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Supramolecular catalysis: Part 2: Artificial enzyme mimics.

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The design of artificial catalysts able to compete with the catalytic proficiency of enzymes is an intense subject of research. Non-covalent interactions are thought to be involved in several properties of enzymatic catalysis, notably: i) the confinement of the substrates and the active site within a catalytic pocket, ii) the creation of a hydrophobic pocket in water, iii) self-replication properties and iv) allosteric properties. The origins of the enhanced rates and high catalytic selectivities associated with these properties are still a matter of debate. Stabilisation of the transition state and favourable conformations of the active site and the product(s) are probably part of the answer. We present here artificial catalysts and biomacromolecule hybrid catalysts which constitute good models towards the development of truly competitive artificial enzymes.

1. Introduction

A conventional route to produce an effective artificial enzyme is to reproduce the sometimes elusive structure of the enzyme active site (model enzymes).[1] An alternative relies on mimicking the functions of enzymes without copying its structure (enzyme models or mimics). Following the Pauling principles, non-covalent interactions were designed to recreate these properties with artificial systems.[2–4]

In the 1970s the first supramolecular catalytic examples featured under the heading of host-guest chemistry or catalysis, and enzymes were the source of inspiration.[5–10] The main idea pursued was the use of the lock-and-key principle borrowed from the knowledge on enzymes; a substrate fits nicely in a host molecule that also carries a catalytic function thus enhancing the rate of reaction, while spatial factors may induce regioselectivity. Alternatively, two substrates may bind into a cavity and undergo for instance a selective Diels–Alder reaction.

It is not surprising that cyclodextrins constitute the first hosts used to reproduce the enzyme hydrophobic pocket at a small molecular level.[11] The pioneering works of Breslow and Tabushi inspired subsequent research and highly efficient catalytic systems, working under enzyme conditions (pH, temperature).[12,13]

Bringing together the reactive site and the substrate(s) is a strategy commonly used in classical homogeneous catalysis. For example, the reactivity of a C–H bond is increased by incorporating a directing group in the substrate that will coordinate the metal centre and bring the targeted bond in close proximity to the metal. However, in catalysis involving a host and one or several guests, concentration of the reactants near of the reactive centre is not the only advantage. Desolvation of the reactants/transition state, stabilisation of the transition state, favourable conformation of the product within the catalytic pocket are other important parameters that occur in enzyme catalysis and that can be used to design artificial catalysts.

Some systems are simple and the development may have been relatively fast, but others are rather complicated and their development and synthesis, for example those involving covalent hosts, may have required several years. Cram reported the thirty-step synthesis of a cryptand incorporating a reactive centre as a mimic of chymotrypsin![14] Dendrimers,[15] molecularly imprinted polymers[16–19] and catalytic antibodies[20] also constituted old approaches inspired by the ability of enzymes to stabilise transition states.[21–23]

In the last ten years, innovative systems were designed based on the well-defined construction of cages and spheres through ligand-metal interactions. Fujita[24,25] and Raymond and Bergman[26] groups notably investigated square and tetrahedral hosts respectively for various catalytic reactions in water. More recently, metal-organic frameworks were used as hosts able to trap and make guests react in their porous network.[27–31] Supramolecular catalysts were not only tested for enzyme reactions but non-natural reactions were also targeted.

In the so-called host-guest catalysis, non-covalent interactions help to construct the hosts, to trap the guests within the host, and to other catalytic aspects such as transition state stabilisation. However, secondary interactions also played a role in others functions displayed by enzymes. In water, the construction of a hydrophobic pocket allows for a close proximity between the reactive centre and the reactants. In self-replication, autocatalysis is also achieved by facilitating the contact between the reactants. This analogy encourages us to incorporate in this review artificial catalysts mimicking these enzyme functions. The reversibility of non-covalent interactions is also used for the design of allosteric catalysts. This field is increasing greatly with the aim of developing catalysts that can be easily switched and modulated during the catalytic process.

Rebek pioneered the field of enzyme mimics. He studied a variety of supramolecular catalysts which copy different functions of enzymes. Probably encouraged by the analogy between the various properties of enzymes, he developed cavitands for host-guest catalysis, very early examples of self-replicators,[32] and allosteric catalysts.[33]

We wish to incorporate in this review efficient artificial catalysts which copy different properties of enzymes. Metal or organic catalysts will be classified according to the enzyme properties they copy, but not the nature of the reaction catalysed. Hybrids between a biomacromolecule or a peptide and a metal or an organic catalyst will also be mentioned in section 6.

It's worth mentioning that previous reviews usually focus on one property of enzyme mimics. Our aim was to stress how supramolecular interactions can be used to copy the various functions of enzymes.[34,35] These catalysts offer innovative approaches toward a better understanding of the enzyme´s mode of action but in addition they can be useful for the discovery of unprecedented reactivity. We will highlight efficient and recent examples but older references will also be provided.

2. Catalysis within a confined environment

2.1 Binding site in close proximity to a catalytic or a reactive centre

Enzyme models were designed following the idea that increasing the concentration of a substrate around its reactive centre should lead to reaction rate enhancement. In enzymatic catalysis and biocatalysis, secondary interactions hold the substrate near the catalytic centre in a favourable position and as a result rate enhancements up to 10^{10} $mol.L^{-1}.s^{-1}$ have been observed.

Initially, small supramolecular catalysts were considered which combined a binding site linked to a reactive centre. Likewise, catalysts acting as templates and possessing two or more binding sites bringing together the two reactants were investigated.[46–49] More recently, host molecules and supramolecules capable of surrounding partially or totally the surfaces of one or two reactants have emerged as catalysts. In these assemblies the structure of the host isolates the included guest from the bulk solution. Cyclodextrin (CD) derivatives present many advantages as supramolecular catalysts.[50,51] They are commercially available or easily accessible, have low toxicity, and apolar substrates are desolvated and trapped in their hydrophobic cavity. Cyclodextrins are water-soluble and they can be easily modified chemically. Thus, it is not surprising that they

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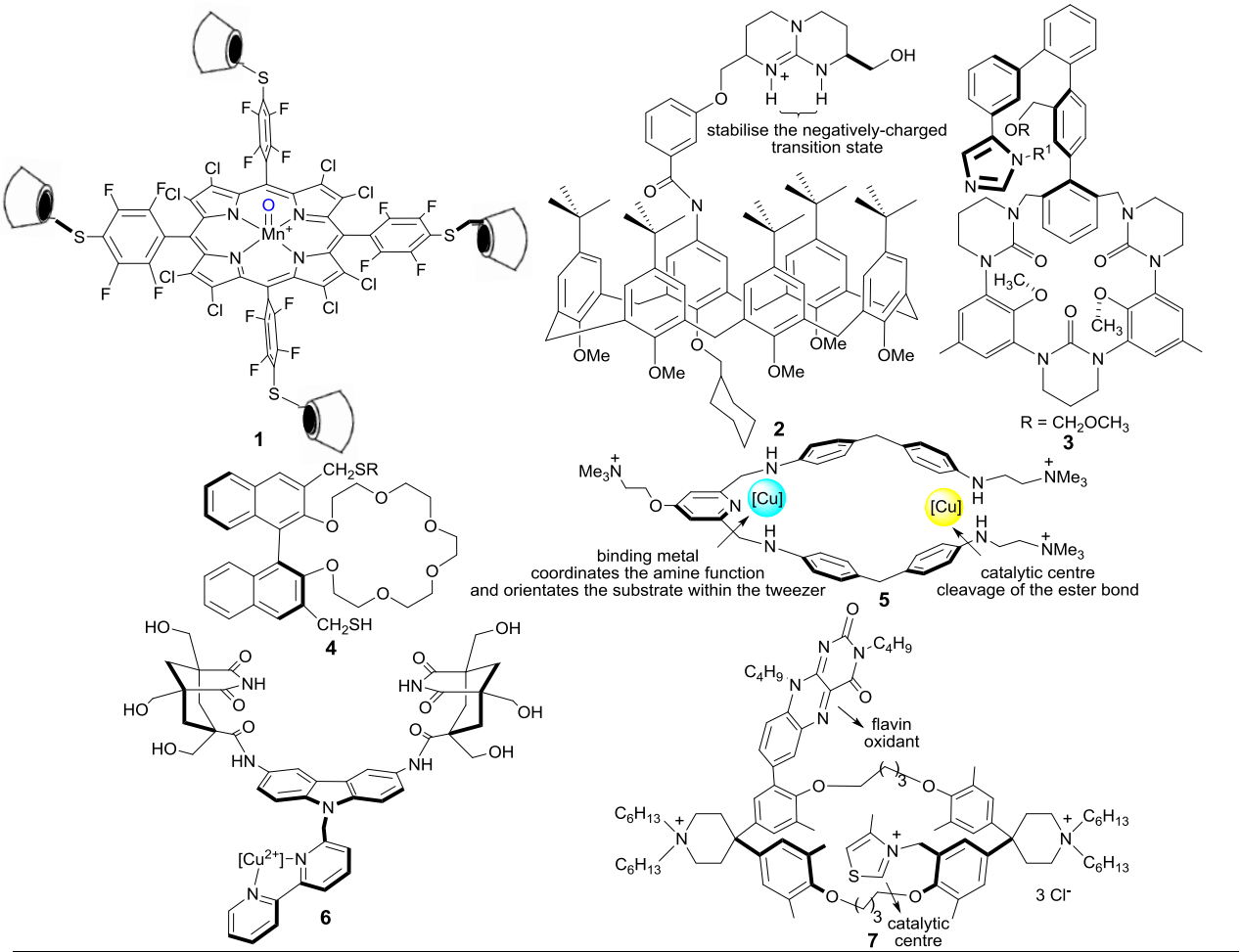

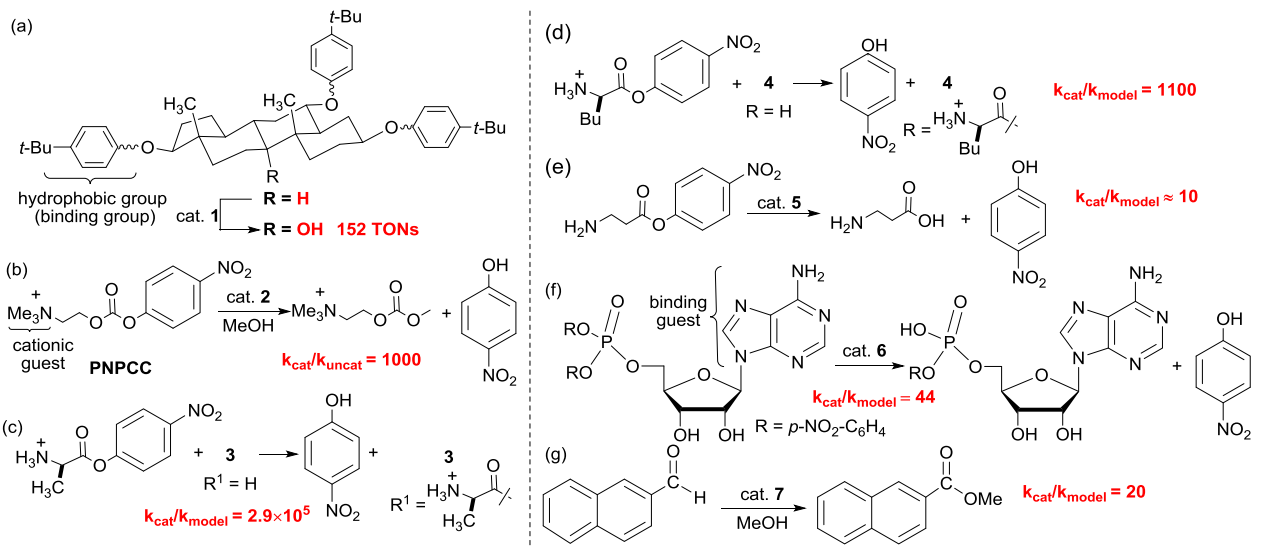

Fig. 1 Early examples of covalent hosts appended with a reactive centre. (a) Mn-porphyrin **1** covalently linked to four β-cyclodextrins for selective C–H hydroxylation (cytochrome P-450 mimic). Pyridine is not represented but is present in the active species to steer the oxygen atom bound to the metal and the bound substrate to the same face of the catalyst. *EM* cannot be determined in this case since the oxidation of this steroid with a Mn catalyst lacking the CD groups would be unselective.[36] (b) Calix[6]arene **2** appended with a guanidinium subunit,[37–39] PNPCC = *p*-nitrophenyl choline carbonate. (c) Spherand **3** bearing a nucleophilic imidazole group behaving as a transacylase mimic.[40] (d) Transacylation between crown ether **4** and an ammonium acid ester salt. **(*S*)-4** is more efficient for the transacylation of (*L*)- over (*D*)-ammonium acid ester.[41] (e) Tweezers-like metalloreceptor **5** for ester hydrolysis.[42] (f) Hydrolysis of phosphate triester with cleft **6** (*EM* from ref[43] = 0.58 M).[44] (g) Oxidation of aromatic aldehydes by the Flavo-thiazolio-cyclophane **7**.[45]

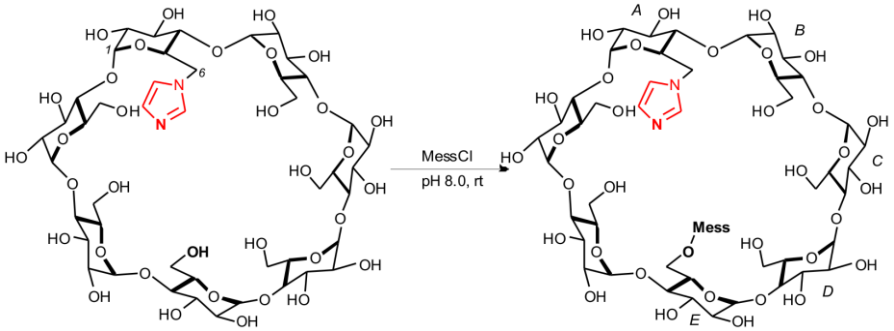

Fig.2 Sulfonylation of (1-imidazolyl)-β–CD afforded selectively 6^{A}-imidazolyl-6^{E}-mesitylenesulfonyl-β-CD. Numbering of the glucose carbons and labelling of the CD rings are indicated in italic. Mess = Mesitylenesulfonyl. Ref: see the text.

are one of the most investigated hosts in this domain. The combination of a cyclodextrin cavity and a catalytic centre probably constituted the older examples of designed supramolecular catalysts and, as a consequence, has been studied thoroughly. The reactive centre can be an organic or a metal-ligand catalyst.

The efficiency of the mimetic approach can be estimated by evaluating the properties of the artificial enzyme model in terms of kinetic behaviour [saturation kinetics characterized by the values of the Michaelis–Menten constant (K_m) and the maximum reaction rate (V_{max})], kinetic efficiency (rate enhancement, selectivity) and operation conditions (mild conditions such as reaction in water, pH = 7, ambient temperature). To determine the efficiency of the rate acceleration related to the increase of the concentration around the reactive centre, Kirby,[52] and later, Mandolini and co-workers[43,53] propagated the use of the effective molarity (*EM*) parameter.[1] This parameter was previously employed for intramolecular reactions: the *EM* was defined as the k_{intra}/k_{inter} ratio and corresponded to the concentration of reactants needed for the intermolecular reaction to proceed with a pseudo-first order specific rate equal to that of the intramolecular reaction.[52,54] Applied to supramolecular catalysts, the calculation of the *EM* is somewhat delicate because the determination of k_{inter} relies on the choice of reference reaction where the environment of the catalyst is similar to that found in the Michaelis complex (or in the host-substrate(s)-reactive centre ternary complex). For the supramolecular catalysts described in this section, the k_{inter} is usually obtained by performing the catalytic reaction with the reactive centre lacking the binding site.

Initially, cyclodextrins,[5,8–11,55–58] calixarenes,[37–39] crown ethers,[41,59–62] tweezers-like metalloreceptors,[42] Cram spherand derivatives,[14,40] Rebek clefts derived from Kemp's triacid[44] and Diederich cyclophanes[45,63–66] were coupled with reactive centre(s) and evaluated as enzyme models (see **1–7**, **Fig. 1**). Common enzymatic reactions such as hydrolysis (nuclease, protease and chymotrypsin mimics), esterification, transesterification (transacylase mimic), benzoin condensation (thiamine pyrophosphate mimics) and oxidations (MMO and cytochrome P450 mimics) have been extensively studied. These examples probably constitute the oldest approaches in the field of supramolecular catalysis and it has been reviewed elsewhere.[12,13,23,35,67–72] More recently, models for antioxidative enzymes (superoxide dismutase (SOD), glutathione peroxidase (GPx) and catalase) have been investigated as well as enzyme mimics for non-natural reactions.[35] However, it must be pointed out that despite the amount of mimics described in the literature only a few of them approach the efficiency of enzymes; some of these recent successful examples will be provided here.

Previously, an impressive 3.2×10^6 rate enhancement was obtained by Breslow et al. for the stoichiometric acylation of β-cyclodextrin by a rigid substrate (a ferrocene moiety appended with a *p*-nitro-phenyl ester group).[73] Recently, Yuan et al. demonstrated that 6-(1-imidazolyl)-α, β and γ-CD can be regioselectively sulfonated.[74] The imidazole group always transfers the sulfonyl function to the 6-OH group of the third glucose ring on the anomeric side of the imidazolyl glucoside residue. For example, the reaction between 6-(1-imidazolyl)-β-CD and mesitylenesulfonyl chloride gave exclusively 6^{A}-imidazolyl-6^{E}-mesitylenesulfonyl-β-CD despite the possible formation of twenty other isomers (**Fig. 2**). The regioselectivity can be explained by (i) the specific geometry of 6-(1-imidazolyl)-CD in which the first subunit of the anomeric side is shielded and (ii) the possible binding of the substrate within the cavity. In the same vein, an excess of a cyclodextrin conjugated with a palladium aqua complex was used for the selective cleavage of a peptide.[75]

Successful uses of the cyclodextrin platform for catalytic reactions were provided recently. Kunishima et al. designed a CD-based artificial catalyst as an efficient mimic of an acyltransferase for the amidation of carboxylates with ammonium salts.[76] Under classical conditions, the reaction requires a catalyst (*e.g. N*,*N*-dimethylglycine ethyl ester, **8**) and a co-catalyst (CDMT, **9**, **Fig. 3**) in order to activate the carboxylate function. The true active species is probably **10**, which results from the coupling of **8** and **9**. The enzyme model of **10**, a β_{Me}-cyclodextrin appended with a *N*,*N*-dimethylglycine ester group in its 6-

