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Enzyme Mimics

Enzyme Mimics Based Upon Supramolecular Coordination Chemistry

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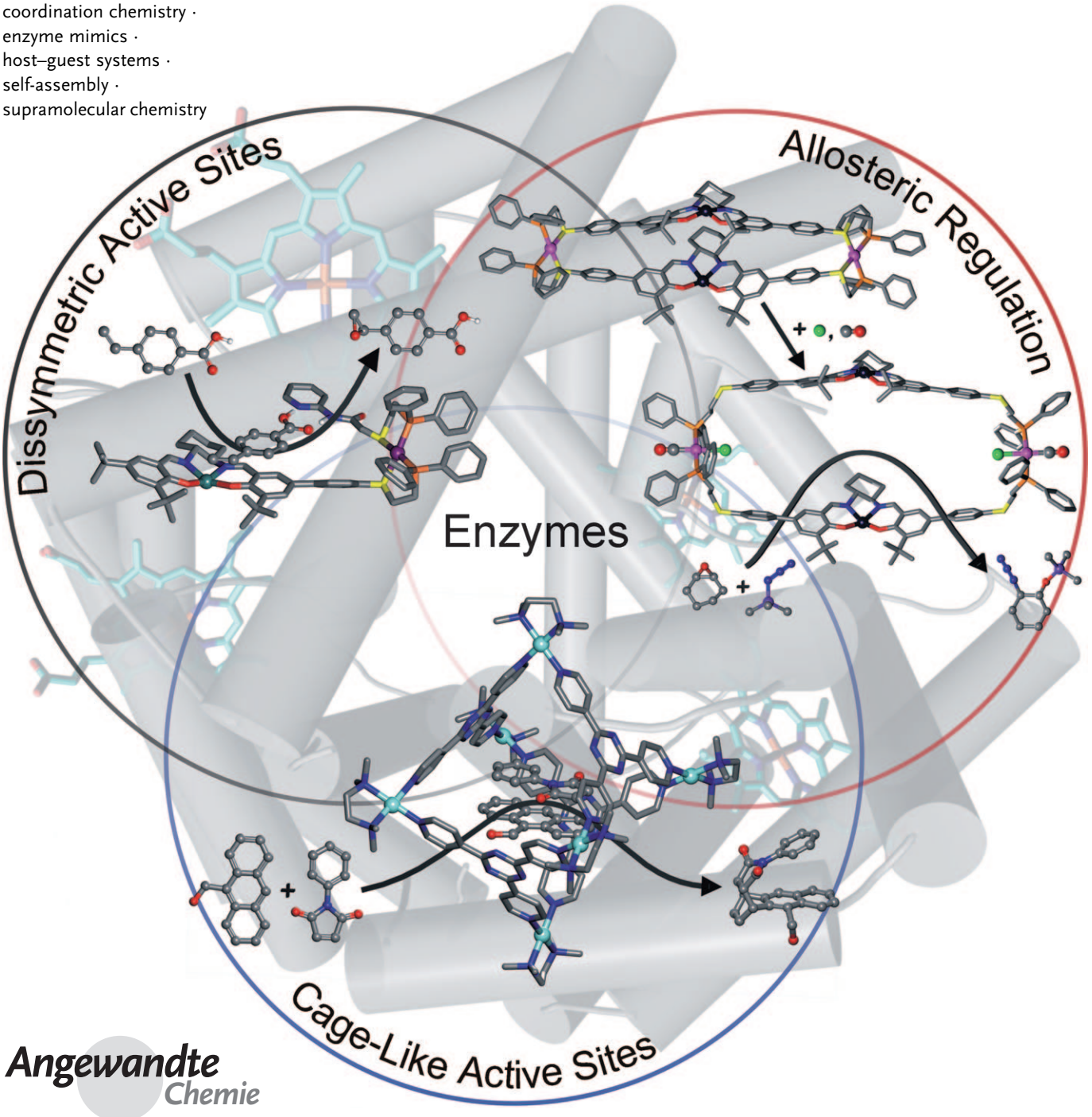

Recent advances in supramolecular coordination chemistry have allowed chemists to synthesize macromolecular complexes that exhibit various properties intrinsic to enzymes. This Review focuses on structures inspired by properties and functions observed in enzymes rather than precise models of enzyme active sites. These structures are synthesized using convergent, modular, and high-yielding coordination-chemistry-based methods, which allow one to tailor the size, shape, and properties of the resulting complexes. Many of the structures discussed exhibit reactivity and specificity reminiscent of natural systems, and some of them have functions that exceed the natural systems which provided the inspiration for initially making them.

From the Contents

1. Introduction

1.1. Background

Enzymes catalyze a wide variety of biochemical reactions that occur in living organisms.[1] Compared to man-made, chemical catalysts, enzymes frequently exhibit superior performance in terms of: 1) rate enhancement, 2) reaction specificity, 3) activity at moderate temperatures and pressures, and 4) capacity for regulation.[1] Structures that mimic enzyme reactivity have been pursued by an active field of researchers for decades with the goals of both developing synthetically useful catalysts inspired by enzymes[2–7] and understanding fundamental questions with regard to mechanisms of enzyme action based on systems that act as models for enzyme active sites.[5–9]

1.2. Scope

The focus of this Review is on structures inspired by properties and functions observed in enzymes (but not precise models of enzyme active sites) that are synthesized based on convergent, modular, and high-yielding multicomponent supramolecular coordination assembly approaches such as the directional-bonding (DBA),[10] symmetry-interaction (SIA),[11] and weak-link (WLA)[12] approaches. Synthetic utility and, in the case of allosteric enzyme mimics, potential utility in the area of detection with catalytic signal amplification will be emphasized.

In categorizing the different approaches to making enzyme mimics, three structural classes and corresponding enzyme-like properties have been identified: 1) assemblies that mimic the cage-like nature of enzymes; every enzyme contains a pocket (active site) in which catalysis occurs; 2) assemblies that mimic the allosteric nature of certain enzymes; regulation of catalytic activity is crucial in many biochemical pathways; and 3) assemblies that mimic the dissymmetric nature of enzyme active sites; enzyme active sites often are not symmetric, as their activity is a result of the interaction of many functionalities, aligned in a highly specific manner, that are essential for reactivity and substrate specificity. A selected number of historically or otherwise relevant examples that involve metal coordination, but are not assembled thorough the DBA, SIA, or WLA, also will be discussed.

1.3. Brief Introduction to Supramolecular Coordination Assembly Approaches

Synthetic strategies that allow one to prepare multimetallic supramolecular macrocycles, tweezers, squares, boxes, cages, and bowl structures can be divided into three main categories, the DBA, SIA, and WLA (Figure 1).[10e,12b] The DBA,[10,12b] or molecular library approach,[10e] is based on transition metal centers containing blocking ligands and weakly coordinating ligands (e.g. **1**) leaving sites at fixed geometries that can direct the assembly of multimetallic squares (**3**),[13] macrocycles,[14] triangles,[15] bowls,[16] and polyhedral[17] cages upon the addition of conformationally rigid multitopic ligands (**2**) that replace the weakly coordinating ligands (Figure 1a). Extensive research has been carried out to synthesize exo- and endohedrally functionalized macrocycles and cages[18,19] as well as metallodendrimers.[20]

The SIA,[11] which is closely related to the DBA, is based on the templating of higher-order structures using transition metals that enforce specific coordination geometries. This templating allows for the rational design of high symmetry polyhedral cages (**5**),[11] macrocycles,[21] helices,[22] coronate,[23] and other structures in the absence of blocking ligands. Typically, chelating ligands (**4**) are used, such as catecholate units that bind to octahedrally coordinated transition-metal

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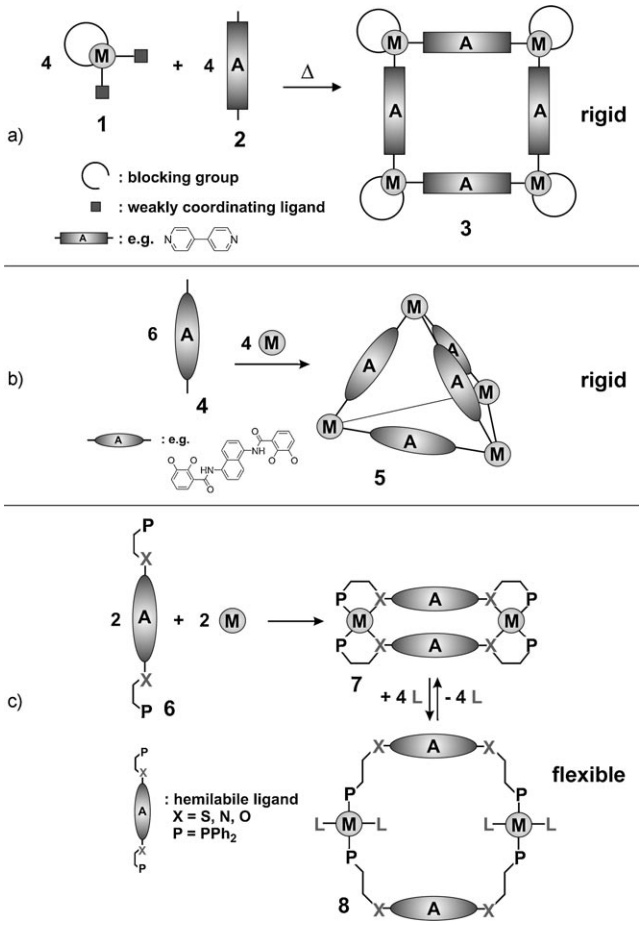

Figure 1. a) The directional-bonding approach (DBA), M: for example, Pd^{II}, Pt^{II}. b) The symmetry-interaction approach (SIA), M: for example, Ga^{III}, Fe^{III}, Al^{III}. c) The weak-link approach (WLA), M: for example, Rh^{I}, Pd^{II}, Cu^{I}, Ir^{I}. Charges and counterions are not shown.

ions in a homochiral fashion (Figure 1b).[24] These cages can undergo partial ligand dissociation at individual metal sites allowing for the encapsulation of guests, while the overall structure of the cage is maintained. Both the SIA and DBA, by design and virtue of the rigid linkers, yield structurally rigid macrocyclic systems.

The WLA[12] allows for reversible in situ modification of metallosupramolecular cyclophanes,[12] three-tiered complexes,[25] tweezers,[26] and other structures. This is achieved by the use of metal ions and flexible hemilabile ligands (**6**), leading to the formation of condensed chelate bi- or multimetallic complexes (**7**, Figure 1c). The WLA does not use rigid directing ligands, and therefore allows for the assembly of structurally flexible complexes. Cleavage of the relatively weak M–X bonds by a variety of small molecules or elemental anions (L), while the stronger M–P bonds stay intact, leads to expansion of the macrocycle or cage structure (**8**), an increase in the distance between the weak-link connectors (A, often aryl groups), a change in the overall charge (for L = anions such as halides and cyanide), and an increase in the overall flexibility of the structure due to the absence of chelation.[27]

Structures formed through these supramolecular coordination chemistry approaches can exhibit catalytic activities reminiscent of enzymes in terms of catalytic acceleration by proximity effects in cages,[10l,28] discrimination between different isomers of a substrate, and regulation in terms of catalytic activity and selectivity. All of these issues will be discussed in this Review. Finally, efforts aimed at synthesizing dissymmetric structures that incorporate multiple functionalities and exhibit unusual catalytic properties will be discussed as well.

2. Coordination Assemblies That Mimic the Cage-Like Nature of Enzymes

2.1. General Considerations

Supramolecular coordination chemistry offers a platform for mimicking the cage-like nature of an enzyme's active site, whereby it is possible to rationally construct open nanoscale structures of various geometries. There are two different approaches to using cage-like complexes for mimicking the active site of an enzyme. The first approach is to construct a supramolecular cage complex that contains a catalytic moiety, such as a porphyrin, where the cage controls the environment around the active site. This serves to either shield/protect the catalyst or control access of the substrate to the catalytic center. The second approach is to use the cavity of the cage complex, without a catalytic moiety, to mimic the pocket of an enzyme. In this way, the cavity typically accelerates the reaction through proximity effects, greatly increasing the local concentration of the substrates (the effective molarity), and/

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or through preorganization of the substrates in the correct orientation to react. While it is important to note that there are also many examples of using organic supramolecular cage-like molecules to mimic an enzyme's active site,[29] this Review is focused on assemblies prepared by coordination chemistry approaches. Specific examples of coordination assemblies that mimic the cage-like nature of enzymes are illustrated below.

