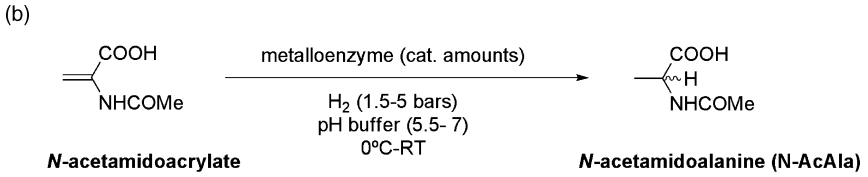
lower activity than that of the complex based on the analogue monodentate ligand, but it exhibited much higher selectivity for the linear product than for the branched product. These results indicated that the supramolecular bisphosphite ligands developed by Reek, van Leeuwen and coworkers had catalytic properties characteristic of bidentate ligands. In terms of enantioselectivity, mediocre results were obtained in the hydroformylation of styrene (33% ee), but these results are better than those obtained with the monomeric building blocks, thus reaffirming the bidentate character of the supramolecular phosphoros-containing catalyst.

Reek, van Leeuwen *et al.* have also reported the template-induced generation of bidentate ligands onto a rigid bis-zinc(II) salphen platform. Homobidentate [41] or heterobidentate [42] *P,P*-ligands have been prepared and tested in hydroformylation and hydrogenation reactions.

1.3 Artificial Biomacromolecules for Asymmetric Catalysis

In the fledgling period of the field of asymmetric catalysis, Whitesides devised a supramolecular catalytic system that relied on the generation of an artificial enzyme by incorporating a metal-containing fragment into a host protein [43]. In this pioneering "chemical mutation" of a protein, Whitesides took advantage of a very strong noncovalent interaction between a protein (avidin) and a small molecule (biotin). Functionalization of biotin with a rhodium diphosphine afforded a metal fragment with high affinity for the host protein. The strength of the avidin–biotin interaction ($K =$ ca. $10^{15}\,M^{-1}$) ensured quantitative binding of the rhodium diphosphine moiety into the chiral protein environment. Thus, an artificial metalloenzyme for the asymmetric hydrogenation of alkenes had been created. Whitesides and coworkers showed that the hydrogenation of *N*-acetamidoacrylate with catalytic metalloenzyme amounts rendered (*S*)-*N*-acetamidoalanine in 41% ee and with full conversion (Figure 1.17). Whitesides' approach remained untouched for 20 years until, in 1999, Chan and coworkers took it up again by linking a chiral diphosphine to biotin [44] and studied the catalytic properties of the resulting complex in the hydrogenation of itaconic acid. Methylsuccinic acids could be prepared with this strategy with moderate enantioselectivity. Ward and coworkers achieved a spectacular breakthrough in the stereoselectivity of this metalloenzyme-catalyzed hydrogenation of acetamidoacrylate derivatives [45] by combining the biotinylated diphosphine (Figure 1.17) with mutated streptavidin (WT Sav), rather than the original host protein (avidin). Quantitative yield and an excellent enantioselectivity (94%) were achieved using this new catalytic system. Using the same approach, Ward and coworkers have identified efficient artificial transfer hydrogenases [46]. Feringa and coworkers have developed a related supramolecular catalytic system that is based on DNA as the biomacromolecule, which provides the chiral environment, and 9-aminoacridine-modified Cu(II) complexes as the metal fragment with high DNA affinity. A hybrid DNAzyme was thus generated, and its activity in an asymmetric Diels–Alder reaction of cyclopentadiene with a





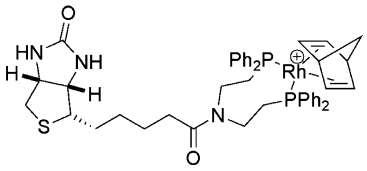
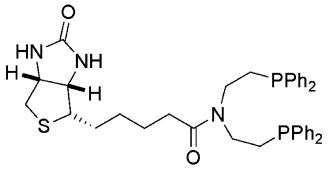
Biotin fragment	Protein	Yield	Enantioselectivity
 Whitesides and co-workers	avidin	100%	41% (*S*)
 + $[Rh(COD)_2]BF_4$ Ward and co-workers	WT Sav	100%	94% (*R*)

Figure 1.17 Artificial metalloenzymes: (a) Strategy to incorporate a catalytically active metal fragment within a host protein. (b) Alkene hydrogenation based on the biotin–(strept)avidin technology.

dienophile that binds the Cu(II) ion through a pyridyl group was studied. High endo: exo diastereoselectivities (91 : 9) and enantioselectivities (90%) were achieved in the optimal case [47]. Lastly, Kamer, van Leeuwen and coworkers have developed phosphine-containing oligonucleotides and have studied their application in asymmetric allylic aminations [48].

1.4 Summary and Outlook

The reader is reminded that this overview of supramolecular catalysis was not meant to be exhaustive, rather it is an introductory chapter. Definitive examples that illustrate the underlying principles of the design of these supramolecular systems have been described. The synthetic chemist has often looked to nature for inspiration in the design of efficient supramolecular catalysts. However, enzymes have evolved to be reaction specific, and supramolecular catalysis continues to be aimed at surpassing this limitation by generating not only effective catalysts for a particular reaction but also for entire classes of related reactions. To this end, the current understanding in the way supramolecular interactions (electrostatic, hydrogen bonding, π–π stacking, and van der Waals interactions, hydrophobic and solvatophobic effects, and metal–ligand interactions) operate, the arsenal of efficient synthetic methodologies and the wide variety of three-dimensional architectures available should foster the design and preparation of novel supramolecular catalysts with ever greater efficiency (i.e., turnover, product inhibition, chemo- and stereoselectivities, etc.).

Acknowledgments

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