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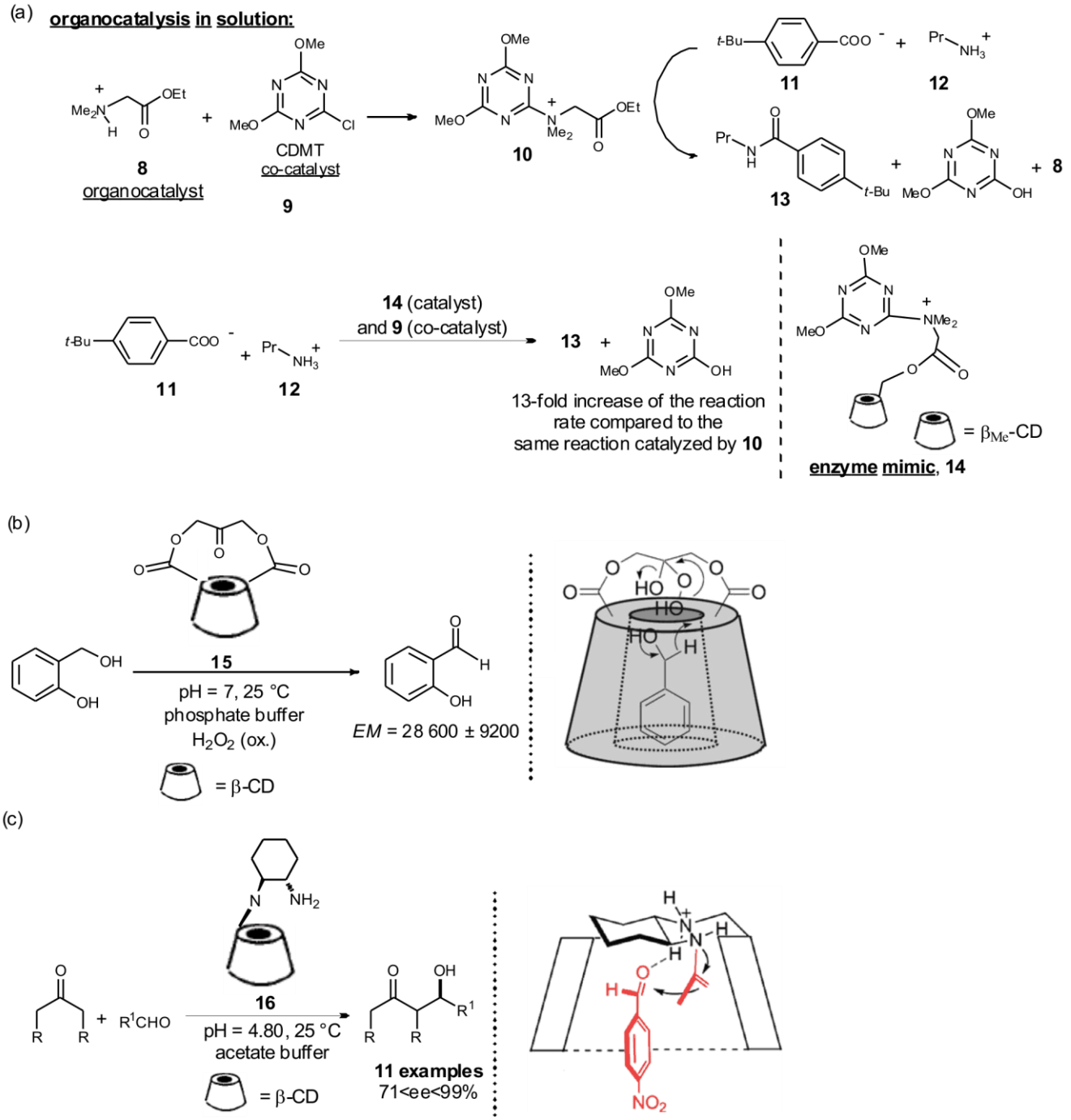

Fig. 3 Enzyme mimics consisting of a reactive centre covalently attached to a cyclodextrin. Refs: see the text. (a) Artificial acyltransferase. CDMT = 2-chloro-4,6-dimethoxy-1,3,5-triazine. (b) β-CD with dihydroxyacetone attached at the primary ring for the oxidation of various benzylic alcohols. Proposed mechanism for the oxidation of bound benzylic alcohol, a hydrogen bond between the hydroxyl group and a Lewis base is suggested. (The proposed mechanism is reprinted with permission from ref. 80. Copyright 2006. John Wiley and Sons). (c) Asymmetric aldol reaction catalysed by a β-cyclodextrin appended with a chiral cyclohexane diamine. Proposed transition state for the reaction between acetone and *p*-nitrobenzaldehyde showing a hydrogen bond between the cyclohexylammonium and the bound *p*-nitrobenzaldehyde. (The proposed transition state is reprinted with permission from ref. 85. Copyright 2010. American Chemical Society).

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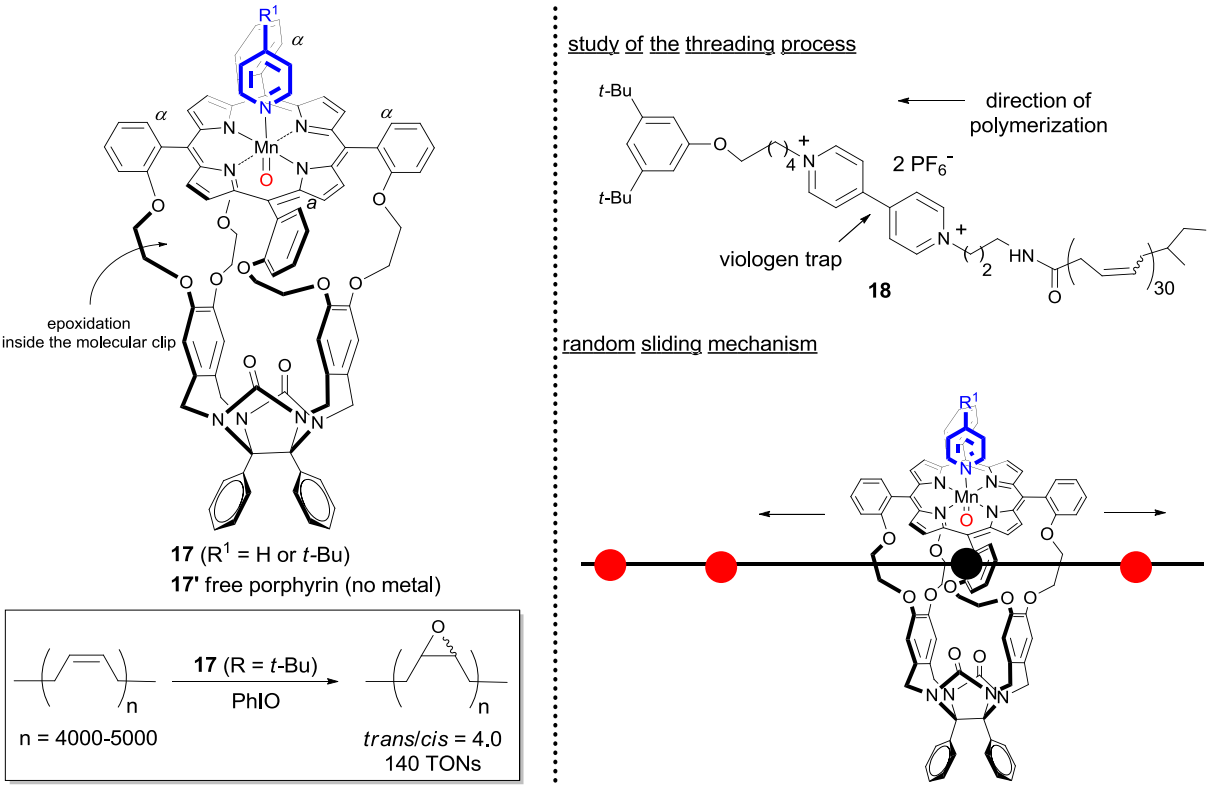

Fig. 4 Left: Oxidation of polybutadiene by catalyst **17** derived from a molecular clip. 80% of the conversion occurs inside the cavity; *trans*/*cis* = 0.3 for a reference catalyst. Oxidation of **18** by **17** and **17'** provided information on the threading process. A more efficient version of catalyst **17**, bearing ethylureapropoxy groups on the aromatic (positions *a*) has been reported recently. Right: representation of the random sliding mechanism. Refs: see the text.

hydroxy position (**14**), selectively amidates 4-*tert*-butyl-benzoate **11** over 3,5-dialkyl-benzoate. For the amidation of 4-*tert*-butyl-benzoate **11** with propylammonium chloride **12**, product **13** is formed with a rate enhancement of 13 in the presence of **14** compared to the same reaction catalysed by **10** (**Fig. 3, a**). Bols and co-workers showed that α- or β-cyclodextrins with a dihydroxyacetone unit attached to the primary rim are efficient catalysts for oxidation reactions.[77–80] For example, for the oxidation of 2-hydroxy benzylic alcohol with H_2O_2, catalyst **15** (**Fig. 3, b**) followed Michaelis–Menten kinetics (k_{cat} = 6.2 × 10^{-6} s^{-1} and K_M = 1.3 mmol.L^{-1}) and provided the product with an *EM* almost equal to 30,000 at enzymatic conditions (room temperature, water, pH = 7).[80] A reaction mechanism is proposed where H_2O_2 first reacts with the bridged ketone and then the bound substrate is oxidized, the oxidation step being probably assisted by hydrogen bond interactions (see the proposed mechanism represented in **Fig. 3, b**). The same group evaluated other cyclodextrin derivatives as catalysts, for example, ones having bridged ketones at the primary rim or ketone/aldehyde functions at the primary/secondary rim. Both types were tested in various oxidation reactions.[81–84] Hu et al. proved that a privileged organocatalytic unit (chiral cyclohexane diamine) covalently linked to the primary rim of β-cyclodextrin constituted an excellent combination. Indeed, the resulting supramolecular catalyst is highly efficient for the direct aldol reaction of symmetric ketones with aromatic aldehydes in aqueous buffer (25 °C, pH = 4.80).[85] Catalyst **16** (**Fig. 3, c**) with a (*S*,*S*)-diamine side chain is a better catalyst than its analogue bearing the (*R*,*R*) enantiomer. Structural orientation of the enamine intermediate, as well as secondary interactions occurring during the transition state inside the β-cyclodextrin cavity, are at the origin of the observed enantioselectivity.

Inoue and co-workers investigated β-cyclodextrins functionalized with a monobenzoate unit for the enantioselective *Z*→*E* photoisomerisation of (*Z*)-cyclooctene in methanol-water mixtures.[86–89] The strategy here is slightly different from the ones described above since the benzoate unit is not really a catalytic centre but rather acts as a photosensitizer that accelerates the rate of energy transfer and probably isomerisation of the cyclooctene molecule takes place inside the cyclodextrin cavity.[90] Careful choice of the substituent introduced to the sensitizer moiety in the modified β-CD promotes the reaction with an ee up to 46% at an

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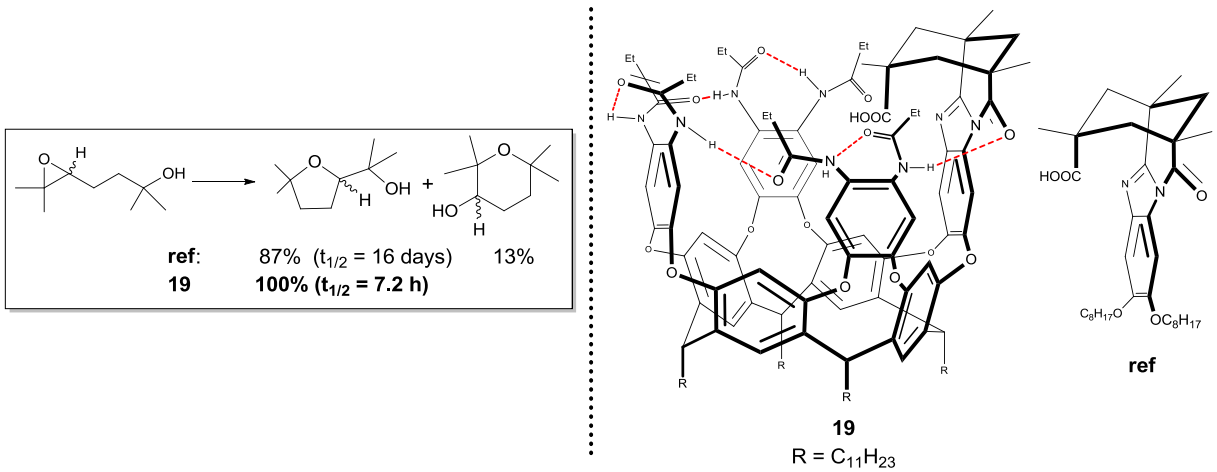

Fig. 5 Cavitand receptor **19** with an inwardly-directed carboxylic acid function catalysed the cyclization reaction of epoxyalcohols. The reaction is totally regioselective as a result of attractive interactions between the substrate and the electron-rich aromatic surface of the cavitand. Refs: see the text.

E/*Z* ratio of 0.24.[91,92] The same group[93,94] reported that anti-Markovnikov photoaddition of water and methanol to 1,1-diphenylpropene is catalysed by a β-CD linked to a 5-cyanonaphthyl group used as sensitizer.[95,96] Recently, cucurbit[7]uril was employed for promoting selective photodeazetation reactions in biphasic medium.[97] The presence of a metal cation located at the upper rim of the cucurbituril host directed the selectivity of the reaction by means of ion-dipole interactions.[98–104]

Crown ethers appended with carboxylic acids were evaluated as mimics of aspartic proteinase.[105] The hydrolysis rate of various *p*-nitrophenyl esters derived from α-ammonium acids was evaluated in the presence of an excess of different supramolecular crown ether catalysts. Depending on the hosts, *EM* varied from 1 to 4000. A mechanism is proposed where the ammonium function is bound by the crown ether, facilitating the reaction between the ester function of the substrate and the appended acid function of the crown ether, the resulting anhydride intermediate being cleaved by a methanolate anion.

Calixarene[106,107] and crown ether[53,108–110] derivatives can be used as first coordination sphere ligands for placing two metal centres in an ideal position for cooperative activation of a substrate. Several phosphine-appended calixarene[111–125] and cyclodextrin[126–132] derivatives have been investigated as ligands in metal catalysis but only in a few cases the importance of the binding of the substrate within the cavity during the catalytic process has been demonstrated.[125,130] The same is true for other types of ligands or organocatalytic functions located at the upper part of calixarene or cyclodextrin backbones.[11,36,71,133–137] The effect in catalysis of a non-catalytically active guest, which blocks the access of the cavity to the substrate, is a suitable control experiment to determine the exact role of the binding pocket. Monflier and co-workers employed a water-soluble diphenyl monophosphane permethylated-β-CD for the rhodium-catalysed hydroformylation of sodium 10-undecenoate, a substrate that interacts with the CD cavity.[130] The activity is high in comparison with catalytic experiments performed with substrates that do not interact with the cyclodextrin pocket. The addition of sodium 1-adamantanecarboxylate that competes with the substrate for binding of the CD cavity strongly reduces the activity of the catalyst. This demonstrates that the presence of the free recognition site in the close proximity of the metal catalyst greatly improves the catalytic activity when the substrate is able to interact with this site.

In addition to cyclodextrins,[138–149] calixarene, cucurbit[n]uril and crown ethers as binding pockets of enzyme mimics, more sophisticated synthetic hosts were investigated in order to broaden the scope of substrate and reaction, and to gain insight in this kind of catalysis.

In the system developed by Nolte,[150] a glycoluril clip molecule is capped with different type of metal complexes and investigated as a catalyst for hydrogenation/isomerisation of olefins,[151,152] phenolic oxidation,[153] oxidation of benzylic alcohols[154] and the epoxidation of simple alkenes and polyolefins in the presence of an oxidant and an axial ligand (**Fig. 4**).[155–161] In the latter case, the nature of the axial ligand is particularly important because the use of a hindered pyridine allows for the catalysis to occur preferentially or completely inside the cavity. As a consequence, catalyst **17**, with pyridine as an axial ligand, is less prone to decomposition than Mn-porphyrin catalysts lacking the binding site.[155] In the presence of *tert*-butyl-pyridine, polybutadiene is oxidized inside the cavity and *trans*-polybutadieneepoxide is obtained selectively (140 turnovers, **Fig. 4**).[156] The threading process of a Zn-analogue of catalyst **17** with a series of polymers was studied in detail. A blocking group and a viologen unit (association constant of 10^6–10^7 L.mol^{-1} for the host) are located

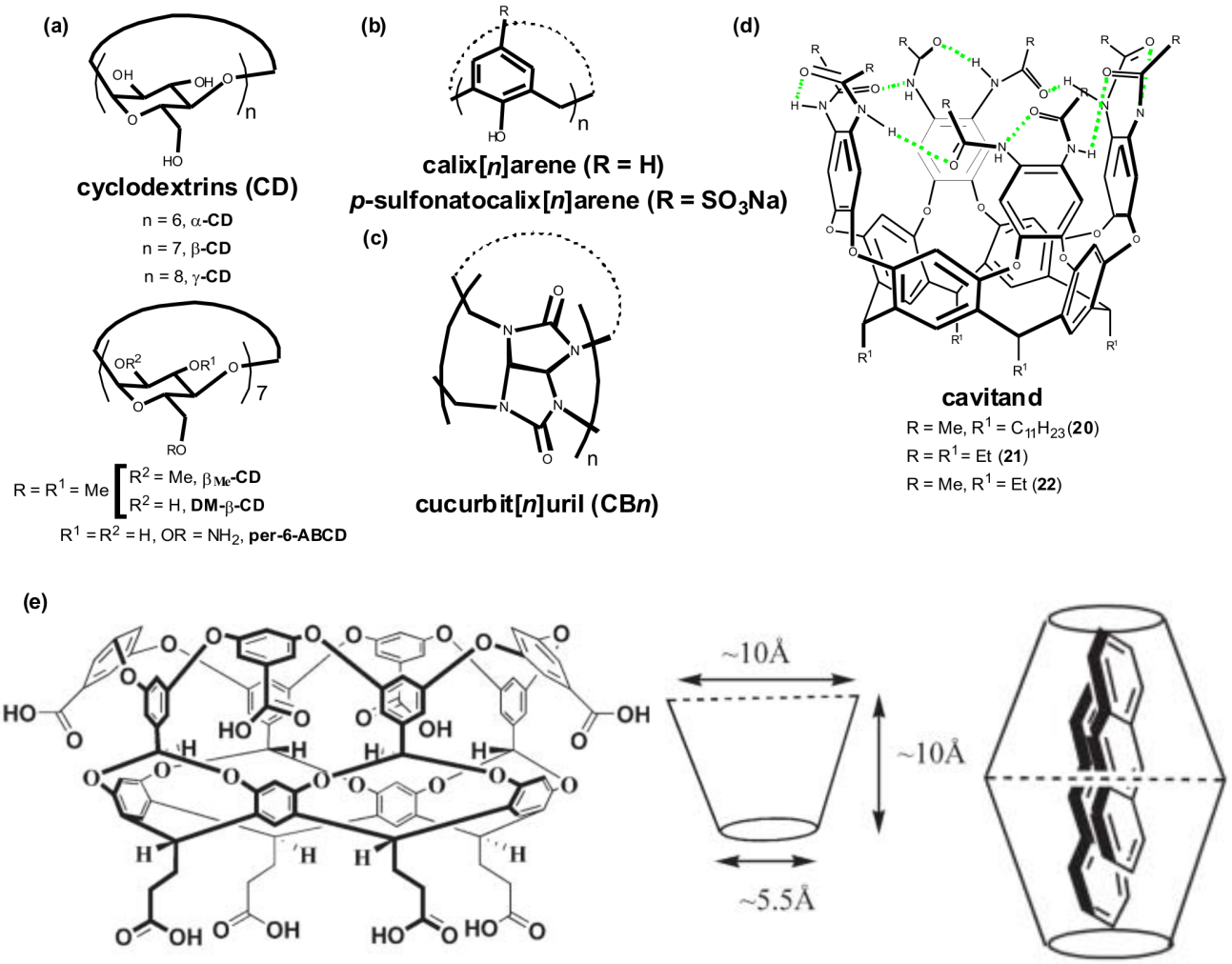

Fig. 6 Examples of covalent hosts used in supramolecular host-guest catalysis. (a) Cyclodextrins. (b) Calixarenes. (c) Cucurbituril. (d) Rebek cavitands **20-22**. (e) Gibb octaacid capsule: upon addition of apolar guests, the two molecules of host form a capsule (the formation of a hydrophobic pocket is the driving force). See here in the case of anthracene guests (host:guest ratio 1:1). (Structure of the octaacid and representation of the host-guest complex are reprinted with permission from ref. 291. Copyright 2007. The Royal Society of Chemistry).

at the end of the polymers, and thus fluorescence quenching of the viologen signified that the macrocyclic host threaded on the polymer and moved toward the viologen trap.[159] The threading is controlled by the presence of the axial ligand *i.e.* that the presence of a pyridine ligand inside the cavity almost completely inhibits the binding of the polymer. The threading has to overcome an entropic barrier likely related to the stretching and unfolding of the polymer chain. This threading process is reminiscent of processive enzymes such as DNA polymerase III and λ-exonuclease.[160] Finally, by comparing the sliding rate of **17** and **17'** along the polymer **18** and the oxidation rate of catalyst **17**, a random sliding mechanism for the oxidation of polybutadiene seems more plausible than a stepwise processive mechanism (**Fig. 4**).[157] A limitation of the system is the need of an excess of bulky axial ligand in order to prevent catalyst deactivation and to promote catalysis inside the cavity. Recently, the catalytic system was improved by attaching ethylureapropoxy tails in positions *a* of complex **17** (**Fig. 4**), one of them being coordinated to the Mn centre.[161] Compared to **17**, this catalyst is more stable and more active, favouring the formation of the *trans*-epoxide product because the polybutadiene is effectively oxidized within the cavity.