2.2. Complexes That Mimic the Active Site of Enzymes by Incorporating a Catalytic Moiety

2.2.1. Incorporation of Blocking Ligands for Improved Stability

Porphyrins are abundant in Nature, and much work has focused on building functional systems based upon this moiety to mimic natural systems.[2,3,5,7–9,30] A major focus in this area has been the exploration of the catalytic oxidation properties of manganese and iron porphyrins.[31] Many of these systems do not rely on supramolecular coordination chemistry but rather on cumbersome, multi-step organic syntheses and are therefore beyond the scope of this Review. Unfortunately, simple monomeric porphyrins typically have low turnover numbers due to their deactivation through the formation of μ-oxo dimers.[31f,32] Consequently, some of the early work on these systems has involved the synthesis of bulky porphyrins or isolation of the catalyst, on a surface or polymer, to prevent or minimize formation of the inactive dimers.[7,8,31,33]

In this vein, the Hupp and Nguyen groups have used coordination chemistry to synthesize a supramolecular mimic of cytochrome P450 composed of a catalytic manganese porphyrin and two Zn^{II}-tetraphenylporphyrins (**9**, Figure 2).[31f] This system uses a bispyridyl Mn^{III}-porphyrin with two Lewis basic pyridyl groups at the 5 and 15 positions of the porphyrin, respectively, forming a 180° angle. These pyridyl moieties can bind to the Zn^{II} Lewis acidic sites of a tetraphenylporphyrin, resulting in complex **9**. In this structure, the Zn^{II}-porphyrins greatly increase the steric bulk of the overall structure, stabilizing the Mn^{III} catalyst. The supramolecular structure exhibits an increase in turnover number, from 59 to 140, for the epoxidation of styrene compared to the free Mn^{III}-porphyrin, and the lifetime of the active catalyst was increased from 10 to 45 min.[31f] Although, this structure is not a true cage complex, it illustrates the ability to significantly increase the activity of a Mn^{III}-porphyrin epoxidation catalyst through the formation of a supramolecular complex with steric blocking entities.

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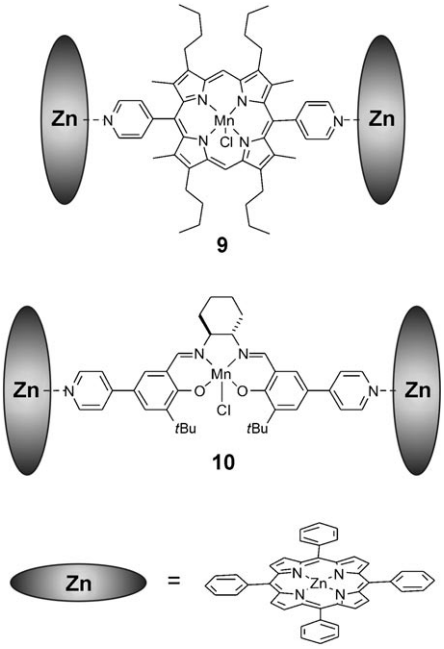


Figure 2. Supramolecular epoxidation catalysts incorporating blocking groups.

In a related study, the Hupp and Nguyen groups used a chiral Mn^{III}-salen catalyst with 5,5′-bispyridyl groups for the asymmetric epoxidation of olefins (**10**, Figure 2).[31g] Using the same bulky Zn^{II}-porphyrin groups, they observed a 20-fold increase in catalyst stability and up to a 3-fold increase in catalytic activity. Although rather simple systems, these structures served as the precursors to real cage structures synthesized by the same groups, instead of complexes with blocking groups (see below).

Building on the two systems mentioned above, the Hupp and Nguyen groups synthesized a more sophisticated mimic of cytochrome P450 by encapsulating a bispyridyl Mn^{III}-porphyrin epoxidation catalyst (**12**) inside a molecular square (**11**, Figure 3).[31h] The molecular square consists of $\{Re(CO)_3Cl\}$ corners and Zn^{II}-porphyrin edges, which are able to bind to the pyridyl groups of the Mn^{III}-porphyrin. By encapsulating the catalytic porphyrin inside a supramolecular cavity, the lifetime and turnover number of the catalyst were greatly increased. In the catalytic epoxidation of styrene, the lifetime increased from 10 min for the free Mn^{III}-porphyrin to over 3 h for the supramolecular complex, and the turnover number increased 10-fold. Additionally, the catalyst's substrate selectivity was enhanced. When a sterically demanding substrate, *cis*-3,3′,5,5′-tetra(*tert*-butyl)stilbene (**15**, Figure 4), was used in a competition experiment with *cis*-stilbene (**14**), it was 3.5 times less reactive with **13** than with the free Mn^{III} catalyst. Additionally, the presence of two free Zn^{II} sites in **13** allows for further fine-tuning of the environment around the Mn^{III}-porphyrin. For example, the addition of 3,5-dinicotinic acid dineomenthyl ester to **13** resulted in an even lower

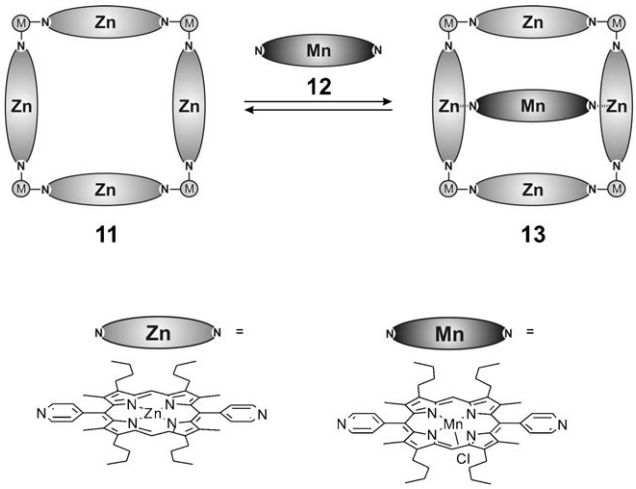


Figure 3. A molecular square containing an epoxidation catalyst. M = {Re^{I}(CO)$_3$Cl}.

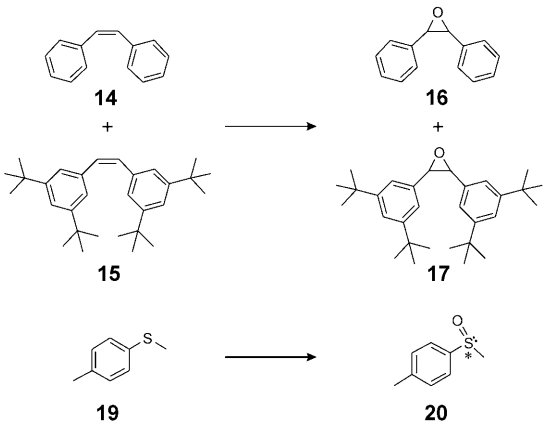


Figure 4. Oxidation reactions catalyzed by **13** and **18a**,**b**.

activity for **15** relative to **14**; indeed, it is 7 times less reactive with the supramolecular complex than with the free catalyst.

In a more impressive demonstration, the Hupp and Nguyen groups synthesized and characterized a supramolecular rectangular box consisting of 18 porphyrins (Figure 5).[34] This box consists of four Zn^{II}-porphyrin trimers, two Sn^{IV}-porphyrin dimers, and one Mn^{III}-porphyrin dimer, the catalytic moiety. Remarkably, the box can be assembled either in a step-wise fashion or in a one-pot procedure, with a self-sorting behavior seen between the Sn^{IV}- and Mn^{III}-porphyrin dimers due to the steric bulk of the carboxylate ligands on the Sn^{IV}-porphyrins (Figure 5).

This supramolecular box has been used in the epoxidation of olefins, *cis*-stilbene (**14**) and *cis*-3,3′,5,5′-tetra(*tert*-butyl)-stilbene (**15**), and in the chiral sulfoxidation of methyl *p*-tolyl sulfide (**19**, Figure 4). When complex **18a** was used for olefin epoxidation, the smaller olefin (**14**) reacted 5.5 times faster than **15**, presumably due to the steric bulk of the carboxylate ligands on the Sn^{IV}-porphyrins surrounding the Mn^{III} catalytic centers in **18a**. When **18b** was used for the chiral sulfoxidation of **19**, an enantiomeric excess of up to 14% *ee* was observed.

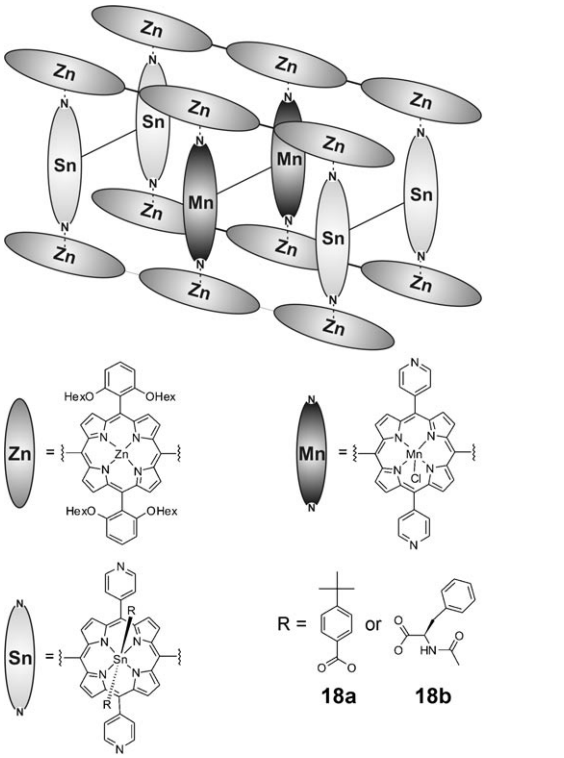


Figure 5. Supramolecular rectangular box for the epoxidation of olefins and chiral sulfoxidation of thioethers. Fused porphyrins are bridged and terminated by alkyne or aryl units (not shown).

This enantioselectivity was proposed to result from a through-space interaction with the *N*-acetyl-D-phenylalanine ligands on the Sn^{IV}-porphyrins. No enantiomeric excess was observed when the free Mn^{III}-porphyrin dimer was used in the presence of free Sn^{IV}-porphyrin.

2.2.2. *Templated Ligand Approach*

In a similar manner to the steric blocking schemes mentioned in section 2.2.1, Reek, van Leeuwen, and coworkers have used pyridyl-based templating ligands and either Zn^{II}-porphyrin or Zn^{II}-salphen blocking groups to encapsulate transition metal catalysts (Figure 6).[35] In this approach, they use templating ligands that contain two different metal binding sites. For example, trispyridylphosphine has three pyridyl groups which can selectively bind to three Zn^{II} blocking groups and a central phosphorous atom which can bind to a catalytic transition metal, such as Rh^{I} or Pd^{II} (**21**–**23**, Figure 6). This approach provides several layers of tailorability, which can be used to fine-tune the product distribution of the desired reaction, when multiple isomers of the product are possible, such as in the hydroformylation of olefins. First, the choice of the catalytic metal binding site can be varied by adjusting the templating ligand (e.g. phosphine or bisimine, **21** or **23**, respectively). Second, the placement of the blocking groups relative to the catalytic metal can be adjusted by varying the substitution of the pyridyl groups (e.g. *meta*- or *para*-substituted, **21** or **22**, respectively). Third, the blocking groups can be varied (e.g. Zn^{II}-porphyrin or Zn^{II}-salphen).

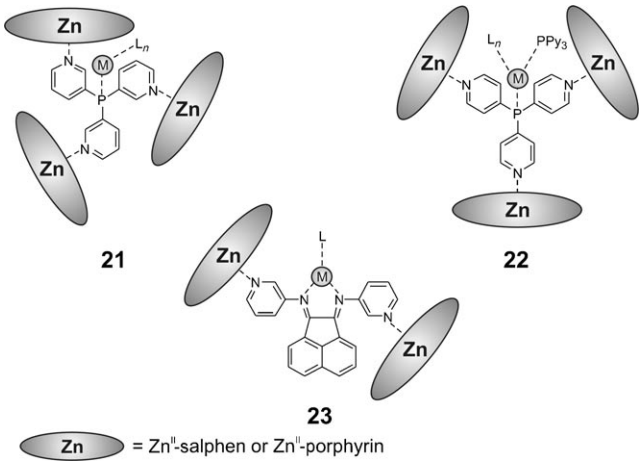


Figure 6. Encapsulated catalysts formed from templating ligands and blocking groups. **21**: M = Rh^I and L_n = (CO)(acac), **22**: M = Rh^I and L_n = (CO)(acac), **23**: M = Pd^{II} and L = Me.

When supramolecular Rh^I complexes **21** and **22** (with Zn^{II}-salphen blocking groups) were used to catalyze the hydroformylation of 1-octene (**24**, Figure 7), interesting

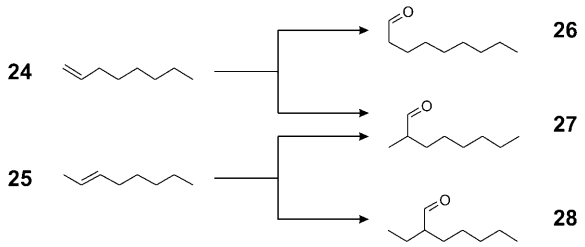


Figure 7. Olefins used in hydroformylation reactions.

product selectivities were observed.[35c] With complex **22**, an approximately 2.5:1 linear:branched product ratio was observed, which was also seen with the unencapsulated Rh^I catalyst (i.e. $[Rh(CO)_2(acac)]$ and trispyridylphosphine without the Zn^{II} blocking groups). However, when complex **21** was used, the ratio of products shifted to around 1:1 (linear/branched). Conversion increased from 15–27% for **22** or unencapsulated catalyst to 97% for **21**. These differences can be attributed to the steric environment around the Rh^I center. In complex **22**, there is enough space for a second trispyridylphosphine to bind to the Rh^I center, leading to a bisphosphine-Rh^I complex and a similar selectivity to that observed with the unencapsulated catalyst. Complex **21** is more sterically encumbered and can only form a monophosphine-Rh^I catalyst, which exhibits a higher preference for the branched aldehyde (**27**).

With internal alkenes a larger difference in product selectivity is observed. When *trans*-2-octene (**25**, Figure 7) is used with the unencapsulated Rh^I catalyst, 2-methyloctanal (**27**) and 2-ethylheptanal (**28**) are formed in a 1.3:1 ratio.[35d] However, when complex **21** (with Zn^{II}-porphyrin blocking groups) is used, the ratio between aldehydes **27** and **28** shifts to 1:9 at room temperature. The selectivity decreases to 1:5 when the reaction temperature is increased to 40 °C.

Extending this approach to templating ligands other than phosphines, the Reek group has synthesized a 1,2-bis(pyridylimino)acenaphthene (Py-BIAN) ligand and investigated the activity of its Pd^{II} complex (**23**) with regard to the copolymerization of CO and 4-*tert*-butylstyrene (Figure 6).[35e] By adjusting the Zn^{II}-salphen blocking group used, the activity of the supramolecular complex was increased up to 1.4 times compared to that of the parent complex, a phenyl-BIAN Pd^{II} complex. Also, while the parent complex produced an atactic copolymer, complex **23** results in a copolymer with up to 87% syndiotacticity. The average molecular weight of the resulting copolymer can also be adjusted in the 44×10^3 g mol^{-1} to 118×10^3 g mol^{-1} range by altering the blocking groups. These examples illustrate how the regioselectivity of different reactions can be affected by adjusting the environment around the catalytic site without changing the active catalyst.

2.2.3. *Chiral Cage Complexes*

In Nature, chirality plays an important role in molecular recognition and enzymatic catalysis.[36] While there have been a few examples of induced enantioselectivity from through-space interactions,[34,37–39] the Lin group has synthesized a series of chiral metallomacrocycles (**29**–**31**, Figure 8) with a

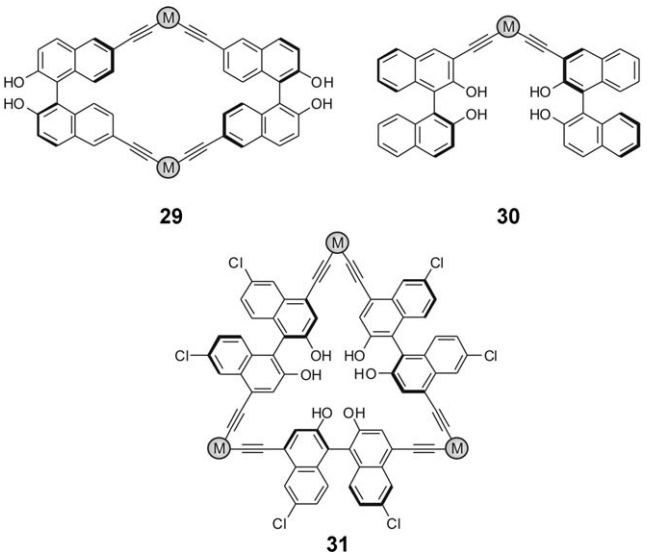


Figure 8. Chiral binol-based complexes. **29**–**31**: M = {*cis*-$Pt^{II}(PEt_3)_2$}.

chiral 1,1′-bi-2-naphthol (binol) moiety incorporated into the rigid organic linking ligands.[40] These complexes differ in the number of catalytic moieties, in their orientation relative to each other, and in the flexibility of the overall structure. The Lin group has evaluated the catalytic properties of the Ti^{IV}-metallated metallomacrocycles in the context of the asymmetric catalytic addition of diethylzinc to a variety of aromatic aldehydes to form chiral secondary alcohols. While all three complexes show > 95% conversion, the molecular triangle **31** showed the highest enantioselectivities, between 89 and 92% *ee* for 6 different substrates, which are higher than the enantioselectivities observed for the analogous monomeric catalyst.[40a]

2.2.4. Sequestration of a Catalyst inside a Supramolecular Complex

The Raymond and Bergman groups have taken a different approach to the incorporation of a catalytic site into a supramolecular structure. As opposed to a catalytic moiety being directly bound to the supramolecular structure, either through metal–ligand bonds or through covalent attachment, they have shown that cationic guests, including some transition-metal catalysts, can be encapsulated inside an anionic tetrahedral cage complex prepared through the SIA (**32**, Figure 9).[24,41] These complexes form as a racemic mixture of homochiral complexes; within one complex all metal centers have either a Δ or Λ configuration, respectively. The two enantiomers can be resolved by the addition of a chiral cation, such as (*S*)-*N*-methylnicotinium iodide, which selectively precipitates the ΔΔΔΔ enantiomer.[42]

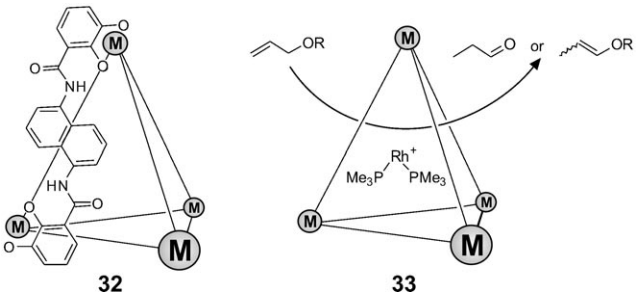


Figure 9. Tetrahedral cage-like complex **32** and the isomerization of allylic substrates by the Rh^{I} containing tetrahedron **33**. M = Ga^{III}. Charges and counterions are not shown.

By encapsulating a cationic catalytic moiety in the cavity of the tetrahedral cage complex, the Raymond and Bergman groups have shown that they can obtain a higher degree of substrate size selectivity than with the unencapsulated catalyst, reminiscent of the selectivity seen in enzymes. They have encapsulated a Rh^{I} catalyst in complex **32** and showed that it can be used in the selective isomerization of allylic substrates (**33**, Figure 9).[43] Compared to the free catalyst, which reacts with a number of different substrates, including branched ones, only 2-propen-1-ol and 3-methoxy-1-propene are small enough to enter the cavity of **33** and react with the active catalyst.

In addition, they have shown that a high degree of selectivity can be achieved in the activation of C–H bonds of various aldehydes using an Ir^{I} complex encapsulated in the cavity of **32** (**34**, Figure 10).[38] The encapsulated complex is able to discriminate between linear aldehydes, which differ by only one carbon atom. For example, linear aldehydes up to butyraldehyde are small enough to enter the cavity of **34** and react with the encapsulated Ir^{I} complex resulting in **35**, while valeraldehyde does not react, presumably because it is too large to enter the cavity of **34**. It should be noted that a modest diastereoselectivity was observed among the aldehydes that did react, ranging from a diastereomeric ratio of 55:45 for acetaldehyde to 70:30 for butyraldehyde.

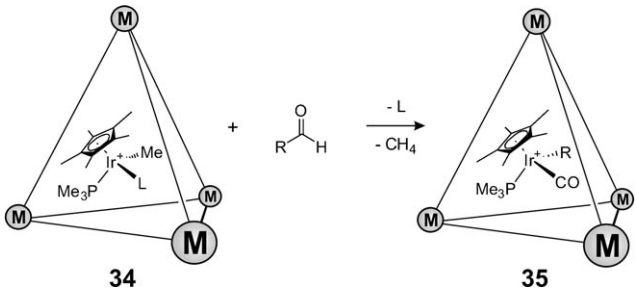


Figure 10. Ir^{I} containing tetrahedron **34** used for the activation of C–H bonds. M = Ga^{III}.

2.3. Cavity-Directed Catalysis without the Use of a Catalytic Moiety

One of the characteristics of the DBA and SIA is that they typically result in structures with rigid, well-defined cavities. In addition, some of these supramolecular complexes are highly charged and can be dispersed in aqueous media, creating a hydrophobic pocket in which to do chemistry, similar to the active site of an enzyme. As opposed to the examples discussed above, the following structures do not contain a catalytic site defined by a metal center, such as a porphyrin or salen, but typically catalyze reactions by proximity effects and/or preorganization of the substrates inside a cavity.[10l,28] It is important to point out that this type of catalysis also has been demonstrated using only organic molecules[29] or extended metal-organic frameworks (MOFs)[44] but these examples will not be discussed in this Review.

The Fujita group has synthesized many cage-like complexes using the DBA and shown that these structures can be used to encapsulate a wide variety of different molecules.[10i,17a,45] They also have reported multiple examples of how these structures can be used for molecular recognition[13a,14a,46] or stabilizing reactive compounds,[47] in addition to catalysis. One of the cage structures that the Fujita group has used as a catalyst, is a complex in the shape of an octahedron, where four ligands occupy half of the faces of the complex (**36a–g**, Figure 11).[17a] This cage complex is synthesized using a tridentate ligand with a triazine core, 2,4,6-tris(4-pyridyl)-1,3,5-triazine, and a Pd^{II} or Pt^{II} precursor with *cis*-chelating blocking ligands. Using a slightly different ligand, 2,4,6-tris(3-pyridyl)-1,3,5-triazine, containing *meta*-substituted pyridines, and a Pd^{II} precursor, the Fujita group synthesized the square-pyramidal bowl complex, **37a**, with one open face (Figure 11).[45a] Both of these complexes are highly charged (+12) and consequently are soluble in aqueous media. They also contain well-defined cavities which can encapsulate hydrophobic substrates, reminiscent of the pocket of an enzyme. The Fujita group has shown that these complexes can catalyze a number of different reactions, in some cases with a different regioselectivity than is seen with the uncatalyzed reactions (see section 2.3.3).

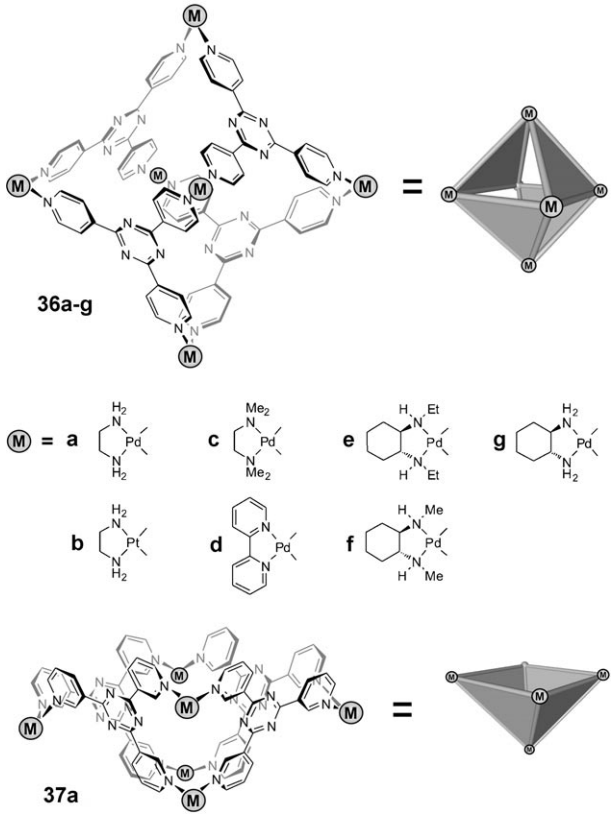


Figure 11. Complexes in the shape of an octahedron **36a–g** and bowl **37a** formed through the DBA. Charges and counterions are not shown.

2.3.1. *Wacker Oxidation*

Wacker-type oxidation of various aromatic olefins, such as styrene, was demonstrated using complex **36a** as a catalyst.[45d] In this case, complex **36a** acts as a phase-transfer catalyst, transporting the substrate into the aqueous phase where it reacts with $[Pd(NO_3)_2(en)]$, the oxidation catalyst, to form the oxidized product (e.g. acetophenone from styrene) in up to 82% yield. As expected, the yield is highly dependent on the affinity of the substrate for complex **36a**, and the reaction can be inhibited by the addition of a strong binder, such as 1,3,5-trimethoxybenzene. When long chain alkane substrates were used in combination with cage complex **36c** in Wacker-type oxidation reactions, the cage complex behaved as the active oxidation catalyst.[48] In this case, the substrates, ω-alkenols such as 8-nonen-1-ol, are proposed to be oriented in the cavity with the double bond near one of the Pd^{II} corners and the terminal alcohol located in the opening of the opposite face of the cage. This conclusion is based upon a crystallographic analysis of a host–guest complex formed from **36c** and a similar guest molecule, 1-nonanol. This oxidation reaction proceeds in up to 66% yield for 8-nonen-1-ol, with lower yields observed for other substrates, which is presumably due to a less favorable orientation of the olefin moiety with respect to the Pd^{II} center.