Based on the resorcinarene backbone, Rebek and co-workers developed a family of self-folding cavitands.[162–164] The hydrogen bonding between the amide functions present at the upper rim led to an energetically more favourable vase-like conformation for these molecules. The chiral, hydrophobic cavity is perfectly designed to encapsulate a variety of guests, mainly stabilised by cation-π and C–H-π interactions, and to isolate them from the bulk solution. Among other applications,[163,165] these cavitands can be used as supramolecular catalysts by positioning reactive groups towards the interior of the cavity.[165–168] Choline and its derivatives are particularly suitable guests for this class of cavitands.[167–169] The aminolysis of *p*-nitrophenyl choline carbonate **PNPCC** (see **Fig. 1** for the formula) is accelerated within a cavitand appended with a pyridone.[166] The same

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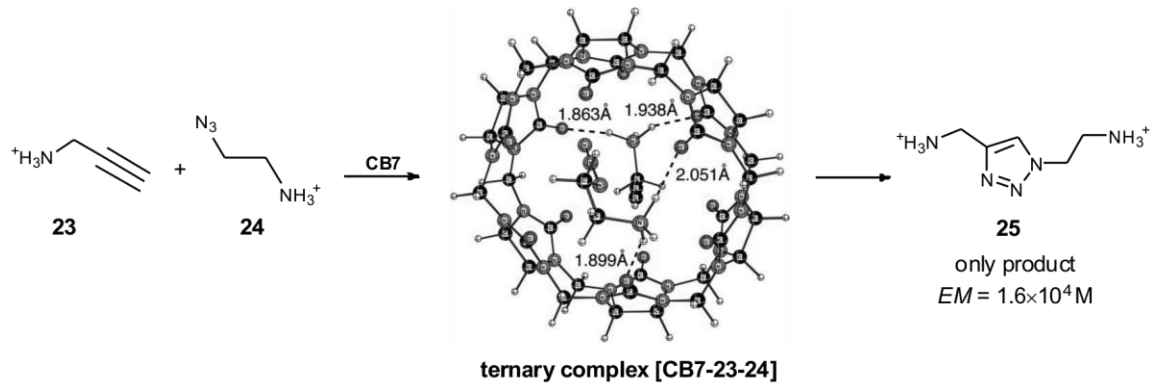

Fig. 7 CB7 strongly accelerates the 1,3-dipolar cycloaddition between **23** and **24**. Structure of the ternary complex as proposed by Maseras and co-workers. (The structure of the ternary complex is reprinted with permission from ref. 238. Copyright 2007. The Royal Society of Chemistry.). Refs: see the text.

substrate is hydrolysed by a cavitand functionalized with a Zn-salen complex at the upper rim. At 20 mol% of catalyst, a 12-fold increase of the reaction rate is observed compared to the uncatalysed reaction (*EM* = 6 if a Zn-salen catalyst lacking the host unit is taken as a reference).[167] The same catalyst is able to selectively acetylate choline over triethylcholine because the latter does not fit inside the cavity.[168] Cavitands have been designed which possess an inwardly-directed aldehyde[170,171] or carboxylic acid function.[172–174] The stoichiometric reaction between the cavitand capped with an aldehyde function and a primary amine allows for the observation of the hemiaminal, a high-energy intermediate towards the formation of the imine bond. The cavitand provides a perfect environment that preorganises the substrate and stabilises the hemiaminal intermediate and in the meantime one of the amide function acts as an acid/base catalyst in the dehydration step.[175] Organocatalysis was successfully performed with **109**, a cavitand that possessed an inwardly-directed carboxylic acid. Intramolecular ring-opening reaction of 1,6-epoxyalcohols was accelerated and gave THF derivatives as the main cyclic ether products (**Fig. 5**).[172] C–H-π contacts between the alkyl chain of the substrate and the aromatic wall of the host allow for the coiling of the substrate inside the cavity. Such coiling is thought to be responsible for both the selectivity and rate enhancement observed with catalyst **19**. Hydrogen bond interactions between the hydroxyl group of the substrate and the carboxylic acid function of the host is required to form the Michaelis complex.[173] However, the hydroxyl group can also interact with the amide function and disrupts the vase-like conformation of the cavitand. At high substrate concentration, this interaction leads to a drastic decrease of the reaction rate.

Up to now, most of the reactive centres have been attached at the upper part of the host. Metallocavitands,[176] for which the metal participates to the construction of the cavity, are of interest for studying chemical reactivity and catalysis only if coordination site(s) on the metal remain available for guest coordination and activation. Kersting and co-workers investigated dinuclear complexes of *Robson*-type macrocyclic ligands.[177,178] The metal-bridging chloride located within the cavity can be replaced by various metal-bridging anions. Unusual selectivities have been observed for stoichiometric dibromination[179] and Diels-Alder reactions[180] performed inside the metallocavitand. A series of hemicryptophanes[181–184] have been studied recently that can bind metals in their inner pocket. It opens new avenues for the development in catalysis of supramolecular hosts that possess an *endohedral* functionalization.

2.2 Host-guest catalysis

Section 2.1 dealt with supramolecular catalysts consisting of a binding cavity and a catalytic centre linked together. The catalytic reaction can be envisioned as intramolecular for the host-guest-catalyst complex. Hosts can also constitute by themselves a platform for reactions involving more than one reactant and, if enough stabilisation of the transition state occurs inside the cavity, no additional functions or catalytic centres are required. However, additional challenges have to be overcome in this case. When two different substrates are involved, the hetero complex involving the host and the two different substrates must be favoured compared to the respective homo complexes. Like in enzymes, the rate-determining step is usually the release of the product from the host and $k_{obs} < k_{cat}$ (k_{cat} being the rate constant of the reaction between the guests within the productive host-guest complex). The *EM* is corrected by taking into consideration the proportion of productive complex in the system but a difficulty here is that the Michaelis complex must be well characterized. To be more efficient than in solution, the reaction between the encapsulated guests must be driven by substrate(s) ground state destabilisation, transition state stabilisation or/and optimal orientation of the substrate (entropic gain), thus obeying Pauling's principles.[2–4] Additionally, solvophobic interactions

within the cavity can play a positive role during the catalysis through desolvation of the reactants or the transition state and lack of solvent molecules reorganisation.

Reactions performed in a confined environment can also lead to unusual selectivity, *i.e.* the reaction pathway of a reaction inside a host will be different from that of the same reaction in solution because of specific orientation of the substrates inside the host. Two different types of hosts have been used: the first category is constituted by covalent, rigid hosts (as the ones mentioned in section 2.1) and the second one is constituted by architectures built on non-covalent interactions. Catalytic reactions in confined spaces (from small well-defined host molecules to macromolecules, biomolecules, polymers and dendrimers) were the subject of recent reviews and here only a few successful and recent examples will be described.[18,25,70,185–187] The most successful examples are constituted by supramolecular systems which are truly catalytic: a challenging task due to commonly occurring catalysis inhibition by irreversible product or substrate binding of the host. Other interesting roles of covalent or non-covalent hosts include the stabilisation of otherwise unstable molecules,[188–200] the chemistry of reactive species within the host,[192,194,197] the reversible encapsulation of reactants,[201–203] self-sorting,[204] social isomerism,[205] the reversible binding of dyes,[206] drug delivery[207] and the monitoring of enzyme reactions,[208–213] all of them are outside the scope of this review.

2.2.1 Covalent hosts

The catalytic behaviour of non-modified cucurbit[7]uril[98-104] (**CB7**) and β-cyclodextrins (**DM-β-CD** and **β-CD**) was compared for solvolysis reactions (see **Fig. 6** for the formulae of the hosts).[214,215] In the case of the hydrolysis of 1-bromoadamantane, both **CB7** and **β-CD** hosts inhibit the reaction (lower rates than those for the reaction performed in water) because of their poor ability to "solvate" the Br^- leaving group. For the solvolysis of benzoyl chloride, a different behaviour is observed. **CB7** catalyses the solvolysis of electron-rich benzoyl chlorides whereas **DM-β-CD** inhibits the reaction. This can be explained by the ability of **CB7** to stabilise the acylium cation, developed in the transition state, through electrostatic interaction with its ureido rim. With electron-poor benzoyl chloride, the reaction is globally inhibited for both guests but **DM-β-CD** catalyses the solvolysis of 3- and 4-nitrobenzoylchloride probably as a consequence of the participation of the hydroxyl groups in the reaction. Cyclodextrins can accelerate the hydrolysis of various acetal[216] and nitrite[217,218] compounds but the efficiency strongly depends on the nature of the CD used (α, β or γ) and the pH of the reaction. Cucurbituril hosts have a positive effect on the hydrolysis of carbamate, amide and oxime functions in water.[219] Once again, the urea functions play a crucial role in the host-guest complex by facilitating the protonation of the substrate. The pKa of the substrate is locally increased, the overall host acting as an "acid substitute". The groups of Divakar,[220] Rao,[221–224] Nageswar,[225–229] and Kaboudin[230] showed that a stoichiometric amount of non-modified β-cyclodextrin strongly accelerates numerous bimolecular reactions in water. Pitchumani et al. used *per*-6-amino-β-cyclodextrin (**per-6-ABCD**, **Fig. 6**) for an asymmetric Michael addition[231] in water (ee up to 87%) as well as for other reactions.[232,233] Even though mechanistic details on these reactions are lacking, the entropic gain due to the fixation of one of the reactants inside the cavity, hydrophobic bonding and favourable control of the respective orientation of the reactants can be at the origin of the enhanced rates.

Breslow and co-workers studied the Diels–Alder reaction between cyclopentadiene and acrylonitrile in water. The observation that the hydrophobic effect led to an enhanced rate of this reaction in water compared to organic media initiated further investigation that will be discussed in section 3.[234] Interestingly, the reaction is further accelerated in **β-CD** (almost 10 fold compared to the reaction in water) but is retarded in **α-CD** because acrylonitrile is too big to be incorporated in this host. Further studies revealed that regioselective Diels–Alder reactions can also be performed inside the **β-CD** cavity.[11] Houk et al. compared the efficiency of various hosts, β-CD, Rebek's softball (**57**, **Fig. 13**), antibodies and RNAses to promote Diels–Alder reactions and computationally studied the reaction between diethyl fumarate and cyclopentadiene catalysed by **β-CD**.[235] Any of the hosts studied were able to strongly stabilise the transition state compared to the reactant or the product. In the case of **β-CD**, the rate enhancement originates from the entropy advantage gained by the binding of the substrates.

A successful example in this field was reported by Mock et al. in the 1,3-dipolar cycloaddition between **23** catalysed **24** catalysed by cucurbit[7]uril (**Fig. 7**).[236,237] The system featured several similarities with enzyme catalysis: (i) a well-defined ternary complex [**CB7-23-24**] is formed in which electrostatic interactions occur between the ammonium group of the substrates and opposite urea functions of the **CB7** host, (ii) the catalyst is highly active ($EM = 1.6\times10^4$ M) and selective (only regioisomer **25** is formed), (iii) the rate-determining step is the dissociation of the product from the host, and (iv) substrate inhibition is observed. Regarding the volume of the cavity (164 $Å^3$),[98] an encapsulated concentration of 10 M is, at the best, reachable by the reactants. Thus, the reaction efficiency is not only due to increased local concentration of the reactants. Mock stated that the rate enhancement can be explained in terms of "overcoming of entropic constraints" and "strain activation of bound substrates". A recent computational study of this system by Maseras et al. clearly argues in favour of the first statement whereas no evidence for transition state stabilisation was found.[238]

Photochemical reactions are a particular class of reactions in which proximity between the reacting groups and stabilisation of a given conformation in the ground and excited states are important parameters which influence the reaction pathway.[239,240] Activity and selectivity are greatly affected by the reaction media: the solid state,[240–246] within a liquid crystal,[247] presence of a stoichiometric[248–259] or a catalytic[260–262] amount of a hydrogen bond template,[263,264] zeolites,[265] dendrimers, micelles, and any other covalent or non-covalent hosts.[239,240] Cyclodextrin,[266–278] cucurbituril,[276,279–286] calixarene, and Gibb octaacid capsule[287–291] (**Fig. 6**) were used as hosts for intermolecular photochemical reactions in solution.[239] Compared to the reaction performed in isotropic solution and other reaction media, the use of these covalent hosts undeniably led to higher selectivity/activity, which can moreover be tuned by modifying the nature of hosts. Chirality is transferred through supramolecular interactions from the host to the guest[292–294] and ee values up to 55% were reported for the photocyclodimerization of anthracenecarboxylate

mediated by γ-cyclodextrin.[278] However, these reactions are not catalytic; the host ⊃ guest(s) complex (where ⊃ denotes encapsulation) is usually prepared stoichiometrically and irradiated. The catalytic use of a host has not been reported and probably it is hampered by product inhibition.

Template and confinement effects can also be used to direct radical reactions.[295] Ramamurthy and co-workers studied the intramolecular recombination of photochemically generated radicals inside water-soluble calixarenes,[296] Gibb octaacid capsule[290,297–300] and cyclodextrins.[301]

Isomerisation reactions in the solid state or in metal-organic frameworks (MOFs) were also reported.[245] For example, Fujita and co-workers used the coordination network of Zn-MOFs to perform olefin isomerisation[302] and the *Z*→*E* photoisomerisation of stilbenes[303] inside the pores. Even though not always catalytic, these reactions are interesting because of the specific reactivity observed in the confined space provided by the host.

Other applications of cyclodextrins and their functionalized derivatives in catalysis have been reported in the literature: i) as a trap for sequestrating a product in the course of a reaction occurring in the solution phase,[304] ii) as phase-transfer agents able to bind substrates and perform catalysis in the aqueous phase or at the organic/aqueous phase interface in the presence of a water-soluble catalyst, iii) as a means to generate low-coordinated organometallic complexes by reversible complexation of a phosphine ligand, and iv) as stabilisers of metal nanoparticles or metal clusters.[305–307] The *p*-sulfanatocalix[*n*]arenes (formula in **Fig. 6**) constitute another famous host family which can bind various guests in water.[69]

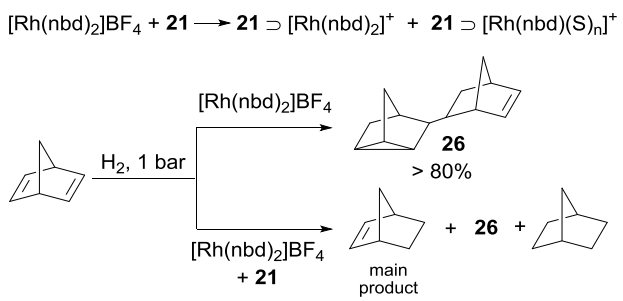

Fig. 8 $[Rh(nbd)_2]BF_4$ encapsulated inside **21** produces norbornene as the main product for the hydrogenation of norbornadiene. S = CH_2Cl_2. Ref: see the text.

Rebek cavitands, already mentioned in section 2.1 (**Fig. 5**), can also catalyse bimolecular reactions. For example, the deuteration of α,β-unsaturated ketones (with DABCO as a co-catalyst),[308] the Diels–Alder reaction[309] and the Menschutkin reaction[310] are accelerated within cavitands **20**–**22** (see **Fig. 6** for the formulae).[311] In all cases, the secondary amides at the rim are not innocent and are involved in hydrogen bond interactions with the reactant, or the intermediates of the reaction. In the case of the Diels–Alder reaction between the *N*-cyclooctylmaleimide and 9-anthracenemethanol, a 57-fold acceleration is observed in the presence of **20** compared to the uncatalysed reaction.[309] The dienophile is bound inside the cavitand *via* the cyclooctyl moiety by means of C–H-π interactions, and is activated *via* hydrogen bonds formed between its carbonyl groups and the amide functions of the cavitand. The diene and the product have low affinity for the cavity and no product inhibition is observed with this system. Two examples of catalysts encapsulated inside cavitands were reported recently. In acetic acid, Rebek showed that the Knoevenagel reaction between various aromatic aldehydes and malonitrile is catalysed in presence of a cavitand (derived from **21**) and piperidinium acetate as co-catalyst.[312] The piperidinium is bound in the cavity with the nitrogen atom near the open end of the cavity. The combined effects of the decrease in the degrees of freedom of the catalyst and the presence of a semi-circle of hydrogen bonding secondary amides probably facilitate the deprotonation of malonitrile which further reacts with the aromatic aldehyde outside the host molecule. One of the walls of the cavitand used in this reaction carries a *cis/trans* diaryldiazene group which renders the conformation of the whole cavitand photoswitchable. Only the *trans* isomer is catalytically active and thus the rate of the reaction can be manipulated with light. Ballester and co-workers showed that $[Rh(nbd)_2]BF_4$ readily loses one nbd ligand upon incorporation inside cavitand **21** (**Fig. 8**).[313] A mixture of **21** ⊃ $[Rh(nbd)_2]^+$ and **21** ⊃ $[Rh(nbd)(S_n)]^+$ catalysed the hydrogenation of norbornadiene into norbornene as the main product (pH_2 = 1 bar). The exact nature of the true active catalyst inside the cavity is unknown but its selectivity differs from that observed for the same reaction catalysed by $[Rh(nbd)_2]BF_4$ which predominantly yields the dimer **26**. The last two examples exploit host-guest affinity to modify the second coordination sphere of metal catalysts;[314] examples of such alteration *via* non-covalent interactions were also provided in **Part 1** of this review.[315]

Numerous other covalent host-guest catalysts were built following the Pauling's principle[2–4] that enzyme efficiency is related to their ability to stabilise the transition state of a given reaction by non-covalent interactions.[316] Sanders and co-workers precisely studied a series of cyclic metalloporphyrin oligomers (**Fig. 9**) as hosts for acyl-transfer reactions,[317] Diels–Alder,[318–320] and hetero Diels–Alder reactions.[321,322] The guests are pyridyl or imidazolyl derivatives which bind the zinc-porphyrin and adopt a respective orientation in the cavity which resembles the transition state of the reaction. For the acyl-transfer reaction between **27** and **28**, a 16-fold increase of the reaction rate is observed inside **29** compared to the uncatalysed reaction, but a more realistic *EM* of 0.67 M was found by Mandolini et al.[43] considering that the reactivity of **27** and **28** is also enhanced by coordination to the Zn centres.[317] Interestingly, no product inhibition occurs in this case. The modest rate enhancement can be explained by the formation of non-productive complexes or/and a non-optimal orientation of the reactants inside the cavity. Diels–Alder reactions are regioselective and exhibit higher enhanced rates.[318–322] They are performed with a stoichiometric amount of the host; in fact the product is so strongly bound that one X-ray structure of the host-product complex was reported.[322] The host presents some flexibility and is substantially distorted to accommodate the product. Recently, covalent Zn- and Al-porphyrin dyads, dimers, and boxes were found to catalyse the methanolysis of phosphate triesters (with a rate enhancement up to 430 compared to the uncatalysed reaction).[323,324]

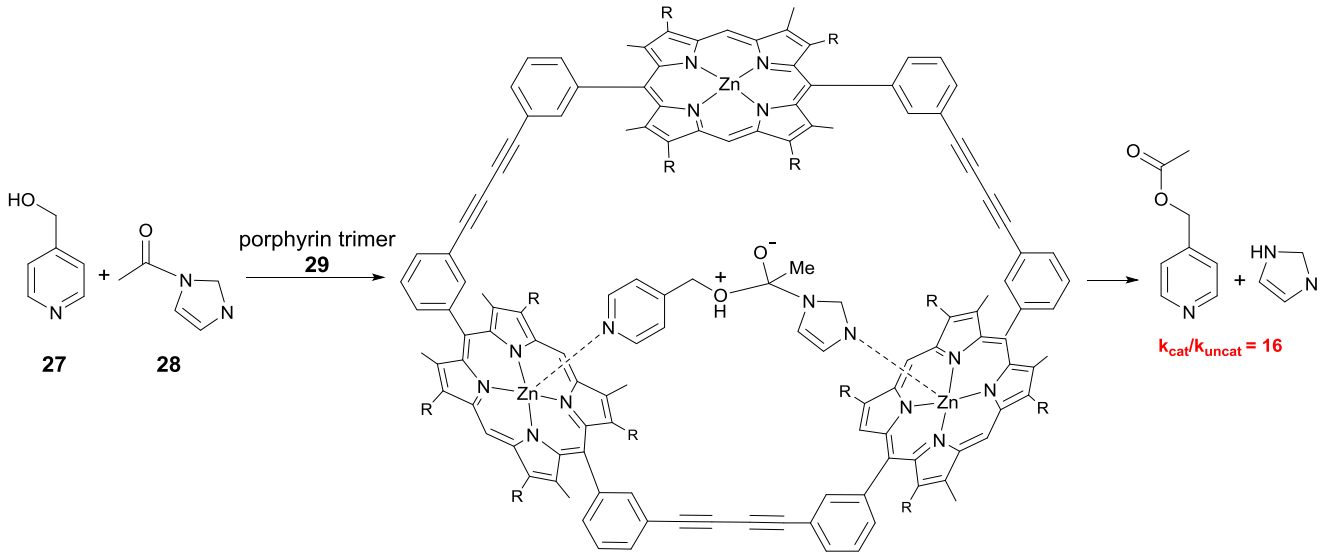

Fig. 9 Acceleration of the acyl-transfer reaction between **27** and **28** by the cyclic metalloporphyrin trimer **29**. Ref: see the text.