2.3.2. *Photochemical Reactions*

Complexes **36a–g** also have been used to accelerate photochemical reactions of many inert alkanes and olefins (Figure 12). In one example, four adamantane molecules (**38**)

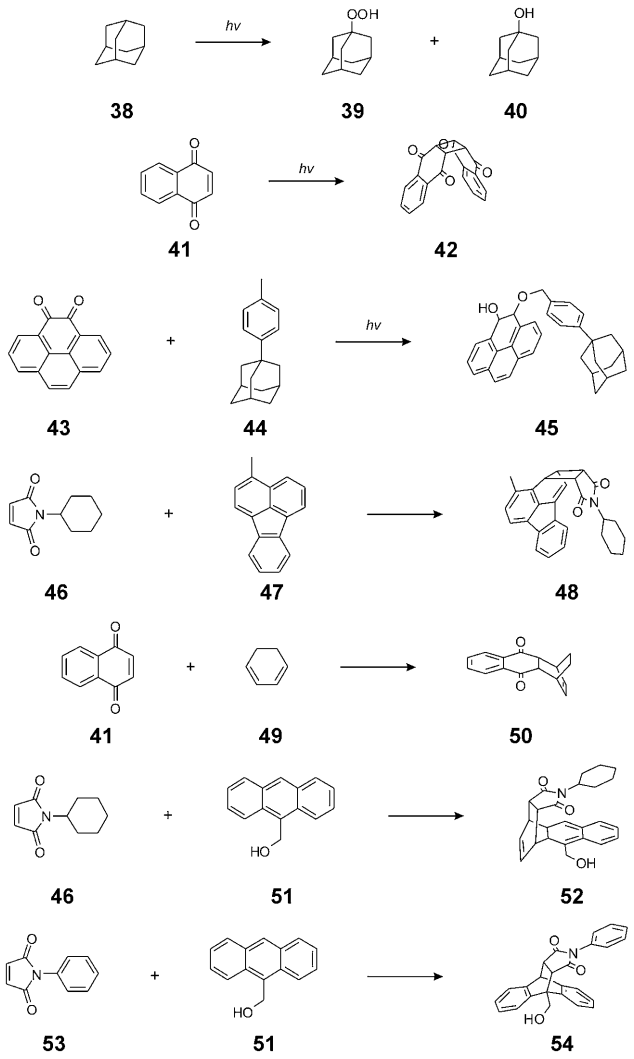


Figure 12. Reactions catalyzed by complexes **36a–g** and **37a**.

were encapsulated in the cavity of **36a–d** and, upon irradiation, one adamantane per cage was oxidized to 1-adamantylhydroperoxide (**39**) or 1-adamantanol (**40**).[49] This reaction has been shown to proceed by a guest-to-host photoinduced electron transfer process, forming an adamantyl radical cation, which is then trapped by O_2 or H_2O to yield the oxidized product.[50] Coordination cages **36a** and **37a** also have been used as stereoselective reactive pockets for the [2+2] photodimerization of bulky olefin **41**, forming one stereoisomer, the *syn*-dimer, exclusively (**42**, Figure 12).[51]

The Fujita group also has synthesized octahedral cage complexes using Pd^{II} precursors with chiral blocking ligands (**36e–g**, Figure 11).[39] These complexes have been used in the asymmetric [2+2] cross photoaddition of olefins. By changing the blocking ligands on the Pd^{II} metal, from achiral to chiral

moieties, they were able to achieve up to 50% *ee* in the cross photoaddition of *N*-cyclohexylmaleimide (**46**) and 3-methylfluoranthene (**47**). Similar to the Hupp and Nguyen groups' supramolecular rectangular porphyrin box structures and the Raymond and Bergman groups' tetrahedral complex (see sections 2.2.1 and 2.2.4), the observed enantioselectivity was proposed to result from through-space interactions between the substrate and the chiral blocking ligands on Pd^{II}. In addition, this was the first report of using a fluoranthene in a pericyclic reaction, either by thermal or photochemical means, as it had generally been considered to be inert. Indeed, the presence of the cage is essential for these reactions to occur and for achieving a high degree of stereoselectivity.

2.3.3. Diels–Alder Reactions

Cage complexes **36a–g** and **37a** have been used extensively to catalyze Diels–Alder cyclization reactions between various dienes and dieneophiles. These complexes considerably accelerate Diels–Alder reactions and in some cases significantly alter the regioselectivity, as compared to the uncatalyzed reactions. For example, the Diels–Alder reaction between naphthoquinone (**41**) and 1,3-cyclohexadiene (**49**) exhibits a rate enhancement of approximately 21 times in the presence of **36a**, compared to the uncatalyzed reaction (Figure 12).[52] Using an acyclic diene, 2-methyl-1,3-butadiene, and naphthoquinone, the rate enhancement is even more pronounced (113-fold). Interestingly, the cage complex **36a** encapsulates two pairs of substrates in each of these reactions. This rate enhancement has been attributed not only to the proximity effect but also to the ability of the cavity to preorganize the substrates.

When larger reactants are used, such as triphenylene and *N*-cyclohexylmaleimide, the complexes **36a–c** can only encapsulate one pair of substrates.[53] In this case, the diene, triphenylene, which ordinarily shows poor reactivity in Diels–Alder coupling reactions, is quantitatively converted to the endo Diels–Alder adduct after 24 h upon heating in the presence of **36a**. Other large aromatic compounds have been reacted with *N*-cyclohexylmaleimide in the presence of **36a–c**, including perylene, pyrene, phenanthrene, and fluoranthene.[53] In all of these cases, only one product is formed, even when multiple reactive sites are present, due to the orientation of the substrates in the cavity of the complex.

When 9-substituted anthracenes and *N*-substituted maleimides are used in the context of Diels–Alder coupling reactions, interesting reactivity is observed in the presence of both complexes **36c** and **37a**.[54] In the case of cage complex **36c**, unusual regioselectivity is observed with *N*-cyclohexylmaleimide (**46**) and 9-hydroxymethylanthracene (**51**, Figure 12). The sole product of this reaction is the 1,4-Diels–Alder adduct **52**, indicating that maleimide reacts at the terminal anthracene aromatic ring rather than the central one, as is typically the case. This phenomenon can be attributed to the steric demand of the *N*-cyclohexylmaleimide, because when a less sterically demanding dieneophile is used, typical reactivity is restored (i.e. the formation of the 9,10-Diels–Alder adduct).

When bowl complex **37a** is used to catalyze the Diels–Alder coupling reactions of different anthracene and maleimide derivatives, the typical regioselectivity is observed, however the reaction exhibits catalytic turnover.[54] With 10 mol% of **37a**, quantitative formation of the 9,10-Diels–Alder adduct is observed within 5 h at room temperature. This catalytic turnover has been attributed to a loss of π stacking between complex **37a** and the anthracene substrate (**51**), because the product of the reaction (**54**) is bent at the 9,10-position of the central anthracenyl ring (Figure 12). It is proposed that this bending disrupts the π stacking between the product and the complex and consequently favors the encapsulation of new substrate.

2.3.4. Tetrahedral Complexes

Raymond, Bergman, and coworkers also have shown that the highly charged tetrahedral complex **32** can be used to catalyze reactions without the incorporation of a catalytic moiety, in a similar manner to the reactions mentioned above. This was first demonstrated using complex **32** to catalyze the aza-Cope rearrangement of **55** to yield **56** (Figure 13).[55] This

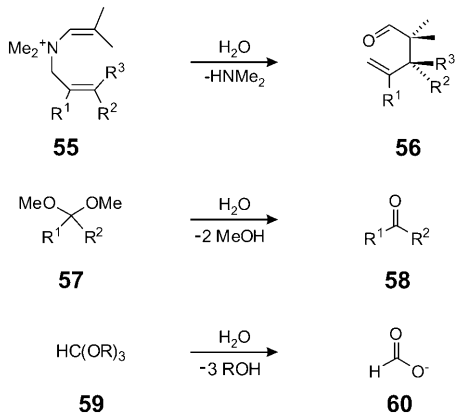


Figure 13. Reactions catalyzed by tetrahedral complex **32. 55–60**: R = H or alkyl.

intramolecular rearrangement is accelerated up to 850-fold by the presence of the cage complex compared to the uncatalyzed reaction. Using enantiopure ΔΔΔΔ-**32**, 6–78% *ee* were achieved.[56] This rate increase is presumed to be due to the substrate being prearranged in the cavity in the correct orientation for the rearrangement to occur. After the rearrangement, the product is hydrolyzed in solution to the neutral aldehyde (**56**), which is a weaker binder than cationic compound **55**, stopping any product inhibition that otherwise might be observed.

Two other important reactions that have been catalyzed by the tetrahedral complex **32** are the hydrolysis of acetals **57**[57] and orthoformates **59** (Figure 13).[58] Both of these reactions typically require acidic conditions, but in the presence of complex **32** they proceed even in basic solutions. The catalytic deprotection of acetals **57** to yield ketones or aldehydes **58** proceeds under mild conditions with only 5 mol% of the tetrahedral catalyst, and interestingly, size

selectivity is observed.[57] For example, 2,2-dimethoxyundecane and 1,1-dimethoxynonane are too large to enter the cavity of **32** and do not react, whereas 1,1-dimethoxyheptane is converted to heptanal in over 95% yield. In the hydrolysis of orthoformates **59**, a rate increase of up to 3900-fold is seen for some substrates, as compared to the uncatalyzed reaction.[58] For example, where triethyl orthoformate (**59**; R = Et) is quickly hydrolyzed to formate (**60**) and ethanol, no reaction is seen with tripentyl orthoformate. The rate increase is presumed to be due to the ability of anionic complex **32** to stabilize the protonated form of substrates small enough to fit inside the cavity. These examples illustrate how the local environment in the cavity of a complex differs from that of the overall solution, as is observed for the active sites of many enzymes.

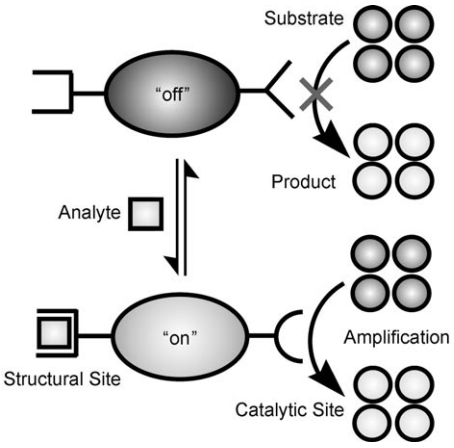


Figure 14. Signal amplification based upon an allosteric catalyst. Adapted with permission from ref. [67b]. Copyright 2007 American Chemical Society.

3. Enzyme Mimics That Exhibit Regulation

3.1. General Considerations

Allosteric regulation plays a key role in organisms, allowing them to regulate enzyme activity for a wide variety of biochemical pathways.[1,59] In such systems, efficient signal-transfer cascades trigger cellular responses based on events that initially occur at the level of individual molecular interactions. Recent synthetic advances in supramolecular coordination chemistry have made it possible to mimic allosteric regulation and realize a new class of structures that have important implications in molecular recognition, catalysis, and ultra-sensitive detection. While many contributions have demonstrated noncatalytic homotropic or heterotropic ligand binding to artificial receptors[60] or regulation of guest transport across membranes,[61] this Review mainly focuses on catalytic turnover of reactant molecules in the context of artificial allosteric regulation[60l,62,63] by supramolecular coordination complexes that exhibit a clear separation between the catalytic and distal regulatory sites, both being a part of the same discrete supramolecule (Figure 14).

Reversible conformational transformations with concomitant changes in activity have to be considered a principal requirement in order for an enzyme mimic to qualify as allosteric, as dictated by both the MWC model[64] and sequential model[65] that describe allosteric regulation based on chemically triggered conformational changes. Therefore, the term allosteric regulation is only used for examples discussed below where reversibility has been demonstrated. The term "up-regulation" or, simply "regulation", is used when reversibility has not been explicitly demonstrated. Such systems are still highly relevant to the field, as a strongly coordinating metal ion or small molecule scavenger to remove the regulator may allow for reversible, allosteric switching in some cases.[66]

The ability to use an external stimulus to trigger a catalytic reaction provides the basis for a general strategy for highly amplified chemical detection systems. Indeed, we have shown that systems can be designed where a trace amount of analyte can induce a conformational change in a supramolecular complex, which turns on a catalytic reaction that, in turn, generates a fluorescent surrogate for the analyte (Figure 14).[12c,67] This detection scheme has led to sensitive detection methods for various small molecule or elemental ion analytes. For example, chloride ions can be detected with this allosteric signal amplification approach at submicromolar concentrations based on a macrocyclic catalyst formed through the WLA.[12c,67] As shown in more detail in section 3.3.1, chloride ions are able to switch the allosteric complex from the inactive (closed) to the active (open) conformation by binding reversibly to the regulatory site. This activation triggers an acyl transfer reaction between 4-pyridylcarbinol (**61a**, Figure 15) and acetic anhydride (**62**), resulting in the formation of acetic acid (**64**), which when coupled to a pH-sensitive fluorescent probe, allows for the readout of the chloride concentration in the system by a

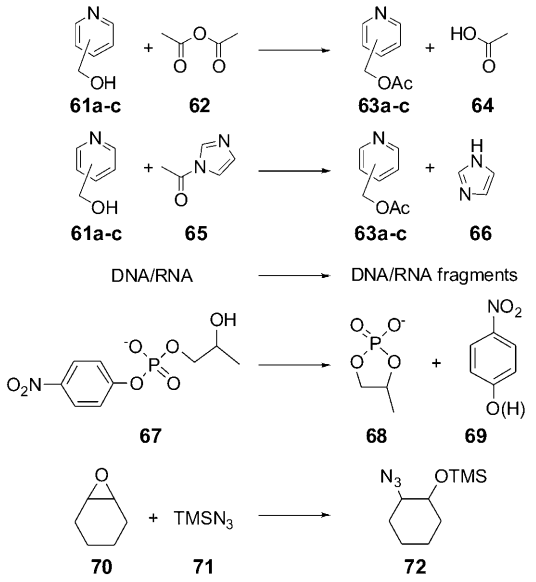


Figure 15. Reactions that can be regulated based on metal-coordination interactions. **61a–c**: 4,3,2-pyridylcarbinol, **63a–c**: 4,3,2-acylpyridylcarbinol.

fluorescence intensity measurement or in some cases with the naked eye.