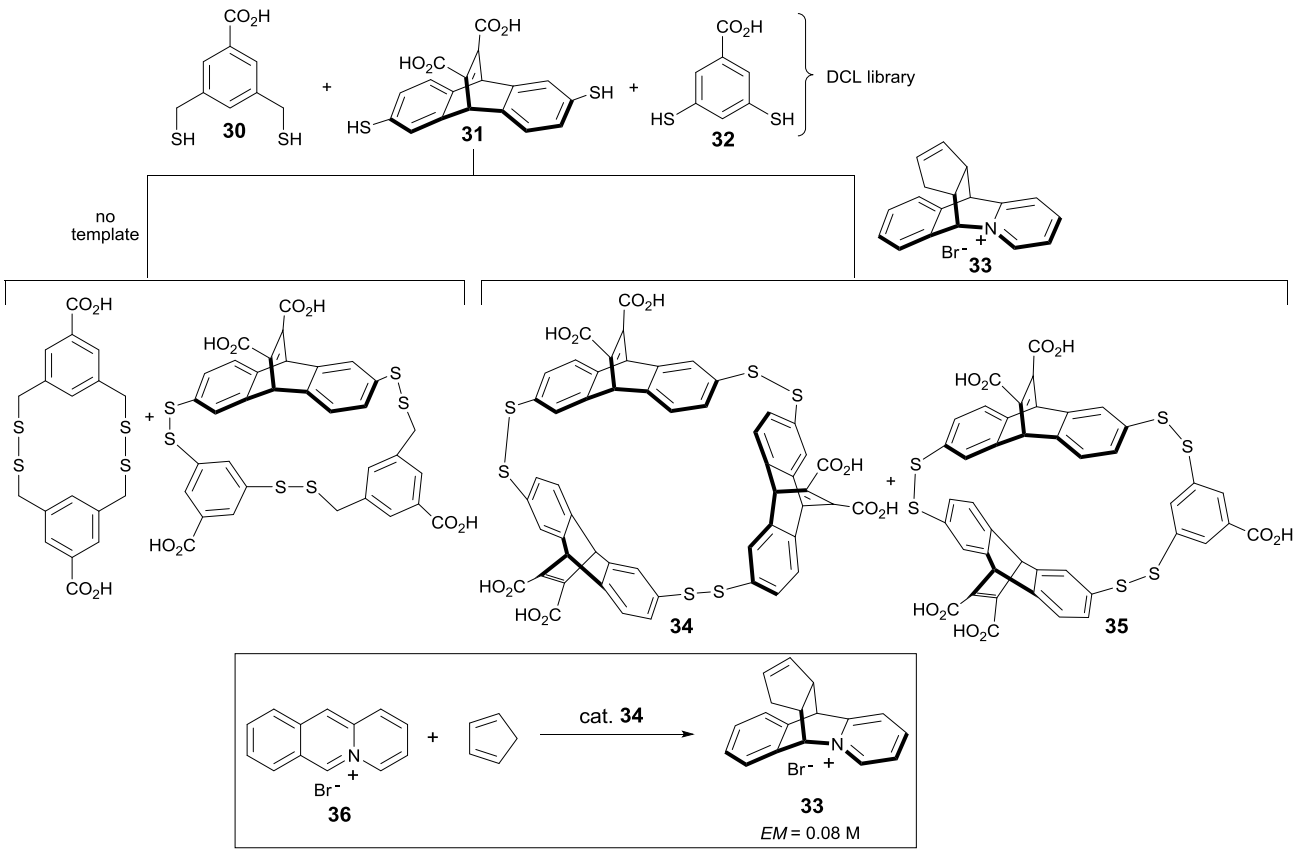

Fig. 10 Application of a DCL library in catalysis. **34** and **35** (as mixtures of stereoisomers) are amplified from the DCL library when **33** is present. Due to the similarity between the product and the transition state in the reaction between Cp and **36**, **34** is found to catalyse the reaction. Ref: see the text.

Always guided by Pauling's principle, hosts which possess high affinity for transition state analogues (TSA) were investigated as enzyme mimics. For example, consistent phosphate and norbornane derivatives are used as TSA of the transesterification (or ester hydrolysis) reaction and the Diels–Alder reaction respectively. Molecular imprinted polymers[16–19] (MIP) and catalytic antibodies[20,23] successfully used this strategy and enhanced rates were observed for a variety of reactions.[22] Early limitations of these systems were: (i) the inhibition of the catalysis by product binding (for the reaction where TSA and product have similar structures), (ii) a limited

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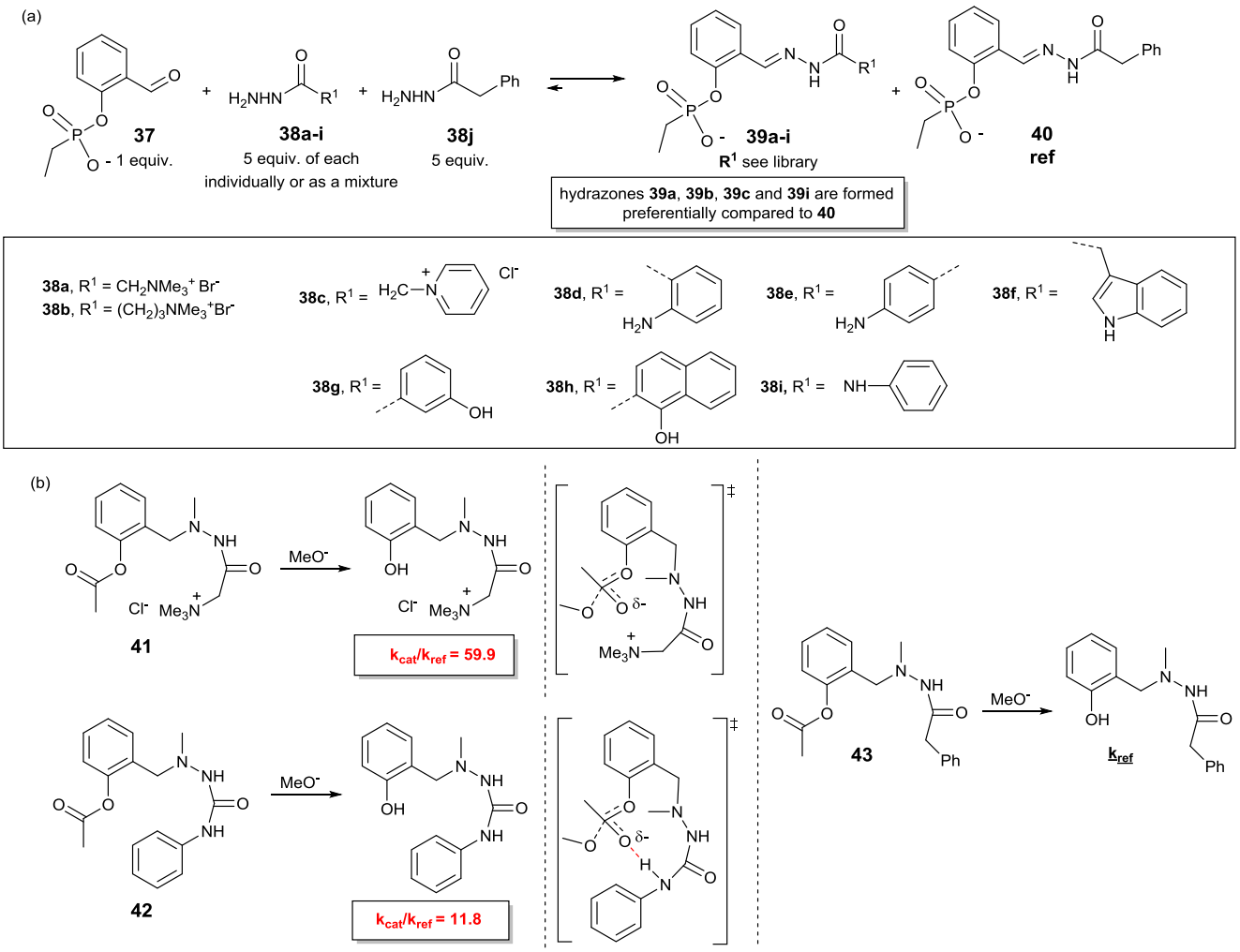

Fig. 11 (a) A hydrazone library is formed by mixing **37**, hydrazides **38a-i** (either as a mixture or individually) and **38j**. Hydrazides **38a-i** were chosen such as it could potentially interact with the phosphonate moiety either by electrostatic interactions (**38a-c**) or *via* the formation of one or more hydrogen bonds (**38d-i**). **38j** is taken as a reference since none stabilising secondary interaction is expected with this compound. Compared to **40**, hydrazones **39a**, **39b**, **39c** and **39i** are preferentially formed as a consequence of an intramolecular interaction between the phosphonate and the functional group present in the hydrazide unit. (b) Due to the analogy between the transition state of the transesterification reaction and the phosphonate group (represented on the right), methanolysis of **41** and **42** was investigated. Indeed, methanolysis of **41** and **42** is faster than that of **43** due to the stabilisation of the transition state through intramolecular secondary interactions. Ref: see the text.

substrate and reaction scope for each catalyst since they are specific of one TSA, and (iii) limited efficiency due to structural discrepancy between the TSA and the exact transition state. In fact, recent examples in both fields highlight the fact that the transition state stabilisation strategy can be surpassed by other approaches; see for example the "reactive immunization" strategy[325] in catalytic antibodies as well as the MIP catalysts developed for esterolysis by Wulff and co-workers.[326–329] MIP can also be used to specifically encapsulate a given enzyme. Once confined within the MIP, the substrate recognition site of the enzyme is hardly accessible; the MIP acts as an efficient inhibitor.[330, 331]

A dynamic combinatorial library (DCL) is composed of several components in thermodynamic equilibrium. The equilibria can be shifted towards one of the library's components by the addition of a template or by applying various stimuli.[332–338] Among other applications, DCL have been used in catalysis. If the template employed for the amplification/selection of DCL members is a TSA, the resulting members of the library with stronger binding capabilities are potential host-guest catalysts.

One example of this concept was reported by Brisig et al.[339] These authors found that the proportion of molecules **34** and **35**

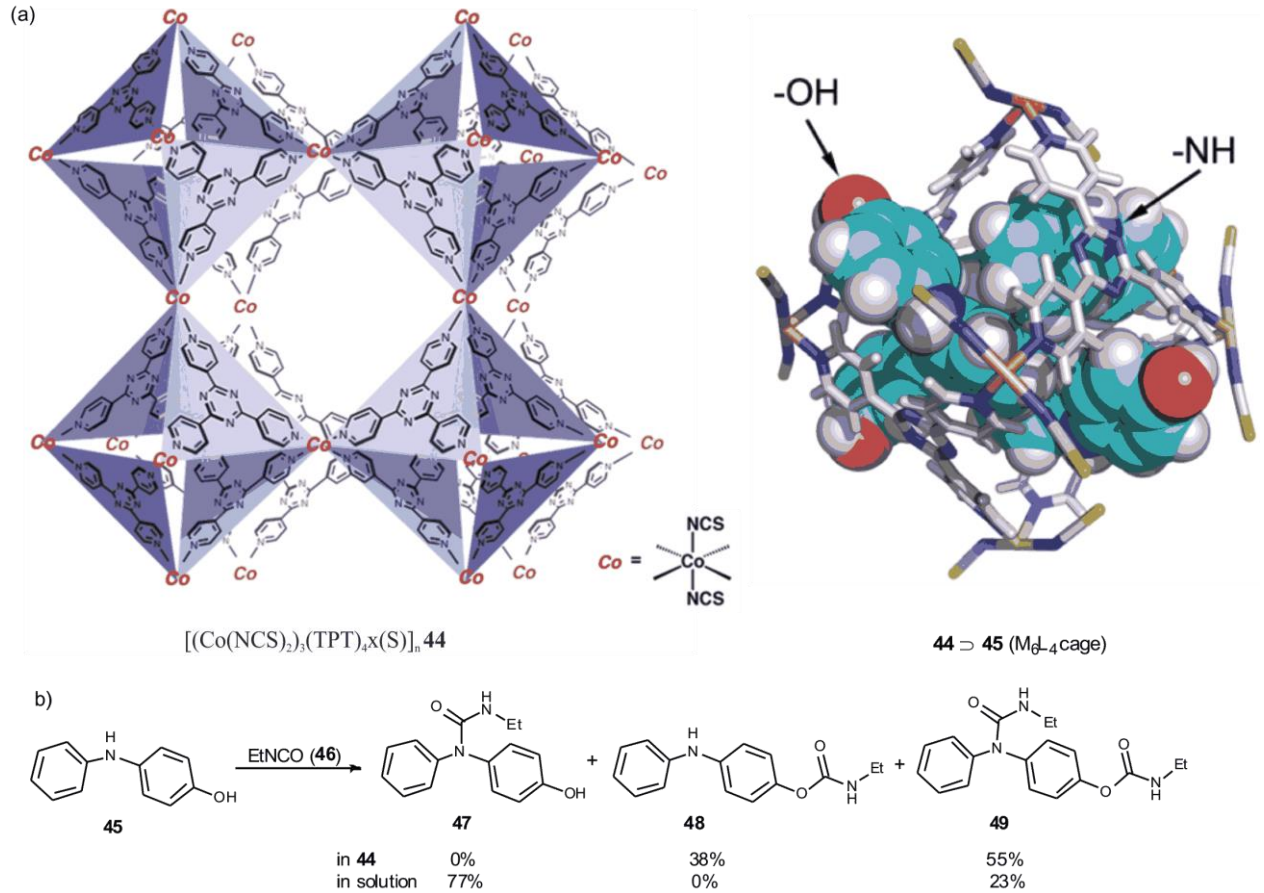

Fig. 12 a) Network of **44** (left) and X-ray crystal structure (right) of the inclusion complex **44** ⊃ **45**. TPT = tris(4-pyridyl)triazine; S = solvent molecules. b) The acylation of **45** within crystal **44** predominantly occurs at the less nucleophilic O atom. (The representation of the network of **44** and the X-ray structure of **44** ⊃ **45** are reprinted with permission from ref. 371 Copyright 2011. American Chemical Society).

(**Fig. 10**), in the DCL obtained from **30**, **31** and **32**, is increased in presence of template **33**. Since **33** is the product (and therefore a TSA) of the Diels–Alder reaction between cyclopentadiene and **36**, macrocycles **34** and **35** were investigated as catalysts for the reaction. Indeed, **34** catalysed the reaction, however with a modest effective molarity (*EM* = 0.08 M). Conversely, **35** is inactive because the affinity of the host for the product is smaller than for the reactants. In other words, the host-product complex is less stable than the host-reactants one and its formation is hampered.

Scrimin and co-workers reported a similar strategy except that the TSA is stabilised intramolecularly.[340] Hydrazones **39a**, **39b**, **39c** and **39i** (**Fig. 11, a**) are formed preferentially compared to **40** in the DCL library comprising hydrazones **39a–i**. Since the phosphate group is a TSA of ester cleavage, ester analogues **41** and **42** of hydrazones **39a** and **39i** respectively were prepared. Methanolysis of **41** and **42** in basic medium showed a 59.9 and 11.8-fold acceleration respectively compared to a reference reaction with the ester **43** lacking the side chain group able to stabilise the transition state (**Fig. 11, b**). Control experiments confirm that electrostatic interaction (for **41**) and the hydrogen bond interaction (for **42**) between the anionic transition state and the side chain group are at the origin of the observed enhanced rates (see the proposed transition state in **Fig. 11**).

Many other rigid systems, *e.g.* dendrimers,[15,341–351] porous clays, silicas and zeolites,[352–359] crystalline covalent-organic framework,[360,361] star polymers,[362–365] and porous organic polymers[366,367] benefit from the effect of molecular confinement (for those soluble in water see section 3).[22] The use of MOFs constitutes a particular case of heterogeneous catalysis, in which the catalytic structure can be fine-tuned.[27–31] Several strategies were employed to design catalytically-active MOFs: using of the framework metal nodes as the reactive centres, using metal catalyst or organocatalyst present in the structure of the MOF, incorporating a metal catalyst or metal nanoparticles[368,369] inside the MOFs, etc.[27–31] Substrate-size selectivity and inactivity of the

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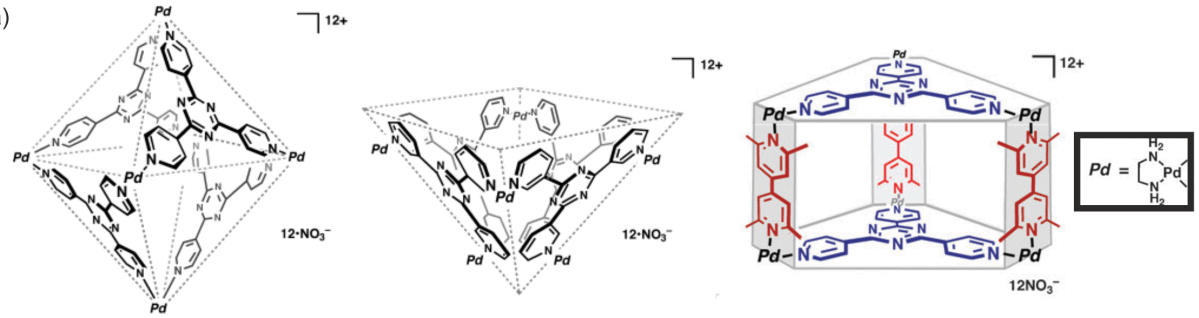

50 **51** **52**

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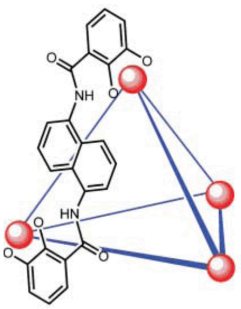

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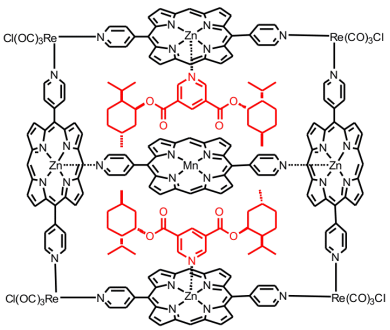

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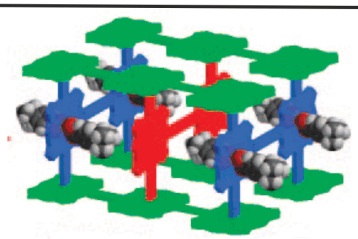
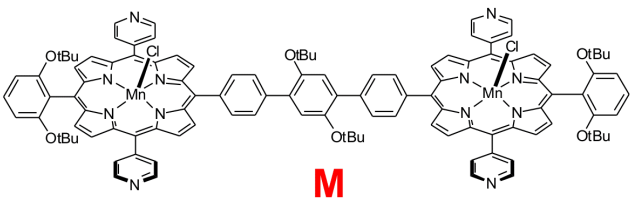


$C_DMC_DT'_4$

55



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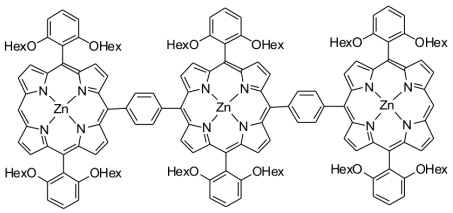

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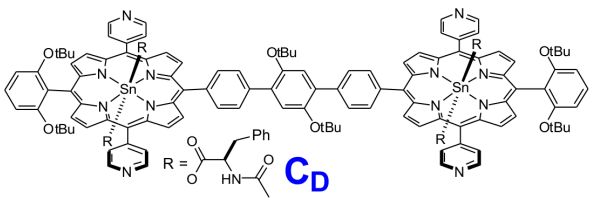

C_D

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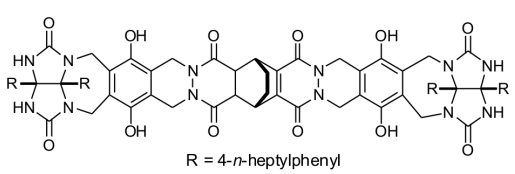
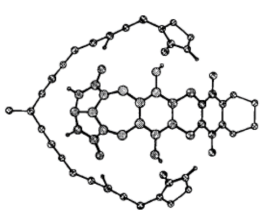


R = 4-*n*-heptylphenyl

56

57 ≡



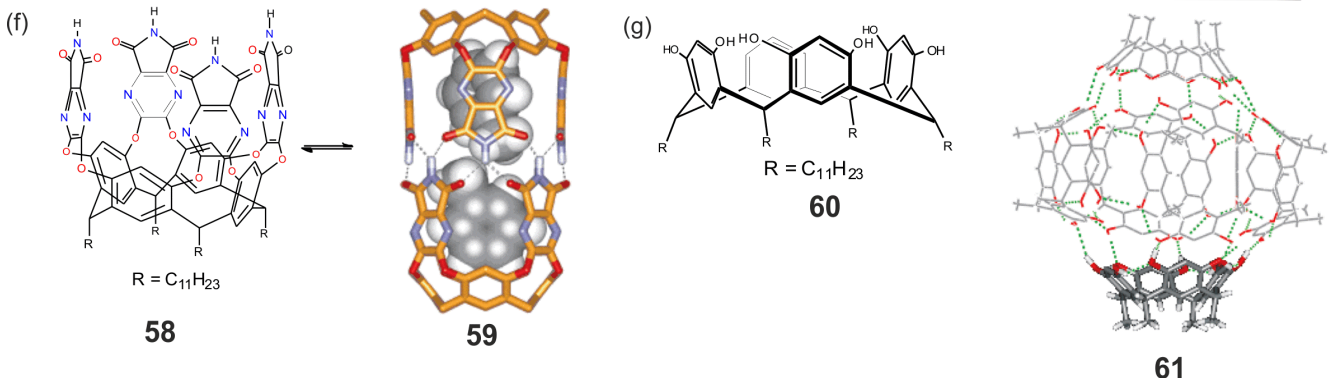


Fig. 13 General structures of the supramolecular cages and capsules used as hosts for supramolecular catalysis. (a) Fujita square **50** $[M_6L_4]^{12+}$, open-square hollow complex **51** $[M_6L_4]^{12+}$, and cylindrical complex **52** $[M_6L_2L'_3]^{12+}$. (The structures of the **50** and **51** are reprinted with permission from ref. 393. Copyright 2002. John Wiley and Sons; the structure of **52** is reprinted with permission from ref. 401. Copyright 2010. The Royal Society of Chemistry). (b) Schematic representation of the Bergman and Raymond tetrahedral cage **53** $[Ga_4L_6]^{12-}$ (only one ligand is shown for clarity). (The structure of **53** is reprinted with permission from ref. 405. Copyright 2007. American Association for the Advancement of Science). (c) Nguyen and Hupp first porphyrin cage **54** incorporating 3,5-dinicotinic acid dineomenthyl ester (in red). (d) Second generation porphyrin cage **55**. (The representation of the supramolecular box is reprinted with permission from ref. 420. Copyright 2008. American Chemical Society). (e) Rebek softball **57** formed by self-association of **56** through hydrogen bond interactions. (The energy-minimized structure of the softball is reprinted with permission from ref. 422. Copyright 1997. Nature Publishing Group). (f) Rebek capsule **59** formed from self-association of two molecules of cavitand **58**. On the right: energy-minimized structure of the complex of **59** and two toluene molecules. (The energy-minimized structure is reprinted with permission from ref. 424. Copyright 2002. American Chemical Society). (g) Hexameric assembly **61** is formed by self-association of resorcin[4]arene **60** in water-saturated solvents. (Representation of the hexameric capsule is reprinted with permission from ref. 428. Copyright 2011. American Chemical Society). Refs: see the text.

soluble MOF supernatant, compared to control experiments, constitute proofs that the reaction occurs inside the porous network of the insoluble MOF.

Fujita and co-workers employed MOF to perform bimolecular reactions by subsequent incorporation of the two substrates inside the cavity of a crystalline MOF.[370–372] Single-crystal-to-single-crystal transformations allow for the reaction to be monitored by X-ray diffraction analysis. For example, they used a MOF of general formula $[(Co(NCS)_2)_3(TPT)_4 \bullet x(S)]_n$ **44** (**Fig. 12;** TPT = tris(4-pyridyl)triazine; S = solvent molecules),[373] which is constituted of an infinite network of M_4L_6 cages, for the regioselective *O*-acylation of 4-hydroxydiphenylamine **45**.[371] The inclusion complex **44** ⊃ **45** is analyzed by X-ray diffraction which shows that the oxygen atom is more accessible than the nitrogen which is shielded by one TPT ligand. Interestingly, the same chemoselectivity is observed when the reaction is performed in solution within the soluble Pd cage **50** (see section 2.2.2 and **Fig. 13**).

2.2.2 Non-covalent hosts

Non-covalent hosts can present several advantages: (i) they can be easily prepared by combining several components which self-assemble through complementary interactions, (ii) they can be conveniently functionalized, and (iii) they present some flexibility, reversibility and dynamic behaviour of importance for accommodating guest(s) and stabilising the transition state structure. As examples of easy-accessibility of these hosts we mention Fujita square cage and Raymond tetrahedral cage which are prepared in high yield and in one step utilizing the directional-bonding[374] and symmetry-interaction[375] approaches.[376] **Fig. 13** presents different hosts built on non-covalent interactions (metal-ligand interactions and hydrogen bond interactions) which have been used in homogeneous catalysis. In most cases strong inhibition of the catalysis was observed due to the more energetically favourable inclusion of the product in the host. However, inhibition can be avoided: (i) if the product has a lower affinity for the host than the substrates,[377–380] (ii) if the product formed in the cavity further reacts,[381] inside or outside of the cavity, to yield a species with poor affinity for the host.[382–386] Each host will be briefly described with a focus on the special features of each system and the most outstanding catalytic results obtained.

Fujita square complex **50**, open-square hollow complex **51** and cylindrical complex **52** are cationic palladium hosts which encapsulate neutral organic molecules in water mainly *via* hydrophobic, C–H-π and π-π stacking interactions.[374,387–392] Many photoaddition or thermally driven cycloaddition reactions were performed within these hosts yielding products with unusual selectivity and/or enhanced activity.[393–399] However product inhibition is observed and the product is so tightly bound to the host that X-ray structures of host ⊃ product were reported.[393–399] A nice feature of these systems is that, by a careful choice of the substrates, hetero pair-wise inclusion (*i.e.* a host containing two different substrates) can be favoured over homo pair-wise complexes. Thus, the respective hetero adducts can be produced in high yields.[394–399] An asymmetric version of a [2+2] olefin cross photoaddition was achieved by introducing a chiral diamine ligand on Pd (ee up to 50%).[397] An example of a Diels–Alder reaction performed inside **50** is represented in **Fig. 14, a**.[398] The reaction between *N*-cyclohexylmaleimide **63** and 2,3-diethylnaphthalene **62** selectively yields **64** indicating that the reaction surprisingly occurs at the non-substituted aromatic ring and only gives the *syn* adduct. The nature of the catalytic reactions within hosts **50**–**52** is not limited to cycloaddition reactions since stoichiometric anti-Markovnikov hydration of alkenes,[400] stoichiometric cyclophane synthesis,[401] Knoevenagel condensation[380] and other reactions[191,193] were also reported. Interestingly, hosts **50**–**52** can exhibit a different catalytic behaviour. Whereas **50** yields regioselectively the 1,4-Diels–Alder adduct in a stoichiometric fashion, **51** allows for the catalytic reaction between **65** and **66** forming the 9,10-adduct

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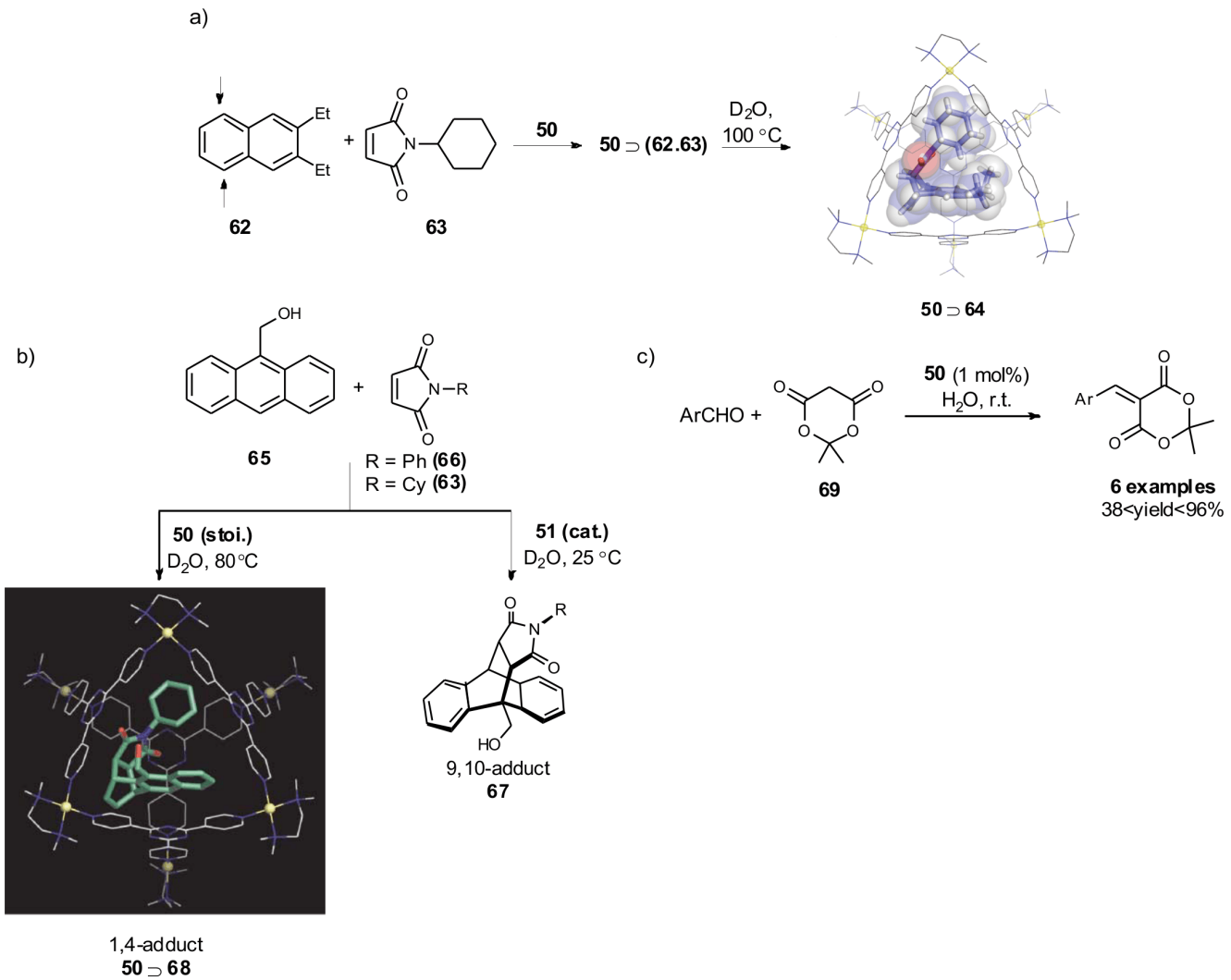

Fig. 14 a) Reaction between *N*-cyclohexylmaleimide **63** and 2,3-diethylnaphthalene **62** selectively yields the adduct **64**. Crystal structure of **50** ⊃ **64**. (The X-ray structure is reprinted with permission from ref. 398. Copyright 2010. American Chemical Society.) b) The Diels–Alder reaction between **65** and **66** is catalysed by **51** and yields the 9,10-adduct **67**. The reaction between **65** and **63** with a stoichiometric amount of **50** yields the 1,4-adduct. Crystal structure of **50** ⊃ **68**. (The X-ray structure is reprinted with permission from ref. 395. Copyright 2006. American Association for the Advancement of Science). c) The Knoevenagel condensation of Meldrum's acid **69** with various aldehydes is catalysed by **50** but not by **51**. Refs: see the text.

(**Fig. 14, b**).[395] The opposite trend is observed for the Knoevenagel condensation of aldehydes with Meldrum's acid **69** (**Fig. 14, c**) since the reaction can be performed with a catalytic amount of **50** whereas **51** is not efficient. This result is probably due to the ability of **50** to stabilise the oxyanion intermediate.[380] This intermediate is most effectively stabilised by the Pd centres sitting at the vertices of **50** and less so by the closely arranged Pd centres of **51**. The reaction is catalytic because of the low affinity of the product for the host (or higher affinity of the host for the substrate than for the product).

Bergman and Raymond tetrahedral cage **53** $[Ga_4L_6]^{12-}$ binds to monocationic organic or organometallic guests in water and constitutes a flexible hydrophobic cavity with an internal volume of 350–500 Å^3.[26,375,402] Probably due to the limited space available within the cavity, only intramolecular and hydrolysis reactions have been reported. It includes the 3-aza-Cope rearrangement of enammonium[382,384,385] and propargyl[383] ammonium cations, the Nazarov cyclization,[386,403] the cyclization of mono-terpenes,[404] and the hydrolysis of orthoformate[405, 406] and acetal compounds[378,379] in basic medium. For the aza-Cope rearrangement performed inside **53**, the enhanced rate (up to 1000 fold) is due to the reduction of the entropy of activation and

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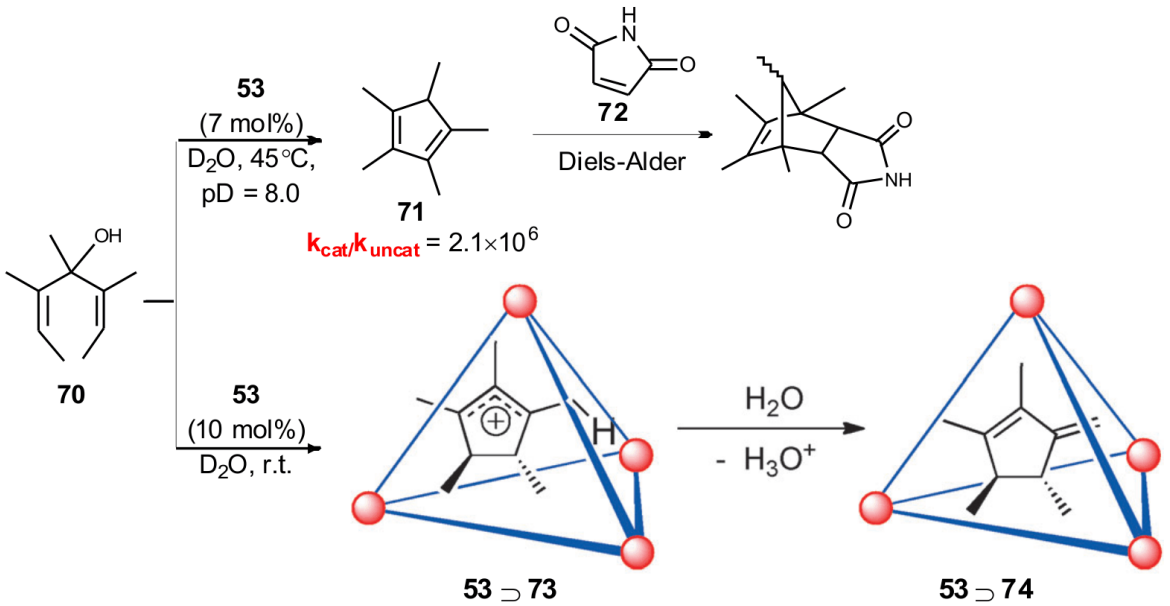

Fig. 15 Nazarov cyclization of **70** within **53**. Above: the formation of **71** is enhanced (2.1 × 10^6 fold) when the cyclization of **70** occurs inside **53**. Below: When the reaction is performed at room temperature in unbuffered D_2O, only **74** (an isomer of **71**) is formed because the deprotonation of the intermediate cation **73** is regioselective inside **53**. **74** is not observed in the first condition because it is immediately converted into the thermodynamic product **71** and trapped by maleimide **72**. (Inclusion complexes **53** ⊃ **73** and **53** ⊃ **74** are reprinted with permission from ref. 403. Copyright 2011. John Wiley and Sons). Refs: see the text.

ground-state preorganisation. The reaction is catalytic because the iminium intermediate (with high affinity for the host) is hydrolysed outside the capsule into a neutral carbonyl compound with low affinity for the host.[382–385] Δ,Δ,Δ,Δ and Λ,Λ,Λ,Λ enantiomers of **53** are resolvable[407] and thus the asymmetric 3-aza-Cope rearrangement of enammonium cations can be achieved with up to 78% ee.[385] As **53** is an anionic cage that stabilises cationic intermediates, reactions involving protonation of substrates were studied. In the case of the hydrolysis of orthoformates in basic solution, the reaction follows an acid-catalysed mechanism (presumably involving deprotonation of water) as a result of the stabilisation of the intermediate cation within the anionic cage **53**. The reaction obeys Michaelis–Menten kinetics with rate enhancement up to 3900.[405,406] Mechanistic investigation reveals that the reaction occurs through an A-S_E2 mechanism in which protonation is the rate-determining step in contrast to the A1 mechanism of the uncatalysed reaction in which the rate-determining step is the decomposition of the protonated substrate. Through a combination of the empirical valence bond (EVB) and free energy perturbation (FEP) computational methods, Warshel and co-workers were able to reproduce the observed catalytic effect for the hydrolysis of orthoformate by **53**.[408] These authors demonstrated the electrostatic origin[409] of the catalytic effect, *i.e.* that electrostatic preorganisation of the active site and electrostatic stabilisation of the transition state are likely at the origin of the observed enhanced rate.