3.2. Reaction Rate Up-Regulation Based on Metal-Induced Structural Changes in Organic Scaffolds

Efforts to use metal-ligand coordination for reaction rate regulation based on conformation changes date back to the 1970s.[68] Original efforts were based primarily on "classical" supramolecular coordination chemistry, in which a conformation change is induced by a metal ion on a single, discrete organic ligand (for example a crown ether),[69] similar to zinc finger proteins.[70] In a groundbreaking system, in 1978 Rebek and coworkers reported an isomerization reaction that can be regulated by taking advantage of transition-state stabilization as a result of metal chelation to a bipyridine unit (Figure 16).[68a,71] In the absence of metal ions, biphenyl derivative

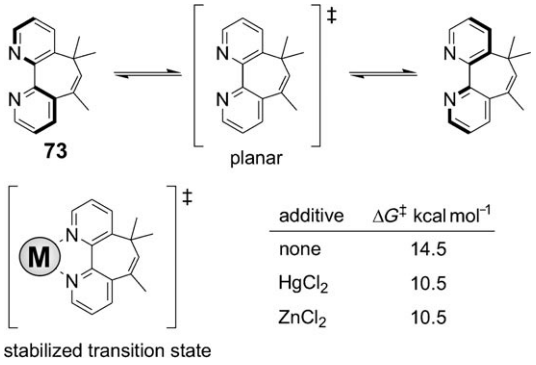


Figure 16. Metal-coordination induced regulation of the racemization reaction of biphenyl derivative **73**.

73 racemizes with a free energy barrier of 14.5 kcal mol^{-1}, as measured with variable-temperature ^{1}H and ^{13}C NMR spectroscopy. Due to the simplicity of the substrate, the transition state of the reaction can be unambiguously identified as a planar intermediate with a biphenyl dihedral angle of 0°. Therefore, the observation of a markedly lower free energy barrier for the racemization reaction upon metal chelation to the *o*-bispyridine unit indicates catalysis by transition-state stabilization. This early system demonstrates metal-coordination induced regulation of a reaction that occurs within the same molecule (no turnover of a separate reactant), but remote from the regulatory site. These studies were followed by additional examples of "remote control" of reactions occurring at a distal site within the same molecule,[60b,68b,72] as well as by studies on the regulation of ion transport between organic and aqueous phases.[61a,73]

Shinkai and coworkers showed that the crown ether flavin mimic **74** (Figure 17) can be activated upon complexation with alkali metal cations, resulting in up to 2.2-fold rate enhancements by complex **75** (for M = Rb^{+}) for the oxidation of NADH model compound **76**, compared to the uncomplexed state (**74**).[74] Addition of an NH_4^+ salt to compound **74** also resulted in up-regulation (2.4-fold rate enhancement).

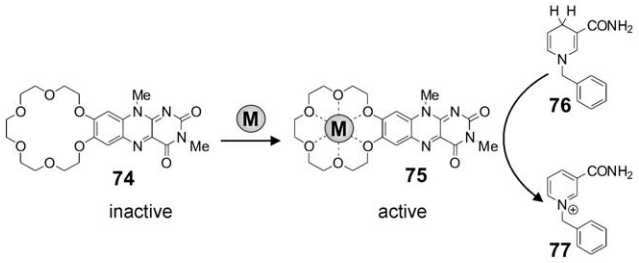


Figure 17. Activation of a crown ether flavin mimic for the oxidation of an NADH model compound. M = alkali or alkaline earth metal ions.

Compounds **74** and **75** exhibit significant differences in their absorption and fluorescence emission spectra, allowing one to track the coordination of the metal ion spectroscopically. This study is an early example of how metal-complexation can be used to up-regulate the stoichiometric conversion of a reactant. In a related example, the photooxidation of benzyl alcohol by a crown ether-flavin adduct was upregulated 4-fold by Ca^{2+} ions.[74c]

In 1987, Dervan and coworkers reported a peptide derivative (**78**) that contains a tetraethylene glycol derived tether that can bind to metal cations in an [18]crown-6-like structure (Figure 18).[75] Upon addition of dithiothreitol in the

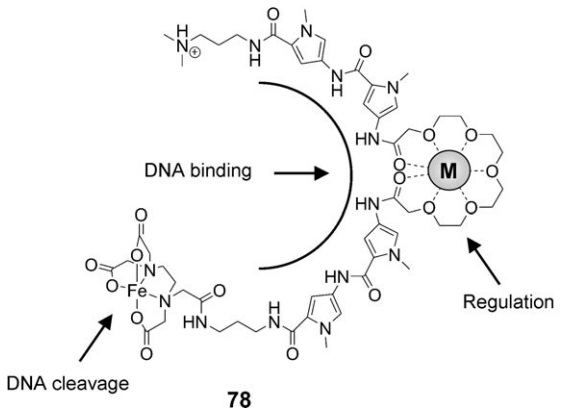
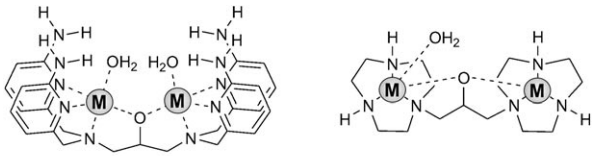


Figure 18. Metalloregulation of a sequence-specific DNA cleavage reaction. M = Ba^{II}, Sr^{II}.

presence of Ba^{2+} or Sr^{2+} ions, which are known to bind well to [18]crown-6 in water, compound **78** exhibits efficient and sequence-specific DNA intercalation and cleavage as measured by gel electrophoresis. Very little DNA cleavage was observed in the absence of these two alkaline earth metal ions as well as in the presence of other metal ions (such as Na^{+}, K^{+}, Mg^{2+}, Ag^{+}, or Cd^{2+}). Since this initial example of metalloregulation of a sequence-specific DNA cleavage reaction by a small molecule, several related examples have been reported.[76]

Mimics for phosphodiesterase enzymes have been targeted extensively because of the capability of these enzymes to accelerate the catalysis of phosphate diester cleavage reactions in nucleic acids by multiple orders of magnitude.[77] In Nature, these enzymes often use divalent metal ion

cofactors that are aligned with respect to each other.[78] Many bimetallic enzyme mimics of such multimetallic enzymes, typically based upon Zn^{II}, have been synthesized and are capable of cleaving DNA and RNA fragments as well as the RNA mimic **67** (Figure 15).[79] Two recent examples of such structures that exhibit 10^6–10^7-fold catalytic accelerations (complex **79**: cleavage of UpU in water[80] and complex **80**: cleavage of **67** in water[81]) have been synthesized (Figure 19).

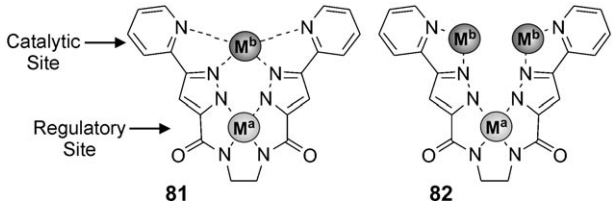


79 **80**

Figure 19. Artificial bimetallic phosphate ester cleavage catalysts. M = Zn^{II}.

Since the efficiency of these man-made catalysts for phosphate diester cleavage is highly dependent on the distance and relative arrangement of two or more metal ions, regulation of the catalytic reaction rate by varying the distance between two or more catalytic metal centers was hypothesized to lead to significant rate differences, which is indeed what was observed by several research groups.

Krämer and coworkers carried out a series of studies based on ligands that contain tetradentate regulatory sites that can undergo strong binding to Cu^{II}, Ni^{II}, Pd^{II}, Pt^{II}, and $Co^{II/III}$.[60l,82] One example of such structures is shown in Figure 20. The largest rate dependence with respect to the

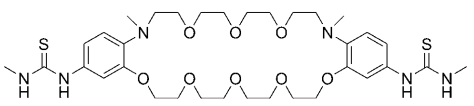


81 **82**

Figure 20. Rate regulation based on a polyaza enzyme mimic. **81**: $M^a = Pt^{II}$ and $M^b = Cu^{II}$, **82**: $M^a = Pd^{II}$ and $M^b = Cu^{II}$.

regulatory metal (M^a) was found in complexes **81** and **82**, with Pt^{II} and Pd^{II} as regulatory metal ions (M^a), respectively, and Cu^{II} as the catalytically active metal ions (M^b). Virtually no reactivity was observed for Pt^{II} as the structural metal, whereas catalytic cleavage of the RNA model substrate **67** (Figure 15) was observed with a pseudo-first order reaction rate constant $k_{obs} \approx 6 \times 10^{-5}\ s^{-1}$ in DMSO/H_2O (1:1) for Pd^{II} as the regulatory metal (M^a). This large rate difference is because only one Cu^{II} ion is present at the catalytic site when Pt^{II} acts as the regulatory metal (structure **81**), whereas two proximal Cu^{II} ions are present when Pd^{II} is coordinated to the regulatory site (structure **82**), resulting in catalytic phosphodiester cleavage of **67** in a bimetallic fashion.

Kubo and coworkers have reported a crown ether bisthiourea compound (**83**, Figure 21), which functions as a

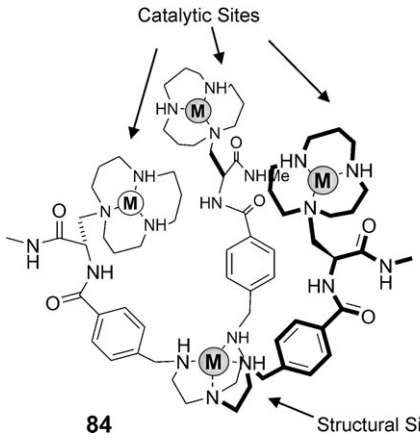


83

Figure 21. A thiourea-based catalyst that is activated upon metal coordination.

phosphate diester cleavage catalyst (substrate **67**, Figure 15), which, upon addition of K^+ ions, exhibits a 400-fold rate increase in acetonitrile ($k_{obs} = (8.0 \pm 0.7) \times 10^{-5}\ s^{-1}$).[83] The addition of other alkali metal cations (Na^+, Cs^+) results in smaller, but still significant, rate increases. An energy-minimized model suggests that the large rate increase is due to the proximity between the thiourea sites in the complexed state, which are proposed to promote the phosphodiester cleavage reaction by hydrogen-bonding interactions that increase the electrophilicity of the phosphorus atom.

Scrimin and coworkers reported several systems capable of phosphate diester cleavage regulation based on cooperative catalysis by Zn^{II} ions bound to three chelating cyclic triaza (tcn) ligands.[84] These ligands are assembled into a cavity by a tripodal tris(2-aminoethyl)amine (tren) ligand that binds to Zn^{II} more strongly than the tcn ligands (Figure 22). The Zn_4 complex **84** exhibits a 30-fold increase in phosphodiester cleavage activity for model substrate **67** ($k_{obs} = 1.1 \times 10^{-5}\ s^{-1}$) compared to a system with unassembled, individual Zn^{II}-tcn and Zn^{II}-tren molecules.[84a]



84

Figure 22. Tripodal enzyme mimic for phosphodiester cleavage catalysis. M = Zn^{II}.