The hydrolysis of acetal derivatives within **53** is catalytic because the aldehyde or the ketone products are bound less tightly to the host than the substrates. Several acetal substrates were hydrolyzed with high yields. The ratio (k_{cat}/K_M)/k_{uncat}, or catalytic proficiency, reflects how encapsulation affects the transition state stabilisation compared to the uncatalysed reaction. **53** hydrolyzed 2,2-dimethoxypropane and 1,1-diethoxyethane with similar catalytic proficiency and so the different rate enhancement (190 and 980 respectively) must be related to the distinct K_M values.[378,379] In the Nazarov cyclization, maleimide **72** was used as a trapping agent to prevent catalysis inhibition. Pentadienol derivative **70** is converted into **71** with a 2.1 × 10^6 fold increase of the reaction rate and a catalytic proficiency of 5.0 × 10^7 M^{-1} in the presence of metallo-cage **53** (**Fig. 15**)! Considering the volume of the cavity, a maximum concentration of 6.6 M is reachable so substrate concentration inside the host is not the only factor that can explain the observed enhanced rate. Rate enhancement is rather due to i) increase in the basicity of the alcohol moiety inside the cavity,[410] ii) transition state stabilisation, and iii) preorganisation of the bound substrate.[386] Precise study of the Nazarov reaction shows that the deprotonation of the cation in the cavity is regioselective due to the specific orientation of the carbocation within the confined

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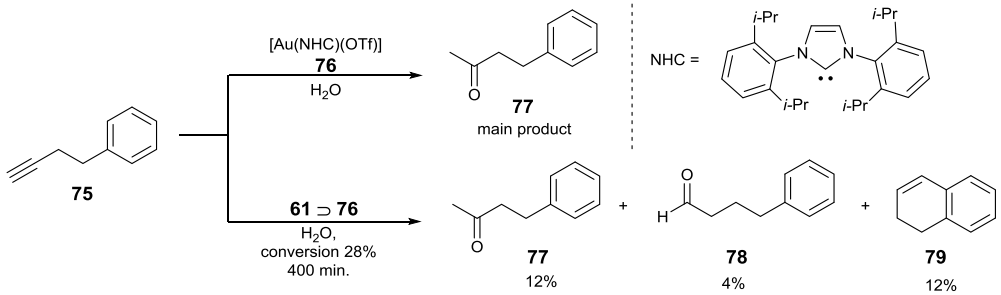

Fig. 16 Hydration of **75** with **61** ⊃ **76** led to unusual selectivity when compared to the same reaction performed with **76** in water. Ref: see the text.

space of the host (kinetically controlled deprotonation led to **74** from **73**, **Fig. 15**).[403] Encapsulation of cationic transition metal complexes inside cavity **53** led to unusual reactivity[411–414] and catalysis.[415,416] **53** ⊃ $[(PMe_3)_2Rh(OD_2)_2]^+$ catalysed the isomerisation of allylic substrates and exhibited substrate-size selectivity.[415] **53** ⊃ $[(PMe_3)Au]^+$ produced an 8.0 ± 0.9-fold acceleration of the hydroalkoxylation of allenes compared to the background reaction. In addition, higher activity (up to 67 TONs) was observed due to enhancement of the lifetime of the catalyst.[416] A very original application of the **53** ⊃ $[(PMe_3)Au]^+$ catalytic system was provided recently: it was used in combination with a lipase enzyme in a tandem hydrolysis/hydroalkoxylation reaction.[417] In the presence of the enzyme, the encapsulated Au gold catalyst is far more active than the free gold catalyst. The incorporation of the gold catalyst within **53** prevents its deactivation by the enzyme, that otherwise occurs probably through coordination of amino-acid residues to the gold atom.

Hupp and Nguyen reported a porphyrin cage comprising four $ReCl(CO)_3$ units at the vertices, four Zn-porphyrin at the sides and one central Mn-porphyrin as a catalytic centre for epoxidation (**54**, **Fig. 13**).[418] On the one hand, the stability of the Mn-porphyrin catalyst within the porphyrin metallo-cage is increased by a factor of 10 or 100 compared to traditional catalysts. On the other hand, the substrate-size selectivity was modest and no ee was detected in the products when a chiral additive was present within the cavity of the catalyst (3,5-dinicotinic acid dineomenthyl ester inside the cavity, **54**, **Fig. 13**). Two reasons can explain this observation: (i) the coordination of pyridine on the outside of (instead of inside) the cavity and (ii) the walls of the cage can rotate.[418] A consistent microkinetic model was established that confirmed the role of the cage as regards enhancing the rate of the epoxidation catalysis compared to a free catalyst.[419] Cooperative binding between partners allows for the preparation of a more elaborated 16-porphyrin rigid box **55** (**Fig. 13**).[420] Bis-Mn porphyrin can be incorporated inside the box and the overall host is used as an epoxidation catalyst.[421] The approach is more successful as substrate-size selectivity, between *cis*-stilbene and *cis*-3,3′,5,5′-tetra(*tert*-butyl)stilbene, of 5.5:1 and ee up to 14% were reported.

Rebek first demonstrated that the glycoluril capsule **57** (called softball, **Fig. 13**) encapsulated neutral guests in apolar organic solvents. The Diels–Alder reactions between *p*-quinone and cyclohexadiene and between maleic anhydride and cyclohexadiene are accelerated within cavity **57** (*EM* = 0.48 M and 0.36 M respectively) but product inhibition occurred in both cases.[422,423] However, 7.5 TONs are observed when *p*-benzoquinone and thiophene dioxide are reacted inside **57** because the higher affinity of benzoquinone reactant for **57** forced turnover.[377] The same author used capsule **59** (self-assembled by dimerization of two molecules of the tetraimide cavitand **58**, **Fig. 13**) for accelerating the 1,3-dipolar cycloaddition between phenyl azide and phenyl acetylene.[424] The reaction yields only the 1,4-regioisomer with a rate enhancement of 240 and an *EM* of 120 M (calculated by Mandolini and co-workers[43]). Considering the volume of the cavity (~ 450 $Å^3$), the reaction rate in the capsule is lower than the estimated rate based on the increase of local concentration of the reactants. It can be explained by the facts that the substrates are not positioned ideally and/or that the transition state is not stabilised in the capsule.

Resorcin[4]arene **60** (**Fig. 13**) self-assembles into a hydrogen bonded-hexameric capsule **61** in water-saturated solvents (*i.e.* chloroform or benzene).[425–427] The capsule has a volume of 1375 $Å^3$ and is a suitable host for cationic species. Reek and co-workers demonstrated that a N-heterocyclic carbene Au(I) complex can be encapsulated within **61** probably with the concomitant decoordination of the OTf anion.[428] Hydration of 4-phenyl-butyne **75** is slower with the encapsulated catalyst but the hydration product **78** and cyclization product **79** are observed in addition to **77**, demonstrating an unprecedented selectivity for such a Au-catalysed reaction (**Fig. 16**).[429]

Other environments,[34,70,430,431] exhibiting variable flexibility and size, can be used as supramolecular and molecular reaction vessels for catalysis including micelles and vesicles (see section 3.2),[70,430–437] cross-linked polymers and microcapsules,[352] layer-by-layer capsules,[430] polymersomes,[430,431,438–440] chemical and physical gels,[433,441–449] carbon nanotubes,[450] liquid crystals,[433] virus capsids,[451,452] and protein cages.[431,453]

3. Catalysis in water

3.1 Hydrophobic interactions

Hydrogen bond interactions[454–456] and hydrophobic interactions (HI) have been identified as the main factors responsible for the rate enhancement and *endo* selectivity observed for various Diels–Alder reactions performed in water.[457–459] Hydrogen bonding between polar groups (usually carbonyl or nitrile moieties) of the dienophile and water molecules enhances the reaction rate and favours the formation of the *endo* adduct. The contribution of hydrogen bonding on the overall reactivity relies on the nature of the substrate. We will focus here on hydrophobic interactions since their effects have driven the design of catalysts working in water. Hydrophobic effects positively affect the reaction: (i) by creating zones where the apolar substrates are stacked on one another to minimize the contact surface area between these and water, thus increasing their local concentration and (ii) by favouring the transition state geometry in which the two substrates are stacked together. For example, the Diels–Alder dimerization of 1,3-cyclopentadiene (Cp) in water has a transition state in which one face of each Cp is hidden from the solvent.[460] The more compact *endo* transition state is also favoured compared to the *exo* one. The primordial role of HI in these reactions is further revealed by the effect of additives on the reaction rate: (i) simple salts like NaCl or LiCl are "prohydrophobic additives" which thus increase the rate of the reaction in water by favouring the HI ("salting-out agents"),[234] (ii) "salting-in" agents (such as $LiClO_4$),[461] as well as EtOH and DMSO, are antihydrophobic additives that decrease the reaction rate, because they disfavoured HI by solvating the hydrocarbon species and reducing aggregation of the non-polar substrates.[457,462] Benzoin condensation,[461,463] ketone reduction with substituted borohydrides[464,465] or amine boranes,[466] olefin epoxidation with oxaziridinium salts[467] and some S_N2 reactions[468] can also benefit from HI occurring in water between the substrates. The role of HI for reactions involving polar substrates and/or charged transition state is more difficult to ascertain because polarity effects, solvation and hydrogen bond interactions can also play a role.

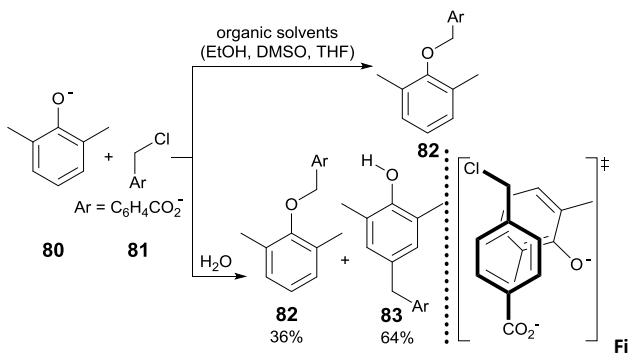

Fig. 17 HI are responsible for the unusual selectivity observed during the alkylation of phenoxide **80** with **81**. In water, the formation of **83** is favoured over **82**. Schematic representation of the oblique overlap in the stacked pair of **80** with **81**. Ref: see the text.

Breslow and co-workers elegantly demonstrated that HI are also involved in reactions involving polar substrates or charged transition states. The authors sorted out the different effects at the origin of the rate variation in alkylation reactions and established a computer model of HI.[469] They were able to explain the origin of the unusual selectivity for the benzylation of substituted phenoxide anions in water. For example, **80** is preferentially alkylated at its *p*-position giving the *C*-alkylation product **83** whereas the *O*-alkylation product **82** is obtained exclusively when the reaction is performed in organic solvents (**Fig. 17**). The authors proposed an oblique packing of the substrates in the TS allowing the overlap of a methyl group of the phenol while minimizing the overlap of the phenoxide oxyanion with the carboxyl group of **81**. Even though HI are more difficult to predict and design than other supramolecular interactions (such as highly directional hydrogen bonds), this result shows how HI can play an important role in directing the reaction pathways of reactions performed in water.[459, 470]

In enzymes, the surface of the reactive centre is not directly exposed to water but rather shielded from the solvent by folding of the enzyme around it. The reaction between the active site and the substrate takes place in the resulting hydrophobic pocket. Formation of a hydrophobic pocket in water has also driven the design of several enzyme mimics. Hydrophobic interactions are important for reactions occurring within a hydrophobic pocket but other forces such as hydrogen bonding and electrostatic interactions also play a role. In the following sections, we made a distinction between catalysis operating in the core of micelles and vesicles (section 3.2), that are dynamic and reversible, and catalysis inside rigid hosts (section 3.3). Biomacromolecule and peptide hybrid catalysts will be described in section 6. Other approaches that do not fit within these categories will not be described here, these include hosts such as hydrogels,[441,442,445, 448,449] virus capsids,[451,452] and protein cages[431,453] that can be used to accelerate reactions within their hydrophobic compartment in water.

3.2 Catalysis in micelles and vesicles

Application of dynamic micelles and vesicles as nanoreactors is well known.[56,393–400] Amphiphilic molecules can solvate organic molecules in their hydrophobic part (and their hydrophilic part) generating a pseudo-phase which can favour chemical reactions in water. Common micelles are based on low-molecular weight surfactants (**Fig. 18**) but polymerized surfactants, block copolymers and amphiphilic peptides/proteins are also extensively employed. The latter category encompasses: (i) naturally occurring proteins, (ii) hydrophilic amino-acid sequences chemically modified with alkyl chains, (iii) peptide and protein-phospholipid conjugates, and (iv) peptide-based copolymers. Vesicles are derived from natural or synthetic phospholipids (**Fig. 18**), a combination of both of them, or polymersomes. The field is far too vast to be described comprehensively[70,430–437] in this review and the following examples (**Fig. 19-21**) just serve as an illustration of the domain.

Two-phase catalysis, comprising a water soluble catalyst and an organic phase to recover the product, usually suffers from low solubility of the substrate in the aqueous phase. Addition of micelles or polymerized micelles can improve the performance of a water-soluble hydroformylation catalyst in water.[471–475] Recently, Desset et al. demonstrated that 1-octyl-3-methylimidazolium, and other alkylimidazolium salts, accelerated the hydroformylation of alkenes in aqueous-biphasic medium.[476,477]

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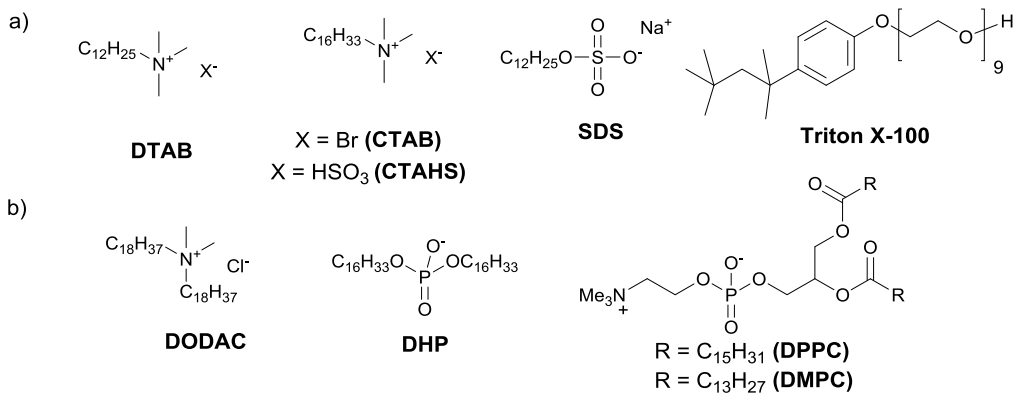

Fig. 18 Chemical structures of common surfactants used to perform catalysis in micelles (a) or in vesicles (b). **DTAB** (dodecyltrimethylammonium bromide), **CTAB** (cetyltrimethylammonium bromide, **CTAHS** (cetyltrimethylammonium hydrogensulfate), **SDS** sodium dodecylsulfate, **DODAC** (dioctadecyldimethylammonium chloride), **DHP** (dihexadecyl phosphate), **DPPC** (L-α-dipalmitoylphosphatidylcholine), **DMPC** (DL-α-dimyristoylphosphatidylcholine).

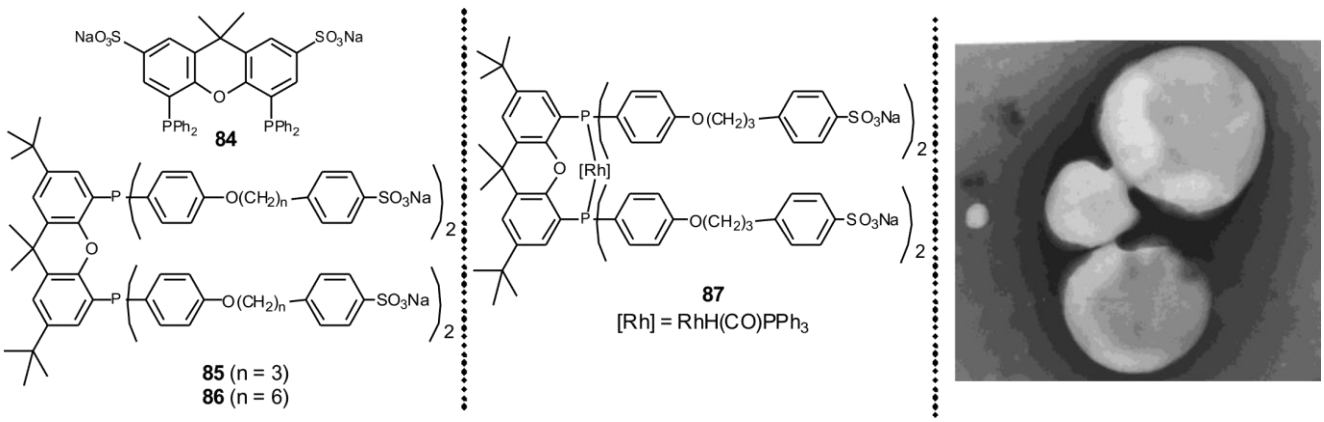

Fig. 19 Amphiphilic Xantphos derivatives **85** and **86**. Formula of complex **87**. Vesicles observed shortly after sonication of a solution of **87** and 1-octene (platinum shadowing technique).The average diameter of the vesicles is 500-600 nm. (The electron microscopy picture of vesicles is reprinted with permission from ref. 482. Copyright 2000. American Chemical Society). Ref: see the text.

Alternatively, surface-active phosphines can be employed that are able to assemble into micelles or vesicles.[472,478–483] Van Leeuwen et al. prepared water-soluble analogues of Xantphos (**85** and **86**, **Fig. 19**) which differ by the number of carbons in the hydrophobic spacer. **85** and **86**, alone as well as coordinated to the Rh precursor gave vesicles in water.[482] Complex **87**, which was obtained by reacting **85** with [Rh(H)CO(PPh$_3$)$_3$], formed vesicles with an average diameter of 140 nm alone and of 500-600 nm in the presence of 1-octene, the substrate for the hydroformylation experiments. When this reaction is performed at 343 K, ligands **85** and **86** are 6 times and 12 times more active, respectively, than the water-soluble diphosphine 2,7-bis(SO$_3$Na)Xantphos (**84**, **Fig. 19**). At 393 K, the relative reaction rate decreased (**86** is only three times more active than **84**) because the vesicles aggregate are partly disrupted at this temperature. Importantly, a high selectivity is maintained with ligands **85** and **86** (l:b = 98:2) and during the recycling process neither emulsions nor transfer of the Rh metal into the organic phase are observed. Thus, several runs with the same catalyst were performed without loss of activity and selectivity.

Monflier, Hapiot and co-workers have investigated the role of various β-cyclodextrins while combined with surface active phosphanes for the hydroformylation of 1-decene[484] and the palladium-catalysed cleavage reaction of allyl undecyl carbonate[485] in water. If micelle destruction is observed at high β-CDs concentration, the use of a stoichiometric amount of cyclodextrin with respect to the surface active phosphine leads to higher conversion without any detrimental effect on the selectivity.

Elias et al. prepared the diphosphine Pd complex **88** based on an amphiphilic poly(ethylene glycol)-*block*-poly(*L*-lysine) backbone (**Fig. 20**).[486] Spherical micelle particles formed with a critical micelle concentration (CMC) equals to 0.09 mg.mL^{-1} and an average diameter of 30–50 nm. **88** catalysed the hydrogenation

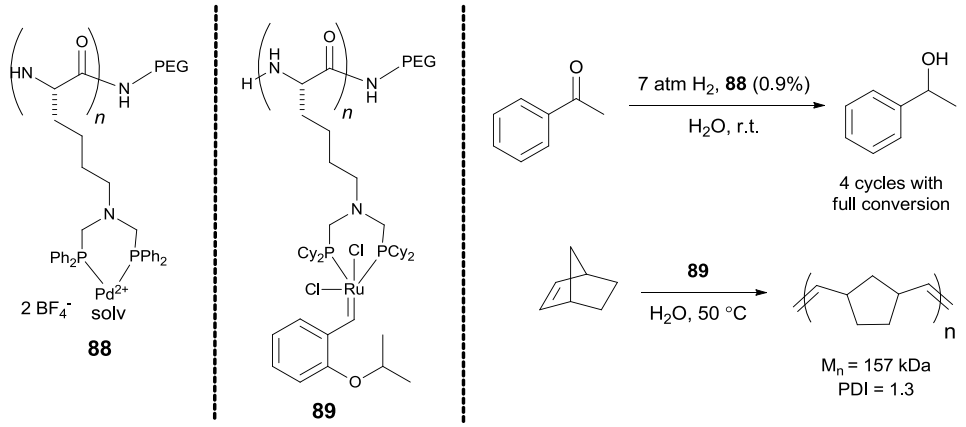

Fig. 20 Amphiphilic block polypeptide-type ligand **88** and **89** for catalytic hydrogenation and ROMP of norbornene in water. The copolymer has a PEG chain with Mw = 5000 Da and contains 8 repeating units of *L*-Lysine. Ref: see the text.

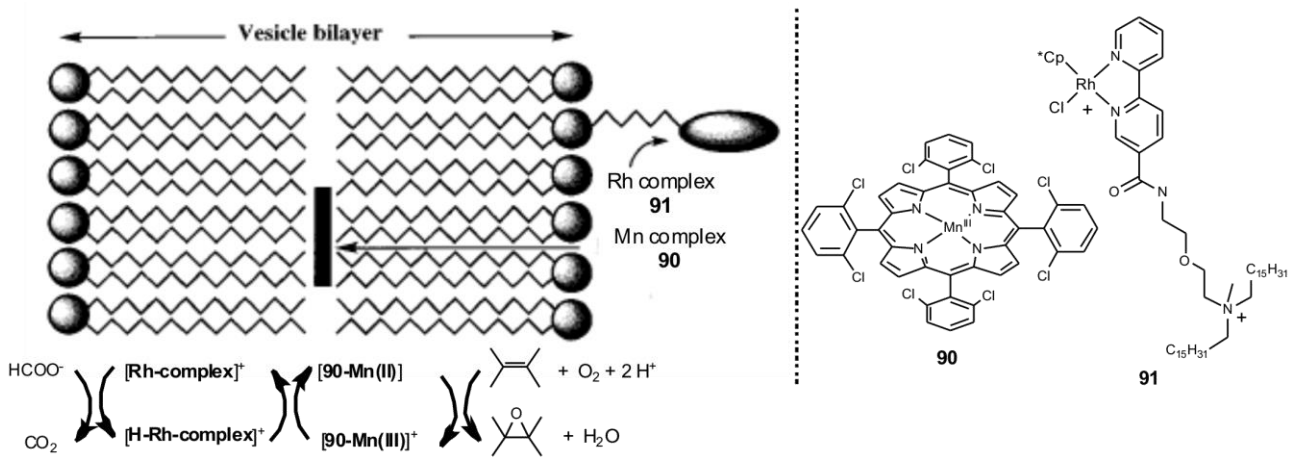

Fig. 21 Supramolecular cytochrome P450 mimic developed by Nolte et al. **DODAC**, **DPPC**, **DPPA** (L-α-dipalmitoylphosphatidic acid) and **DHP** are the surfactants used for the formation of the vesicles. Ref: see the text. See **Fig. 18** for the name and formulas of **DODAC**, **DPPC** and **DHP**. (The schematic representation of the P450 mimic is reprinted with permission from ref. 498. Copyright 1998. John Wiley and Sons).

of acetophenone into 1-phenylethanol in water (full conversion, 7 atm of H_2, 0.9% per Pd) and can be recycled 4 times without loss of activity. Control experiments confirmed that the presence of micelles in the medium is required to achieve high activity. Complex **89**, a Ru analogue of **88**, is used for the ring-opening metathesis polymerization (ROMP) of norbornene and the resulting poly(norbornene) contains *ca.* 74% of *trans*-alkene and showed a very high molecular weight and a low polydispersity (M_n = 157 kDa, PDI = 1.3). The high molecular weight obtained is probably the result of a good solubility of the growing polymeric chains in the micelle particles. The use of surface-active catalysts presented here avoids the need of a huge excess of surfactants.

A plethora of amphiphilic ligands containing oxygen- and nitrogen-donor atoms were coupled to metal catalysts (mainly Zn and Cu) and the resulting metallomicelles investigated as enzyme mimics in reactions such as the hydrolysis of esters.[434–436] Anchoring of the amphiphilic ligand on nanoparticles constitutes a solution to the inherent instability of micellar systems (kinetic lability and stability dependence on the CMC).[487–491] The group of Mancin and Scrimin reported a very successful utilization of this strategy.[491] By means of the strong thiol-Au interaction, gold nanoparticles were capped with a unit containing an ethylene glycol chain and a unit comprising an amphiphilic N,N,N pincer ligand. Combined with Zn^{II}, the resulting self-assembled system turned out to be very active for the cleavage of bis-*p*-nitrophenyl phosphate (BNP, a DNA model substrate): 300,000-fold rate acceleration was observed! DNA could also be cleaved by the same catalytic system with less impressive activity but with an unprecedented ability of double strand cleavage. This reflected the cooperative nature of the active sites within the catalyst which cleaved simultaneously several esters bonds of the polymeric DNA backbone.[492,493]

The groups of Groves[494] and Nolte[70,495–498] employed synthetic vesicles as a medium for oxidation reactions. Schenning et al. reported a cytochrome P450 mimic which combined i) a synthetic phospholipid vesicle, ii) a metallo-porphyrin catalyst **90** trapped in the membrane of these vesicles, iii) an axial-ligand (*N*-methylimidazole), iv) a combination of a Rh(III) complex **91** and formate anions as a reducing agent, and v) molecular oxygen (**Fig. 21**).[498] Initial TOF for the epoxidation of α-pinene into α-pinene oxide is higher than that obtained in a two-phase system

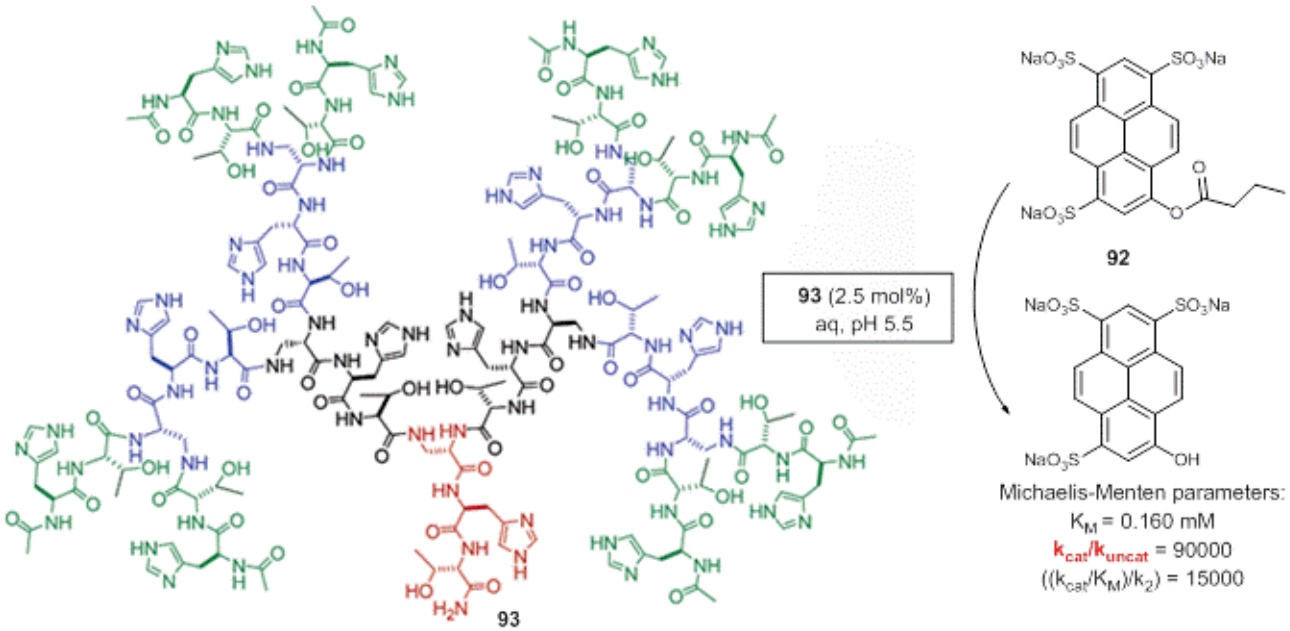

Fig. 22 Peptide dendrimer **93** catalysed the hydrolysis of pyrene sulfonate **92** in water. The value of $((k_{cat}/K_M)/k_2)$ is referred as the specific reactivity enhancement where k_2 is the kinetic constant of the reaction catalysed by the reference catalyst 4-methylimidazole. (The structure of the dendrimer **93** is reprinted with permission from ref. 517. Copyright 2006. American Chemical Society.). Ref: see the text.

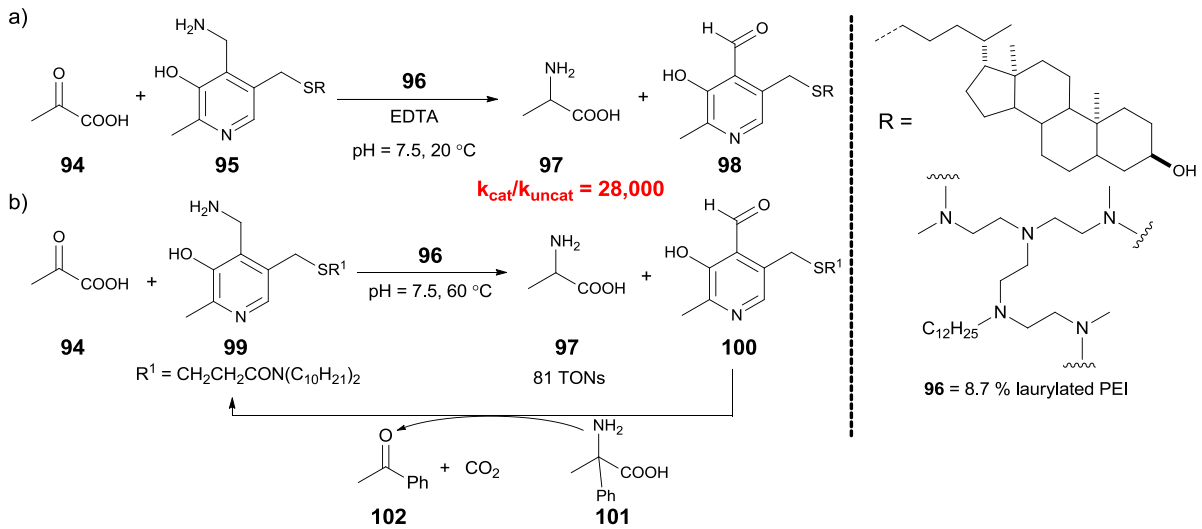

Fig. 23 a) The transamination reaction between pyruvic acid **94** and pyridoxamine **95** is accelerated in the presence of PEI polymer **96**. b) Catalytic version of the reaction for which the pyridoxal **100** is converted into the pyridoxamine **99** by reacting with 2-amino-2-phenylpropionic acid **101**. Up to 81 TONs in **97** were observed. Refs: see the text.

and similar to the rate observed for the natural system.

The use of amphiphilic catalysts is not limited to metal catalysis and numerous surface-active organocatalysts have also been reported including LASC[437] (Lewis-acid surfactant combined catalysts), STAOs[499–504] (surfactant-type asymmetric organocatalysts) and catalytically active supramolecular amphiphiles.[505,506]

3.3 Catalysis inside rigid hosts

Depending on the catalytic reaction, rigid hosts can be more suitable than the reversible micelles and vesicles mentioned in section 3.2.

Water-soluble dendrimers (Diederich's dendrophanes,[66,507] peptide dendrimers, commercial poly(amidoamine) PAMAM and its derivatives), hyperbranched polymers (commercial polyethyleneimine PEI and its "synzymes" synthetic derivatives), amphiphilic monodisperse polymers,[508] star polymers,[509,510] folded polymers[511] and synthetic foldamers[512] all contain water-free hydrophobic zones in their inner core which can concentrate substrates and stabilise transition states.[23,346,470,507,513–515] Compared to micelles and vesicles, the stability of these macromolecules is not dependent on temperature and

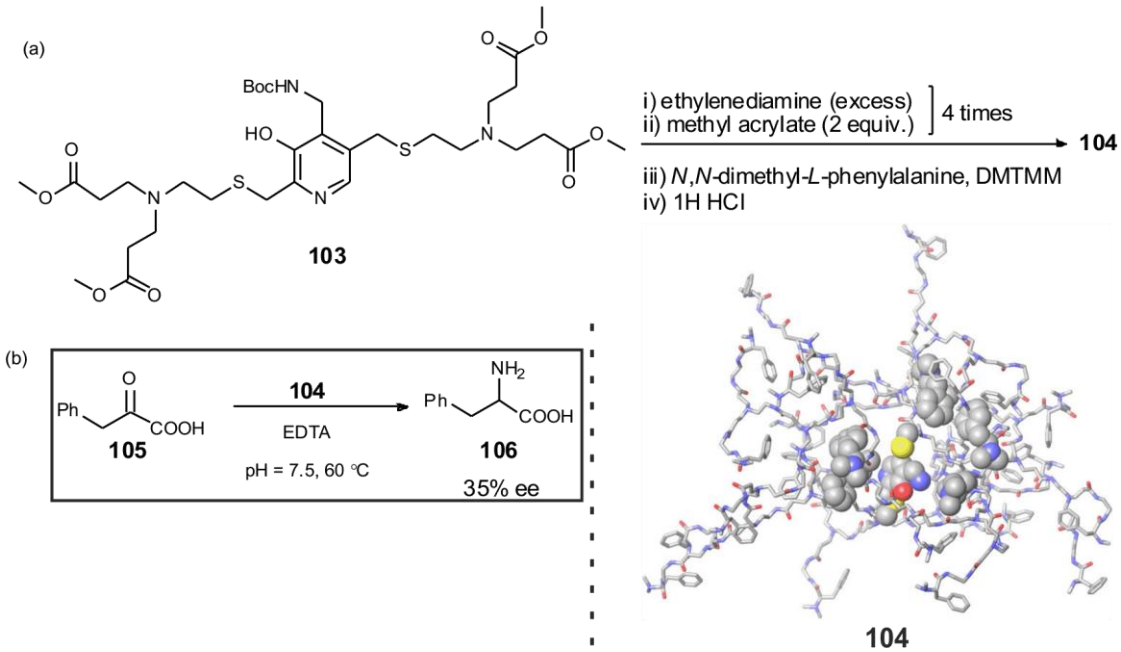

Fig. 24 (a) Synthesis of the chiral dendrimer **104**. DMTMM = 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride (b) The chiral dendrimer **104** is used for the asymmetric transamination of **105** and yielded **106** with 35% ee. The fourth generation dendrimer **104** has a pyridoxamine cofactor at its core and 32 terminal *N*,*N*-dimethyl-*L*-phenylalanine groups as chiral inducers. Right: Energy-minimized structure of **104** with the *N*,*N*-dimethyl-*L*-phenylalanine groups surrounding the pyridoxamine are emphasized. Refs: see the text. (The energy-minimized structure is reprinted with permission from ref. 534. Copyright 2009. Elsevier.)

concentration. Peptide dendrimers represent successful examples of water-soluble dendrimers which display an enzyme-like behaviour in water.[515–519]

Reymond prepared a series of "apple trees" dendrimers based on the dendron Dap-His-X (Dap = (*L*)-2,3-diaminopropionic acid, His = histidine, X = various α-amino acids) and studied the catalysis activity of several third-generation dendrimers for the hydrolysis of acyloxypyrene trisulfonate derivatives.[517] The hydrolysis followed an acid-base mechanism mediated by the histidine residues. The third-generation dendrimer based on the dendron Dap-His-Threonine **93** catalysed the hydrolysis of **92** with a rate enhancement of 90,000 and a specific reactivity enhancement of 15,000 (**Fig. 22**). Commercial, synthetically-modified or totally synthesized PAMAM and PEI derivatives were investigated as enzyme models for benzoin condensation,[520] hydrolysis,[521–525] aminolysis,[526,527] decarboxylation[528] and transamination.[514]

Notably, Breslow and co-workers incorporated covalently attached pyridoxamine units, the cofactor for transamination reaction, in various positions of PAMAM dendrimer or PEI polymers.[529–531] In an early version of the reaction, a pyridoxamine with a hydrophobic chain (**95**) was employed that can be incorporated non-covalently within the core of a fully methylated PEI polymer carrying 8.7% of lauryl groups (**96**, **Fig. 23, a**). A 28,000 enhanced rate was obtained for the transamination of pyruvic acid **94** into **97**, however pyridoxamine transforms irreversibly into its pyridoxal analogue, preventing true catalysis. The problem was solved by adding 2-amino-2-phenylpropionic acid **101**, which reacts with pyridoxal **100** to give acetophenone **102** and regenerates pyridoxamine **99**; up to 81 TONs can be obtained and both the transamination and the decarboxylation are catalysed by PEI catalyst **96** (**Fig. 23, b**).[528,532]

Asymmetric transamination, leading to (*L*)-α-amino acid with an ee up to 35%, was performed with a chiral PAMAM **104** for which the pyridoxamine cofactor was located into the core of the chiral dendrimer (**Fig. 24**).[533,534] Fréchet and co-workers entrapped proline inside the hydrophobic core of a PEI derivative *via* hydrogen bond interactions and demonstrated that the resulting supramolecular catalyst preferentially yielded cross-aldol products, as α,β-unsaturated ketones, in various cross ketone/aldehyde condensations.[535]

Even though water-soluble well-defined dendrimers and polymers were mostly used as organocatalysts, metal catalysts were also incorporated within PAMAM dendrimers,[536] and star polymers.[509, 510]

Supporting organocatalysts on hydrophobic polymers, amphiphilic resins, hydrophilic PEG chains or polyether dendritic wedges have also been described as a successful method to perform reactions in water and catalyst recycling.[537–544]

Meijer and co-workers prepared an amphiphilic segmented terpolymer comprising hydrophilic poly(ethylene glycol) methyl ether methacrylate (PEGMA) chains, hydrophobic chiral benzene-1,3,5-tricarboxamide-bearing methacrylate (BTAMA) chains and catalytically active diphenylphosphinostyrene-Ru (SDP-Ru) units (**107**, **Fig. 25**).[511] Several analyses confirmed that the helical self-association of the chiral BTA units in water within **107** led to the folding of the polymer, generating a hydrophobic cavity (TEM indicated a diameter around 3-4 nm for the nanoparticles). In basic media, folding of the PEGMA/BTAMA/SDP-Ru terpolymer still occurs and the resulting compartmentalized system is capable of catalysing the

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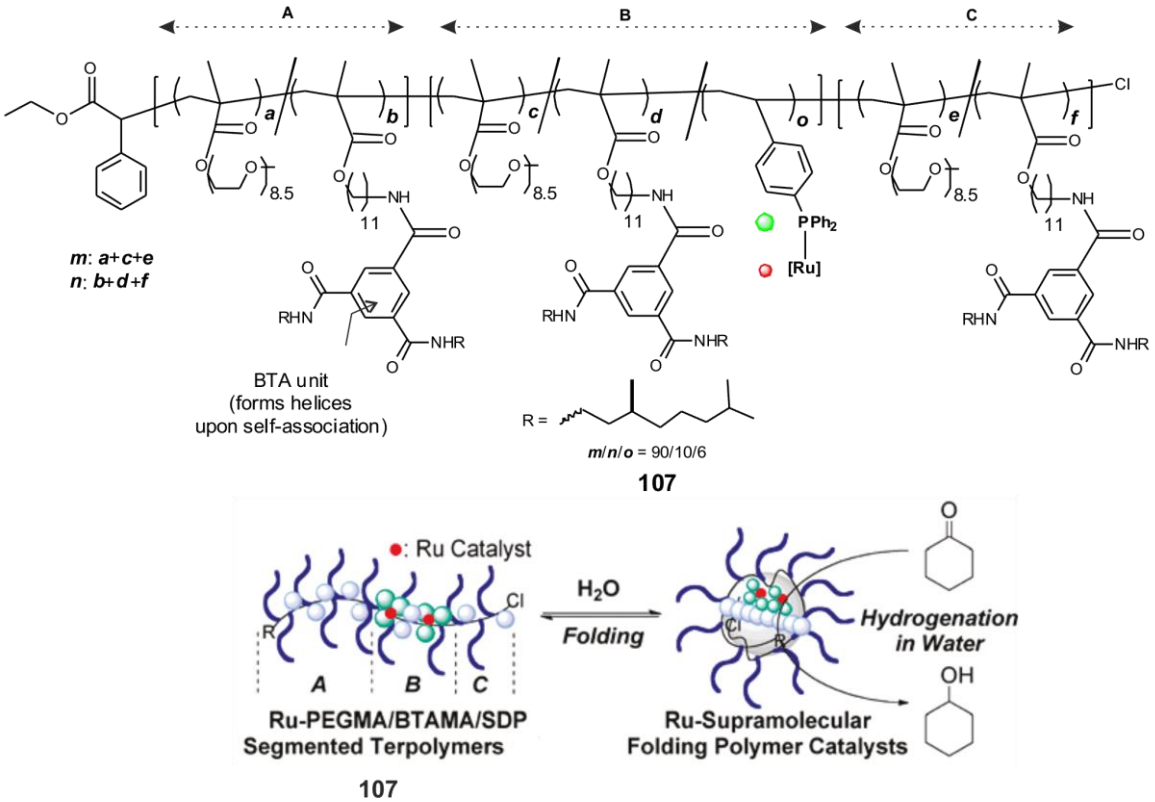

Fig. 25 Above: formula of the Ru-PEGMA/BTAMA/SDP segmented terpolymer **107**. In water, the chiral BTA units self-assembled into helices *via* 3-fold hydrogen bonding. Below: the self-assembly of the chiral BTA units triggers the single-chain folding of polymer **107**. The inner phase of the folded polymer, containing the Ru catalytic centre, accelerated the hydrogenation of cyclohexanone. PEGMA = poly(ethylene glycol) methyl ether methacrylate, BTA = benzene-1,3,5-tricarboxamide, BTAMA = BTA-bearing methacrylate, SDP = diphenylphosphinostyrene. Ref: see the text. (The representation of the compartmentalized catalyst is reprinted with permission from ref. 511. Copyright 2011. American Chemical Society).

reduction of cyclohexanone and acetophenone in water (TOF = 10–20 h^{-1}). The high solubility of the catalyst in water (due to the PEG chains) and the fact that the catalyst is embedded in its hydrophobic compartment explain this good result. The same strategy was used for the construction of analogues of **107** in which the catalytic unit was a (*L*)-proline.[545] These organocatalysts accelerated the aldol reaction between cyclohexanone and 4-nitrobenzaldehyde in water (ee = 71% at 74% conversion). Compartmentalization of the proline units within the pocket of the folded polymer was required for the catalytic reaction to occur. In the best case, the catalytic efficiency ($k_{cat,app}/K_{M,app}$) is comparable to those of some aldolase mutants.