Shinkai and coworkers reported a system that exhibits in situ activation upon addition of several equivalents of Cu^{II} or Zn^{II} ions to ligand **85** (Figure 23), which contains two tridentate 2,2′-dipicolylamine (dpa) sites and one 2,2′-bipyridine (bpy) site.[85] The dpa sites bind more strongly to Cu^{II} and Zn^{II} than the bpy sites; therefore, the first two equivalents of metal ion lead to compounds **86a,b**. These complexes are relatively catalytically inactive in terms of phosphodiester cleavage due to the transoid conformation of the bpy ligand. Addition of one more equivalent of the same metal ion to

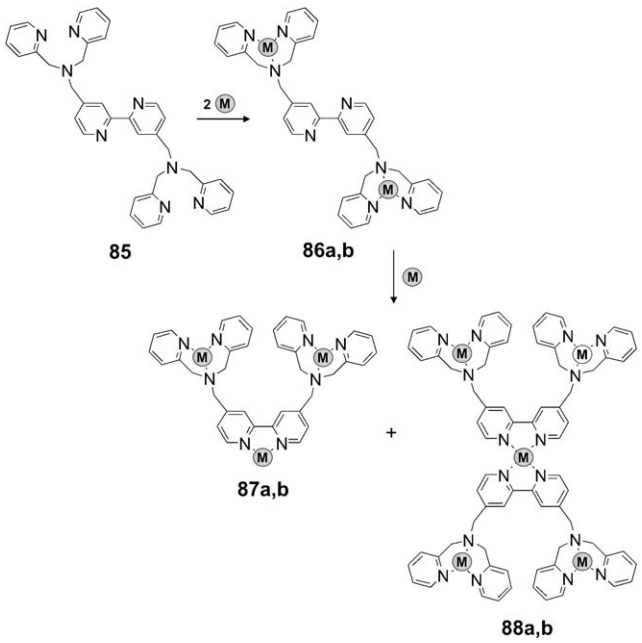


Figure 23. Up-regulation due to a metal ion triggered conversion of the transoid to cisoid bpy conformation. **86a–88a**: M = Cu^{II}, **86b–88b**: M = Zn^{II}.

86a,b leads to a mixture of complexes **87a,b** and **88a,b**. In the case of Cu^{II} (**87a** and **88a**), a 19.4-fold increase in the pseudo-first order reaction rate constant ($k_{obs} \approx 1.2 \times 10^{-3}\ s^{-1}$) for the cleavage reaction in EtOH/H_2O (1:2) is observed. A similar but smaller effect is achieved for the Zn^{II} complexes (**87b** and **88b**). These rate increases were attributed to the formation of cisoid complexes **87a,b** and **88a,b**, in which the dpa bound metal ions are in close proximity to each other, allowing for cooperative catalysis.

Thus far, the systems presented here are all up-regulating systems triggered by metal coordination to a structural site. These are one way transformations, with the reverse processes not studied. In many respects, they resemble zinc finger proteins more so than reversible allosteric structures in the biological context. In classical zinc finger proteins, a Zn^{II} ion binds to Cys and His residues in a β hairpin and an α helix, which results in a unique three dimensional conformation of the protein that is frequently involved in transcription regulation through binding to DNA.[70] Zinc finger proteins tend to undergo little structural rearrangement upon binding to their recognition unit and the interaction between Zn^{II} and the corresponding ligands is considered to be rather strong. The following section describes supramolecular coordination structures that exhibit allosteric regulation induced not by metal ions, but rather by small organic molecules and elemental anions that allow for reversible switching of reaction rates in most cases. These heterometallic structures have well defined regulatory and active sites with chemistries that are orthogonal to one another.

3.3. Small Molecule and Elemental Ion Induced Allosteric Regulation and Up-Regulation Based on Macrocycles and Tweezers Synthesized Through the WLA

The WLA allows for reversible in situ structural modification of enzyme mimics, resulting in allosteric responses in several cases.[12c,26b,67,86,87] Substrate self-regulation[67c] and discrimination between different substrate isomers[67b,88] have also been demonstrated. Based on these regulatory responses, small-molecule sensors that incorporate signal amplification reminiscent of ELISA (enzyme-linked immunosorbent assays)[67a,b] and PCR (polymerase chain reaction)[67c] have been developed.

3.3.1. Salen Based catalysts

The incorporation of Zn^{II} or Cr^{III} catalytic moieties (Figure 24) into macrocycles generated through the WLA leads to allosteric catalysts **89a–d** in which the distance between the two catalytic sites can be regulated by the combined addition of CO and chloride, resulting in open complexes **90a–d**.[67,86] Reversible switching is achieved by

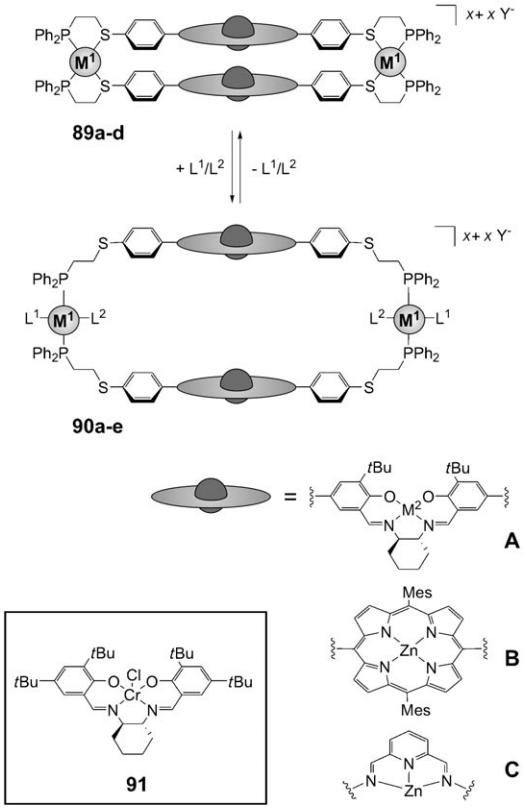


Figure 24. Allosteric catalysts based on macrocycles formed through the WLA. **89a** (catalyst **A**, M^1 = Rh^I, M^2 = $Cr^{III}Cl$, x = 2, Y = BF_4); **89b** (catalyst **A**, M^1 = Rh^I, M^2 = Zn^{II}, x = 2, Y = BF_4); **89c** (catalyst **B**, M^1 = Rh^I, x = 2, Y = BF_4), **89d** (catalyst **C**, M^1 = Rh^I, x = 6, Y = BF_4/OAc); **90a** (catalyst **A**, M^1 = Rh^I, M^2 = $Cr^{III}Cl$, L^1/L^2 = Cl/CO, x = 0); **90b** (catalyst **A**, M^1 = Rh^I, M^2 = Zn^{II}, L^1/L^2 = Cl/CO, x = 0); **90c** (catalyst **B**, M^1 = Rh^I, L^1/L^2 = Cl/CO, x = 0), **90d** (catalyst **C**, M^1 = Rh^I, L^1/L^2 = Cl/CO, x = 4, Y = BF_4/OAc), **90e** (catalyst **A**, M^1 = Rh^I, M^2 = Zn^{II}, L^1/L^2 = OAc/CO, x = 0).

purging complexes **90a,b,d** with nitrogen or removal of CO in vacuo, resulting in condensed structures **89a,b,d** (for **90c**, reversibility was not studied).

The initial catalytic rate of asymmetric ring-opening of cyclohexene oxide (**70**, Figure 15) with trimethylsilyl azide ($TMSN_3$, **71**) to form azide **72** is approximately two times faster with the open Cr^{III}-salen complex **90a** than with the closed structure **89a**.[86] An *ee* of 68% was observed in the closed state, which was significantly higher than the *ee* observed for the analogous monomeric Jacobsen catalyst **91**[89] (Figure 24) under the same reaction conditions (12% *ee*). While this initial result attested to the feasibility of allosteric regulation based on macrocycles formed through the WLA, the allosteric effect was relatively modest.

The rate difference between "off"- and "on"-states was improved by focusing on a different metal (Zn^{II}) salen core and the catalytic acyl transfer reaction between 4-pyridylcarbinol (**61a**, Figure 15) and acetic anhydride (**62**). Zn^{II}-salen catalyst **90b** (open state) catalyzes the acyl transfer reaction between pyridyl carbinol and acetic anhydride with a rate enhancement of approximately 25 times compared to the closed state (**89b**).[67a]

This rate difference has been attributed to a (at least partial) switch between a Lewis acid catalyzed monometallic reaction pathway in the closed state and a bimetallic reaction pathway in the open state. Since acetic acid (**64**) is one of the products of the reaction, a pH-sensitive fluorophore (diethylaminomethylene anthracene) can be used for signal readout, resulting in amplification of the signal induced by the analyte (chloride) and a convenient fluorescence readout, which can be accomplished with a fluorometer or even the naked eye down to a chloride concentration of 800 nM (Figure 25). Therefore, this system illustrates the feasibility

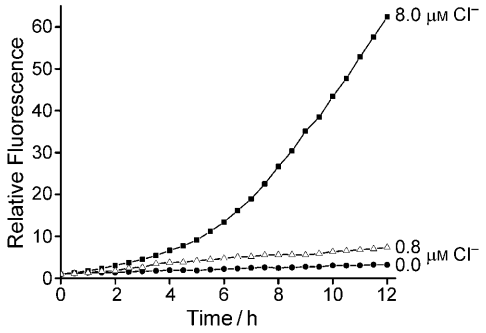


Figure 25. Fluorometric detection of chloride concentration based on allosteric regulation. Reprinted with permission from ref. [67a]. Copyright 2005 American Chemical Society.

of an allosteric detection and amplification system for small molecules that is reminiscent of ELISA, but based on supramolecular coordination complexes rather than proteins.

In a detection system using a supramolecular catalyst based on Cu^{I} instead of Rh^{I} ions at the structural site, various N- or C-donor molecules were identified with detection limits as low as 200 nM (for phenanthroline).[67b] No reversibility was demonstrated in these cases, making them more like the up-regulating systems described above than true allosteric systems.

3.3.2. Porphyrin Based Catalysts

Porphyrins and their derivatives have unique physicochemical characteristics that give them very important roles in biology and chemistry.[2,3,5,7–9,30–35] An example is photosynthesis, where porphyrin derivatives (chlorophyll) are arranged in a specific geometry with respect to each other in the photosynthetic reaction center and in the light-harvesting complex.[1,90] Synthetic cofacial assembly of porphyrins has been the target of many synthetic efforts, and a number of enzyme mimics based on porphyrins have been discussed in section 2. The WLA allows for cofacial arrangement of porphyrins in high yield in the context of supramolecular chemistry, as well as an in situ conformational change of the relative alignment between porphyrin sites by small regulatory molecules.[12d,88,91]

The closed and open Rh^{I}–Zn^{II} porphyrin structures **89c** and **90c** (Figure 24) were both synthesized and spectroscopically characterized in solution, and the structure of **89c**⊃DABCO (DABCO = 1,4-diazabicyclo[2.2.2]octane; ⊃ denotes encapsulation) was additionally characterized in the solid state by a single-crystal X-ray diffraction study that showed the cofacial alignment of the porphyrin units which were coordinated to the two nitrogen atoms in DABCO.[88] The acceleration of the acyl transfer reaction for three different pyridylcarbinol isomers **61a–c** (Figure 15) and 1-acetylimidazole **65** has been studied with complexes **89c** and **90c** as catalysts, respectively. Rate increases were observed for 4-pyridylcarbinol (**61a**) and 3-pyridylcarbinol (**61b**), whereas 2-pyridylcarbinol (**61c**) exhibited no increase in catalytic rate between closed catalyst **89d** and its open form **90d**, as well as compared to a monomer catalyst. These studies illustrate the ability of these macrocyclic catalysts to discriminate between different regioisomers of a molecule. The unfavorable geometry of 2-pyridylcarbinol in the bimetallic transition state was suggested as the reason for the absence of a rate increase in this case. These results show the shape-selective nature of porphyrin based, enzyme-like pockets formed through the WLA.

3.3.3. Pyridine-Bisimine Based Catalysts

The catalysts based on the WLA discussed thus far illustrate the feasibility of allosteric regulation induced by small molecules and elemental ions based on coordination chemistry and how these systems can be used for small-molecule detection. However, significant background reactions are observed, and detection occurs over the course of hours and only in organic solvents. These limitations were addressed through the design and synthesis of complexes **89d** and **90d**.[87] Complex **90d** was designed to catalyze the hydrolytic cleavage of phosphate diester **67** (Figure 15) under pseudo-aqueous conditions ($MeOH/CH_2Cl_2/H_2O$). Compounds **89d** and **90d** each have cofacial Zn^{II}–pyridine-bisimine based catalyst cores (catalyst **C**, Figure 24) assembled into a closed and open macrocycle, respectively. An X-ray crystallographic study of **89d** in the solid state showed that the two Zn^{II} centers are bridged by an acetate ion, suggesting that substrate access to the Zn^{II} sites is hindered, if not

completely blocked, in the closed state. Consequently, no catalytic activity was observed for complex **89d**. Opening inactive complex **89d** with CO/Cl^- led to the highly active catalyst **90d**, resulting in quantitative cleavage of **67** within 40 min. This efficient catalytic activity is likely a result of bimetallic catalytic phosphodiester cleavage by the two proximal Zn^{II} ions. This system is capable of reversible "off"/"on" switching with a 10^2 allosteric effect in terms of the reaction rate. The situation when the "off" state is completely inactive is a major attribute, as background catalysis leads to background signal and a corresponding lower sensitivity for any detection system based upon allosteric catalysts.

3.3.4. Tweezer Catalysts

In an effort to realize tweezer type salen-based catalysts, a hemilabile dissymmetric P,S-salen ligand was synthesized. Two equivalents of this ligand react with a Rh^I precursor to form the closed tweezer Rh^I complex **92** (Figure 26) with a cofacial arrangement of the two Cr^{III}-salen sites.[26b] Unlike the closed macrocycles, the catalyst sites in this tweezer complex are highly accessible to substrate molecules. In the open state, the two phosphines are arranged *trans* with respect to each other, with CO and Cl^- ligands occupying the remaining positions of the square-planar Rh^I site with a relative arrangement of the Cr^{III}-salen sites that is highly flexible due to the absence of chelation. The change from a macrocyclic to a tweezer allosteric catalyst results in an inversion of the catalytic behavior of the system. The closed, more rigid state exhibits a faster reaction rate (ca. 2-fold) compared to the open state in the catalytic ring opening of cyclohexene oxide (**70**) with $TMSN_3$ (**71**, Figure 15). This observation suggests that in the tweezer system, preorganization of the catalytically active Zn^{II} ions in the closed state facilitates catalysis. The system exhibits excellent reversibility, with CO gas acting as the allosteric effector that can easily be added and removed from the system (Figure 26).

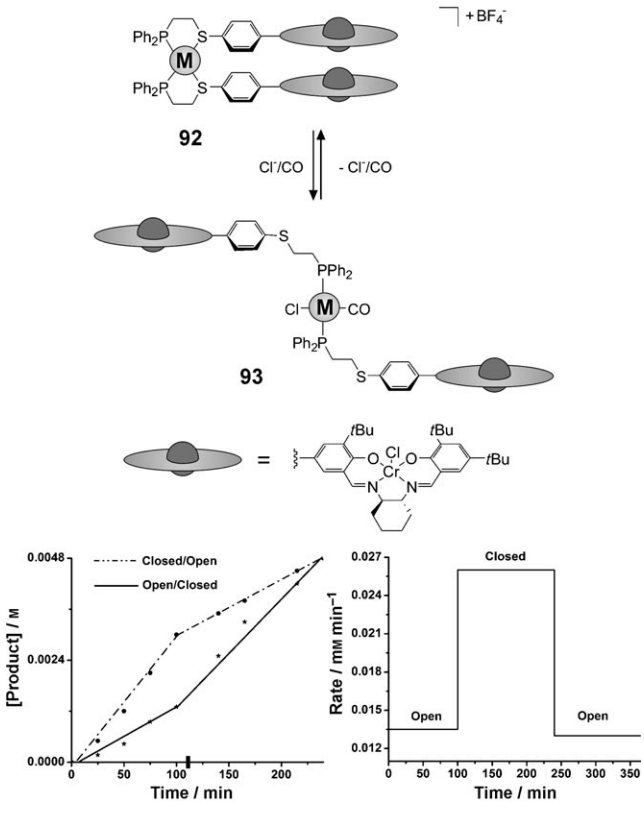


Figure 26. Top: Allosteric catalysts based on tweezers formed through the WLA. Bottom: Illustration of reversibility; left: Closed/Open and Open/Closed cycles of allosteric catalysis, (■) indicates the CO saturation/desaturation point where the system was switched between the two states; right: rate changes in an Open/Closed/Open cycle. From ref. [26b].

Enantioselectivities have been compared between open and closed complexes **92**, **93**, and monomer **91** (Figure 24) at different concentrations. The *ee* and reaction rate are highest in closed complex **92**. The monomer[89] shows a significantly lower *ee* and catalytic activity (at 7.2 mM catalyst concentration, **92**, **93**, and **91** generate *ee*'s of 80%, 74%, and 26%, respectively). The allosteric selectivity ratio (% *ee* of the product formed when using **92**/% *ee* of the product formed when using **93**) increases significantly as the catalyst concentration is lowered (highest ratio: 2.3). This observation can be explained by comparing the concentration-dependence of the intermolecular versus intramolecular reaction mechanisms. While the rate of the intramolecular reaction pathway is expected to stay approximately the same at different concentrations, the intermolecular bimetallic reaction rate is expected to slow down significantly at lower concentrations. Therefore, the more selective intramolecular reaction pathway becomes dominant at low catalyst concentrations.

3.4. Target Amplification by a PCR Mimic Based on the WLA

Signal detection systems based on the WLA presented thus far conceptually resemble ELISA, in which a target-binding event mediates a catalytic event that produces a chemiluminescent or fluorescent signal. In contrast, PCR is based on the amplification of the target itself, which results in amplification factors that are much larger than those from ELISA. The implementation of a self-amplifying detection scheme based on metal coordination chemistry potentially allows for the detection of a large range of analytes not accessible by traditional PCR.

In a proof-of-concept study related to the salen systems discussed in section 3.3, acetate was detected in a PCR-like target amplification scheme, resulting in characteristic sigmoidal reaction curves (formation of acetyl ester **63a**, Figure 15) that are consistent with target amplification (Figure 27).[67c] These reaction curves arise because of the ability of acetate to open complex **89b** in the presence of CO, resulting in open complex **90e**. Since acetic acid is formed in the presence of a base (the fluorescent probe 9-(*N*,*N*-diethylaminomethyl)anthracene), each turnover of the reaction results in an additional equivalent of acetate that can generate the catalytically active open form of the allosteric complex (**90e**), leading to self-amplification through a cascade of additional catalytic reaction cycles. The reaction was initiated by the addition of a minimal amount of

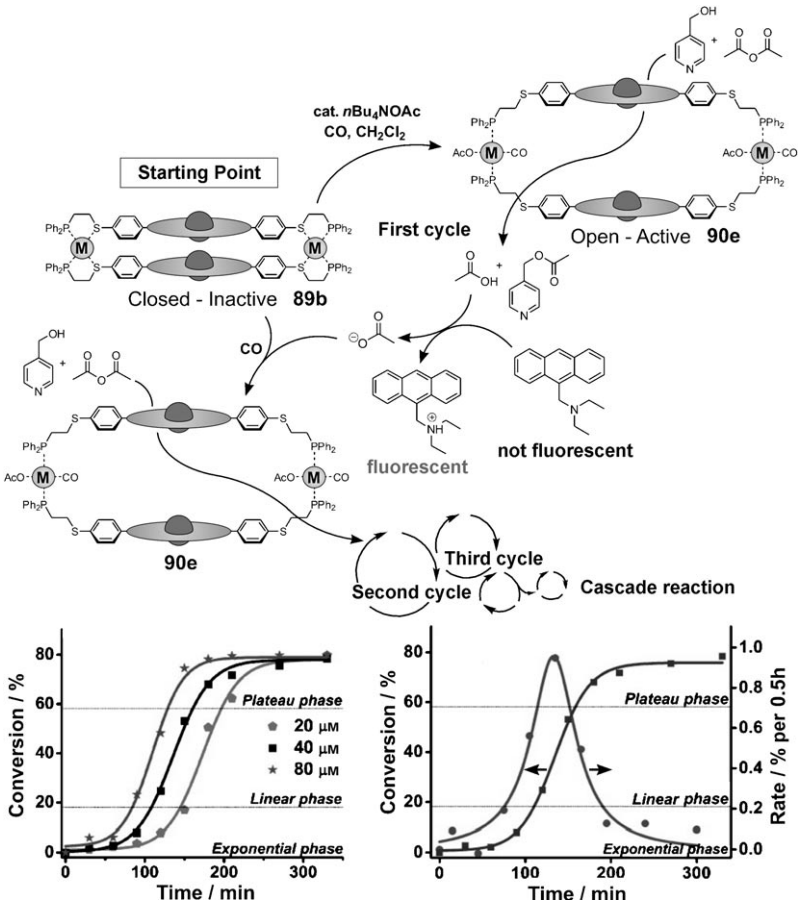


Figure 27. Top: Cascade reaction induced by the target molecule acatete. Complex charges and counterions have been omitted. Bottom: Sigmoidal reaction curves at different concentrations of the analyte nBu$_4$NOAc (20–60 μM). Catalyst concentration: 0.4 mM. Reprinted in part with permission from ref. [67c]. Copyright 2008 American Chemical Society.

nBu$_4$NOAc to the reaction solution. Therefore, amplification of the target molecule (acetate) was achieved by a cascade of amplification cycles and read out by detection of the protonated fluorescent probe. The amplification process is reminiscent of signal cascades observed in biological systems. To our knowledge, it is the first demonstration of a PCR mimic based upon a supramolecular coordination complex. Although challenging, the detection strategy should be applicable to numerous small molecule analytes, provided recognition events can be coupled with appropriate catalytic reactions that generate the entity to be recognized.

4. Assemblies That Mimic the Dissymmetric Nature of Enzyme Active Sites

The examples presented thus far illustrate how the assembly of multiple components based on supramolecular coordination chemistry is an efficient strategy for the synthesis of structures comparable in size to small enzymes, mimicking the cage-like nature of enzyme active pockets and their regulatory functions. While these structures are impressive in terms of their size, their symmetry is generally much higher than in enzymes, especially enzyme active sites. This means that the introduction of different kinds of functional groups that, for example, catalyze a reaction by a triad-like mechanism or by covalent bonding interactions[92] remains difficult to achieve.

For all three supramolecular coordination chemistry approaches described in section 1.3, methodologies have been developed to synthesize heteroligated coordination structures (Figure 28).[93,94] Fujita and coworkers used a combination of sterically hindered and unhindered pyridines to synthesize heteroligated complexes (Figure 28a), rectangular squares, and box structures using the DBA.[95] Lehn and coworkers took advantage of the preferred five-fold coordination mode of Cu^{II} ions with respect to bis- and tripyridines, in addition to a steric effect induced by methyl groups, to synthesize heteroligated helices through the SIA (Figure 28b).[96–98] Using the halide-induced ligand rearrangement (HILR) reaction and the WLA, macrocyclic and tweezer (Figure 28c) coordination structures can be synthesized with cofacial alignment of two different functional groups, such as two different porphyrins.[12d,26a,c,91,99,100] The position between functional groups A and B can be regulated in situ in a reversible fashion by the addition of small ancillary ligand molecules or elemental anions.

An enzyme mimic (**107**) in which a receptor and a catalyst are aligned in a tweezer fashion[2,3,31i,j,101] has been synthesized through the HILR and the WLA.[100] A hydrogen bonding amidopyridine receptor has been combined with a chiral, catalytically active Mn^{III}-salen unit that is reminiscent of Jacobsen–Katsuki catalysts (Figure 29). Isothermal titration calorimetry (ITC) measurements and a conformation search simulation show that two-point hydrogen bonding between the amidopyridine group in **107** and the substrate molecule 4-vinylbenzoic acid results in the alignment of the olefin group with respect to the catalyst with a Mn^{III}–olefin distance (3.9 Å) that is suitable for a Mn catalyzed epoxidation of the olefin while the hydrogen bonds to the amidopyridine group are maintained. A catalytic study in which an equimolar two olefin pool of styrene (which does not bind to the amidopyridine receptor) and 4-vinylbenzoic acid was oxidized to the corresponding epoxides exhibits an inversion of the major epoxide product from styrene oxide (for complexes without an amidopyridine receptor) to 4-oxiranylbenzoic acid (for **107**), resulting in 4.7-fold overall change in product selectivity between the two epoxides. Addition of the inhibitor 4-ethylbenzoic acid leads to diminished selectivity, suggesting that the preferred formation of 4-oxiranylbenzoic acid is indeed a consequence of supramolecular hydrogen bonding interactions between the substrate and the supramolecular catalyst.

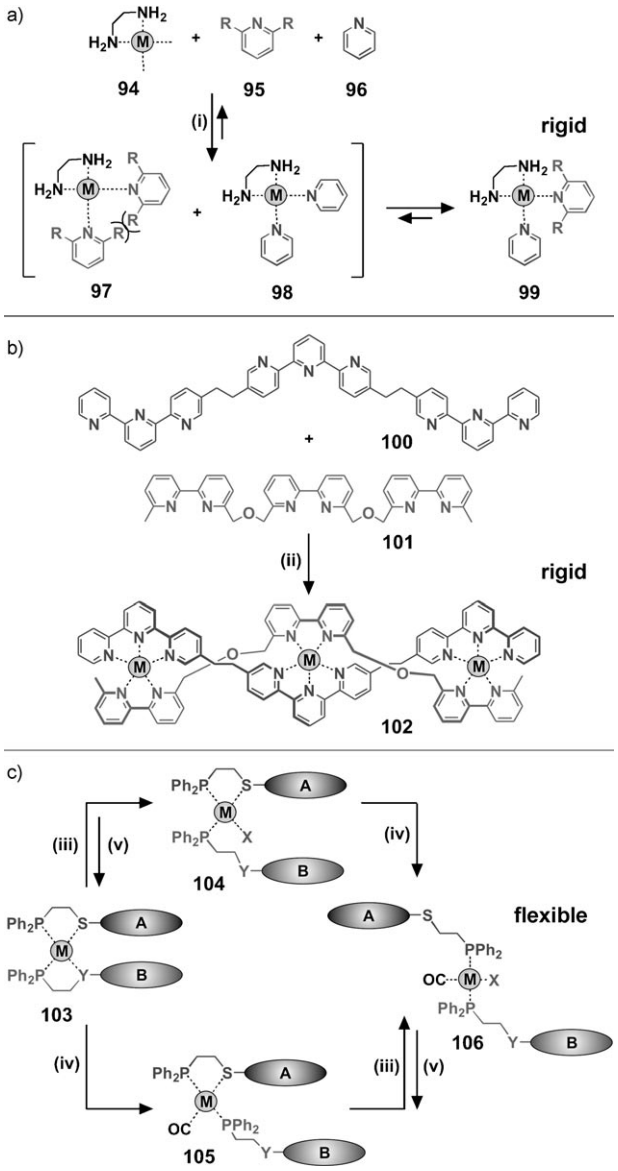


Figure 28. Assembly of heteroligated coordination structures based on a) the DBA; b) the SIA; c) the HILR and the WLA. (i) D_2O, heat; (ii) $3\,Cu(CF_3SO_3)_2$, CH_3CN, RT; (iii) halide source; (iv) CO (1 atm); (v) halide abstraction agent (e.g. $NaBAr^F_4$). R = Me, X = halide; Y = S, O. Complex charges and counterions have been omitted.

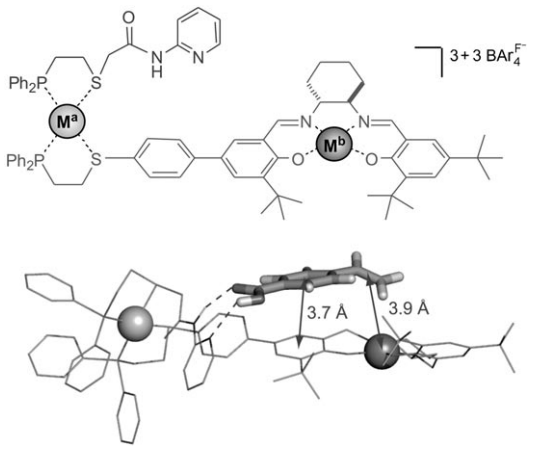


Figure 29. Top: Receptor-catalyst tweezer adduct synthesized through the HILR and the WLA. $M^a = Pt^{II}$, $M^b = Mn^{III}$; Bottom: Global minimum structure obtained from a conformation search simulation (Macromodel, MM2) of a hydrogen bonded complex between **107** and the substrate molecule 4-vinylbenzoic acid. Reprinted in part from ref. [100]. Reproduced with permission of The Royal Society of Chemistry.

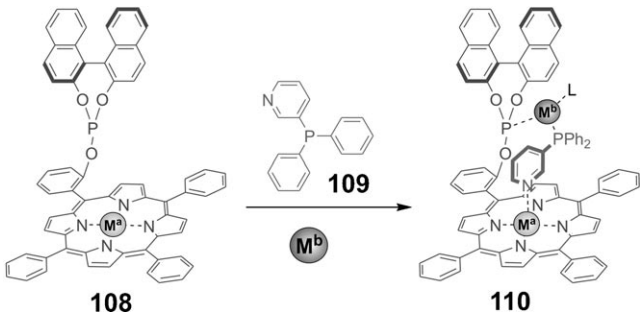


Figure 30. Assembly of heterobidentate phosphine catalyst **110** based on metallosupramolecular interactions. $M^a = Zn^{II}$; $M^b = Rh^I$, L = 1,5-cyclooctadiene (cod).

Several additional synthetic approaches based on metal-coordination chemistry have been developed that are suitable for the assembly of either different ligands that can coordinate to a single catalytically active metal (Figure 30 and 31) by chelation or the assembly of chromophores and a hydrogen generation catalyst (Figure 32). Reek, van Leeuwen, and coworkers have developed the highly modular supraphos approach,[102] which is based on pyridine–porphyrin interactions, resulting in the assembly of heterobimetallic complexes that exhibit heterobidentate ligand coordination around the catalytically active metal center. This approach offers high tailorability for the optimization of selectivity and turnover in a variety of catalytic reactions. Figure 30 shows the assembly of complex **110** by the combination of porphyrin binol-phosphite **108** and pyridylphosphine ligand **109**. This ligand combination was found from a library (96 catalytic runs) of 7 phosphite porphyrin ligands (Zn^{II}-metalated and unmetalated porphyrins) as well as 14 phosphorus ligands containing pyridyl or other N-donor groups that can undergo chelation with Rh^I in a supraphos system.

Complex **110** exhibits the best performance in terms of conversion (100%) and *ee* (94%) in the asymmetric catalytic hydrogenation of *N*-(3,4-dihydro-2-naphthalenyl)acetamide among all combinatorial runs and is the only system that exhibits an *ee* higher than 60%, illustrating the importance of ligand screening in catalysis, which was greatly facilitated by the supraphos approach (Figure 30).[102g] Previously reported Rh^I catalysts for this reaction exhibit *ee* values of $< 72\%$. Similar improvements in catalytic performance were achieved in hydroformylation[102h–n] and allylic alkylation reactions.[102a,b,m,n,103]

In separate but related work, Takacs and coworkers reported catalysts based on heterobidentate ligands assembled by metal-coordination chemistry[104,105] (Figure 31) that

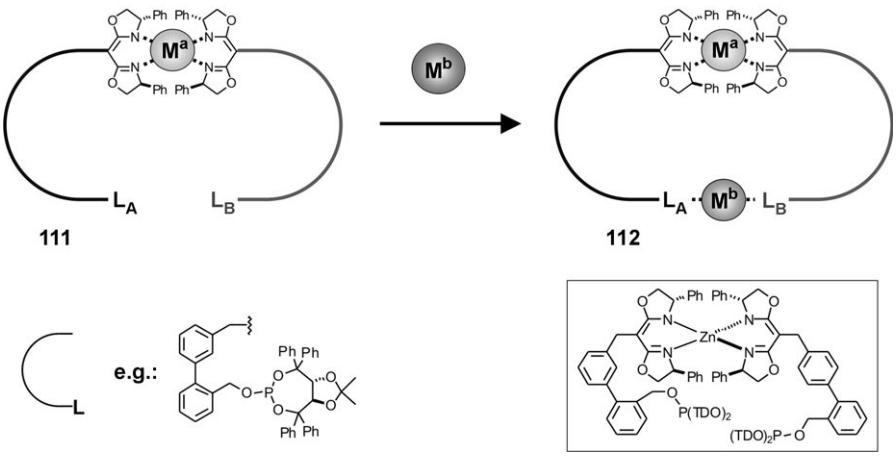


Figure 31. Heterobidentate phosphite catalyst **112** assembled by heteroligated bisoxazoline metal-coordination ($M^a = Zn^{II}$, $M^b = Pd^{II}$, Rh^I). The inset shows the ligand combination that leads to the highest *ee* (97%) in the context of an allylic amination reaction. TDO = (*R*,*R*)-taddol.

are different but complementary to the ones developed by Reek, van Leeuwen, and coworkers. In this case, the observation that the combination of Zn^{II} ions with two bisoxazoline ligands of opposite chirality preferentially results in the heteroligated (racemic) combination compared to the homoligated (homochiral) combination was exploited to form heterobidentate phosphite ligands (**111**) that coordinate to a Pd^{II} or Rh^I catalytic center, leading to complex **112**. In an initial study, 50 ligand combinations were screened for the Pd-catalyzed allylic amination of racemic 1,3-diphenyl-2-propen-1-yl ethyl carbonate, with the same taddol-derived phosphite ligand and bisoxazoline, but numerous variations of the ligand backbone. These variations led to *ee* values between 20 and 97% (achieved using a heteroligated system with two different backbones, see inset Figure 31), illustrating again the importance of combinatorial screening approaches to asymmetric catalysis.[105]

Recently Reek, van Leeuwen, and coworkers reported a supramolecular hydrogenase mimic that is able to produce molecular hydrogen using light as an energy source (Figure 32).[106] A series of structures were prepared using the supraphos approach, with Zn^{II}-porphyrin or Zn^{II}-salphen blocking groups, pyridylphosphine templating ligands, and a core catalytic moiety, a bis(thiolate)-bridged diiron cluster, [2Fe2S], which is known to photocatalyze the reduction of protons to molecular hydrogen (Figure 32).[107] In this system, the blocking groups not only add stability to the catalytic moiety by preventing the formation of the inactive dimeric $[FeFe]_2$ species,[108] but, as chromophores, they can absorb light and can transfer electrons to the [2Fe2S] core.[109] The photocatalytic activities of a number of different systems were investigated using diisopropylethylammonium acetate, $NiPr_2EtH{\cdot}OAc$, as a proton source and sacrificial electron donor. Interestingly, the only active and stable structure was a dissymmetric one, where two different porphyrin blocking groups were attached to the diiron core (Figure 32, **116bc**). The dissymmetric complex was characterized in solution and the CO-stretching bands were monitored by IR. The active complex exhibited at least 5 turnovers based on the amount of H_2 collected, and the turnover could be considerably higher taking into account the amount of H_2 dissolved in solution. Similar systems have been recently reported; these consist of either a tetraphenylporphyrin covalently bonded to a bridging azadithiolate diiron core or a Zn^{II}-tetraphenylporphyrin noncovalently linked to an azadithiolate diiron core through a pyridyl moiety.[110] These systems exhibited significantly lower turnover numbers of 0.31 for the covalently bonded one[110c] and 0.16 for a noncovalently assembled structure.[110b,111]

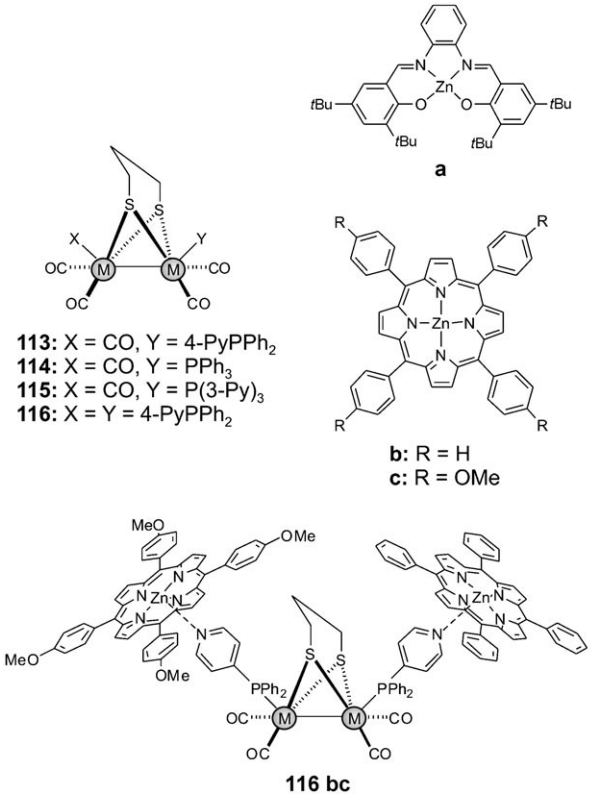


Figure 32. Supramolecular hydrogenase mimic. $M = Fe^{I/II}$.

5. Future Directions

Impressive advances have been made in the assembly of discrete man-made structures, many similar in size to small enzymes, which can mimic their functional aspects. These structures have been divided into three distinct classes based upon the enzyme-like properties they exhibit: 1) assemblies that mimic the cage-like nature of enzymes, 2) assemblies that mimic the allosteric nature of enzymes, and 3) assemblies that

mimic the dissymmetric nature of enzyme active sites. Though there has been a great deal of progress made in the assembly of such structures, there is still very little overlap seen between these classes. The ultimate goal of an enzyme mimic is the design of a structure that combines aspects of all three classes into one entity. A promising avenue appears to be the significant recent progress in the design of functionalized endohedral macrocycles and capsules,[19] which in combination with heteroligated approaches could lead to more sophisticated enzyme mimics that combine rate increase as a consequence of proximity effects with transition-state stabilization by several functional groups.[92] The screening approaches discussed in section 4 may facilitate the identification of such species. In the realm of allosteric detection, the expansion of target molecules may be most important. The integration of regulation, recognition, and catalysis as observed in enzymes and the formation of active pockets that contain multiple catalytically active functional groups remains a major challenge.

6. Addendum

The field of supramolecular enzyme mimics is rapidly progressing and significant advances have been made since the submission of this Review. Two relevant review articles on supramolecular catalysis have recently been published by Yoshizawa and Fujita[112a] and Meeuwissen and Reek.[112b] In addition, there have been numerous reports of related work that have recently appeared in the literature, including the enzyme-like catalysis of the Nazarov cyclization by complex **32** (see section 2.2.4) by Raymond, Bergman, and coworkers,[112c] and the synthesis of an allosteric supramolecular triple-layer catalyst used for the ring-opening polymerization of ε-caprolactone by our group,[112d] among others.[112e–s]

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