The examples described here deal with the preparation of efficient synthetic catalysts following different strategies inspired by the mode of action of enzymes in water. Other rigid hosts working in water have already been mentioned elsewhere in this review: cyclodextrins and *p*-sulfonatocalix[*n*]arene (**Fig. 6**), cucurbit[n]urils (**Fig. 7**) and non-covalent hosts **50**–**53** (**Fig. 13**). De Simone and co-workers recently demonstrated that hydrophobic interactions and electrostatic interactions are not the only driving forces for the complexation of neutral hosts inside cucurbit[n]urils.[546] The best host-guest affinity will be reached by i) guests that are able to displace all water molecules present in the host cavity, ii) host-guest candidates that can interact directly, for example through electrostatic or hydrogen bond interactions and iii) hosts that incorporates high-energy water molecules. These factors can encourage the design of new hosts that perform catalytic reactions in water.

4. Self-replicators

The investigation of self-replication processes at the molecular level is of importance to better understand the complexity of biologic machinery. In seminal work, the self-replication properties of biological "synthons" such as oligonucleotides and deoxyoligonucleotides,[547–553] peptides[554–557] and fatty acids[558, 559] were demonstrated. In parallel, the groups of von Kiedrowski[560] and Rebek[32,561–565] found out that other types of complementary groups also allow small molecules to replicate. The reaction only

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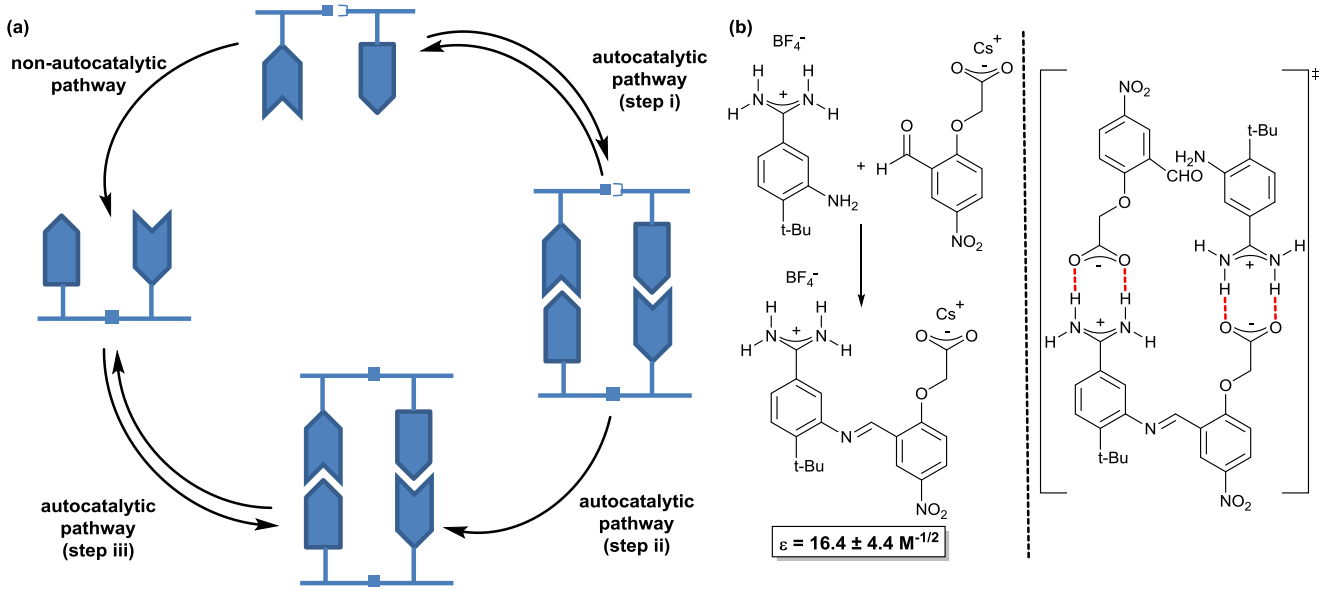

Fig. 26 (a) Representation of a minimal self-replicating system. The autocatalytic pathway involves three steps: i) coordination of the reactants to the template, ii) reaction between the two bonded reactants within the termolecular complex, iii) dissociation of the two molecules of template. (b) von Kiedrowski seminal work: example of a minimal self-replicator based on the complementary amidinium and carboxylate groups. **ε** is the autocatalytic efficiency and has been defined as the factor by which the rate of the autocatalytic synthesis exceeds that of the non-autocatalytic synthesis, for a template concentration of 1 M. The kinetic profile is satisfactorily approximated with a square-root model (reaction order p = 0.5). The reaction order p is defined as $[dc(T)/dt]_{initial} = k_a c_0 T^p + k_b$ where $[dc(T)/dt]_{initial}$ is the initial rate of template formation, k_a and k_b are the kinetic constants of the autocatalytic and non-autocatalytic pathways respectively, and c_0T is the initial template concentration. Refs: see the text.

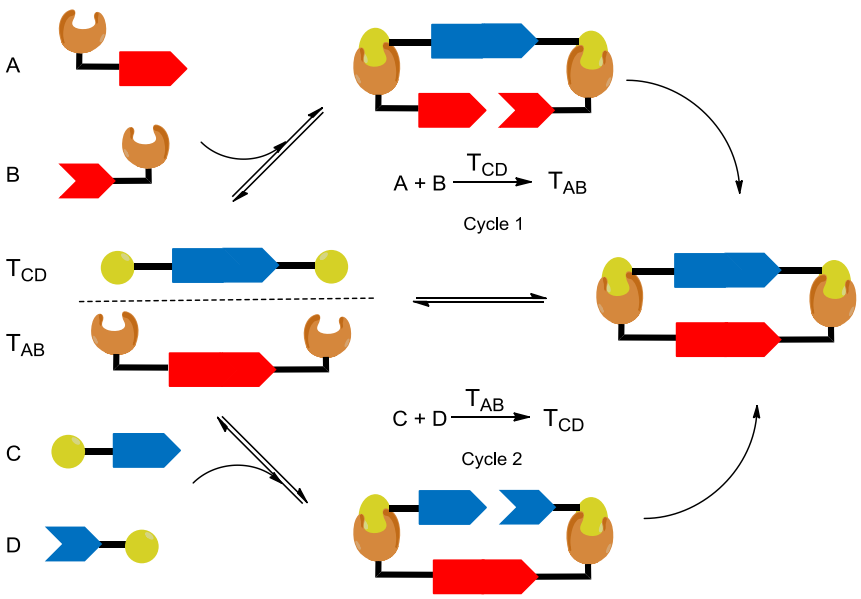

Fig. 27 Formal reciprocal replication system where T_{AB} serves as a template for the formation of T_{CD} and *vice versa*. The scheme does not include the formation of the "native" templates which can be added in small amount to start the cross-catalysis or formed *via* a non-templated route.

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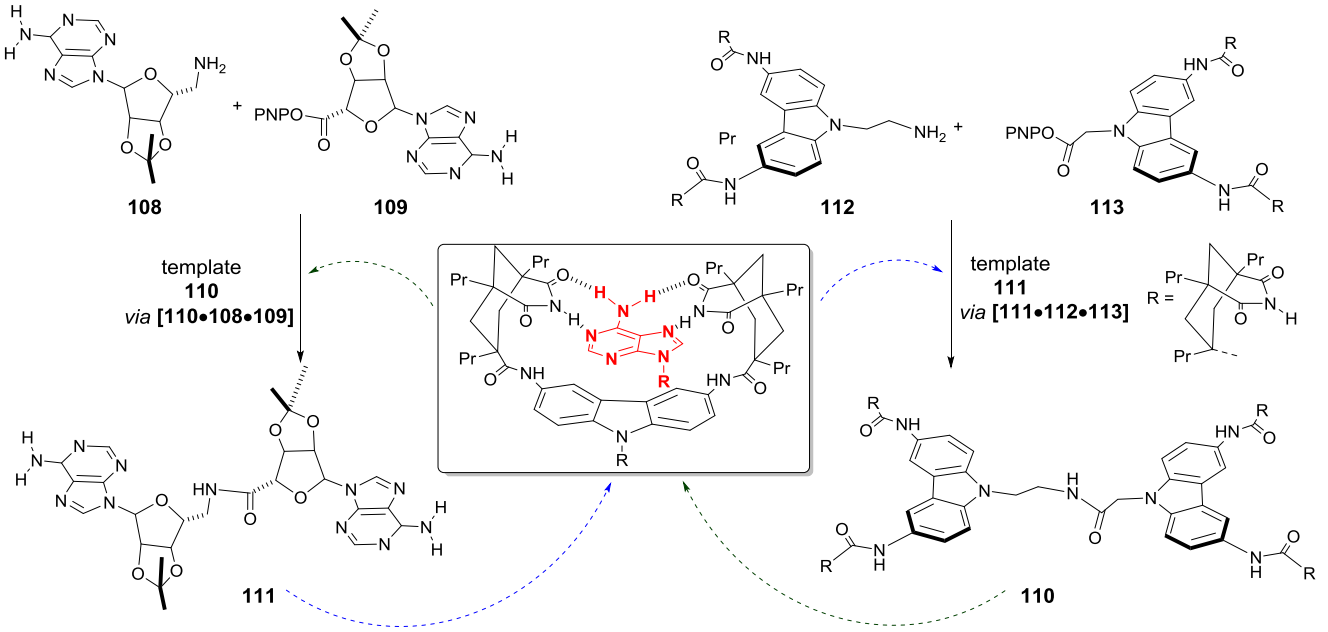

Fig. 28 Rebek and co-workers attempts towards an artificial reciprocal replication system. Templates **110** and **111** are able to copy each other but a true reciprocal system is prevented by the fast reactions between **108** and **113** and between **109** and **112**. Hydrogen bond interactions between the imide functions of **110** and the purine moiety of either **108** or **109** are represented at the right of the first equation. PNP = *p*-nitro phenol. Refs: see the text.

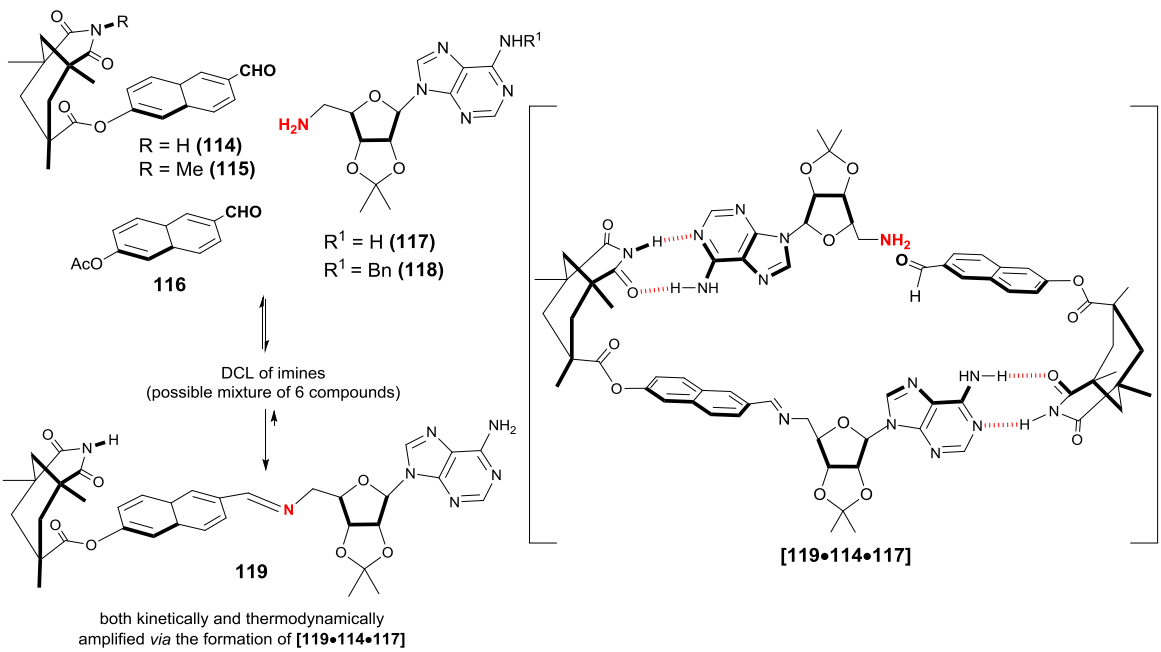

Fig. 29 Imine **119** is enhanced both kinetically and thermodynamically from the DCL library because of its ability to self-replicate through the formation of the termolecular complex **[119•114•117]**. Ref: see the text.

involves two components and the product is called a minimal self-replicator (**Fig.26** left). In a minimal self-replicating system, the product of the reaction (the replicator) accelerates its own formation by acting as a template which brings the reactants together. In the template, the entropy of activation of the reaction is reduced, resulting in an acceleration of the reaction rate. Non-

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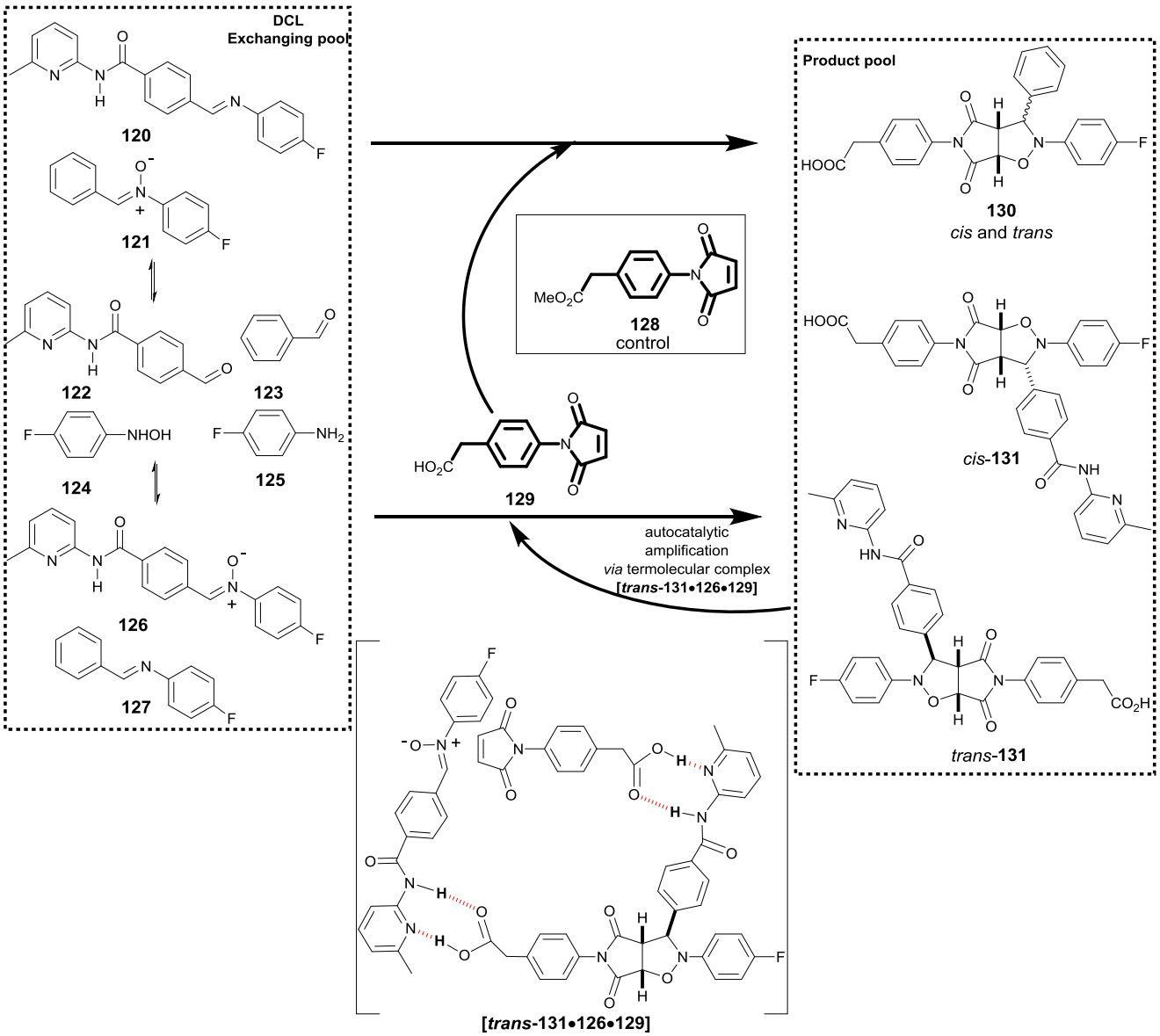

Fig. 30 *Trans*-**131** is amplified from a dynamic reagent pool composed of **120–127** because it is able to catalyse its own formation through the carboxylic acid amidopyridine termolecular complex **[*trans*-131•126•129]** represented below. Ref: see the text.

covalent interactions, mainly hydrogen bonding and hydrophobic interactions are the driving forces for the formation of the replicator-reactants complex. In a seminal example, the complementarities between the amidinium and carboxylate groups allowed for the self-replication of an imine compound (**Fig. 26** right) with autocatalytic efficiency of 16.4 ± 4.4 $M^{-1/2}$.[560] Kinetic studies provide information on the efficiency of these auto-catalysts: concentration versus time profiles of reactions seeded with an incremental amount of preformed template informs about the reaction order of the reaction (for the definitions of the autocatalytic efficiency and the reaction order see the caption of **Fig. 26**).[566–568] Up to now, most of the minimal self-replicators follow a parabolic growth (*i.e.* the reaction order is equal or close to 0.5) because the dissociation of the template-template complex is rate-limiting. More efficient auto-catalysts have recently been designed that approached the optimal *p* value of 1 (exponential growth).[569,570]

Several synthetic replicating systems were investigated in which the autocatalysed reaction was the formation of an amide,[32,561–565,567,571,572] an imidazolidinone ring,[573] an

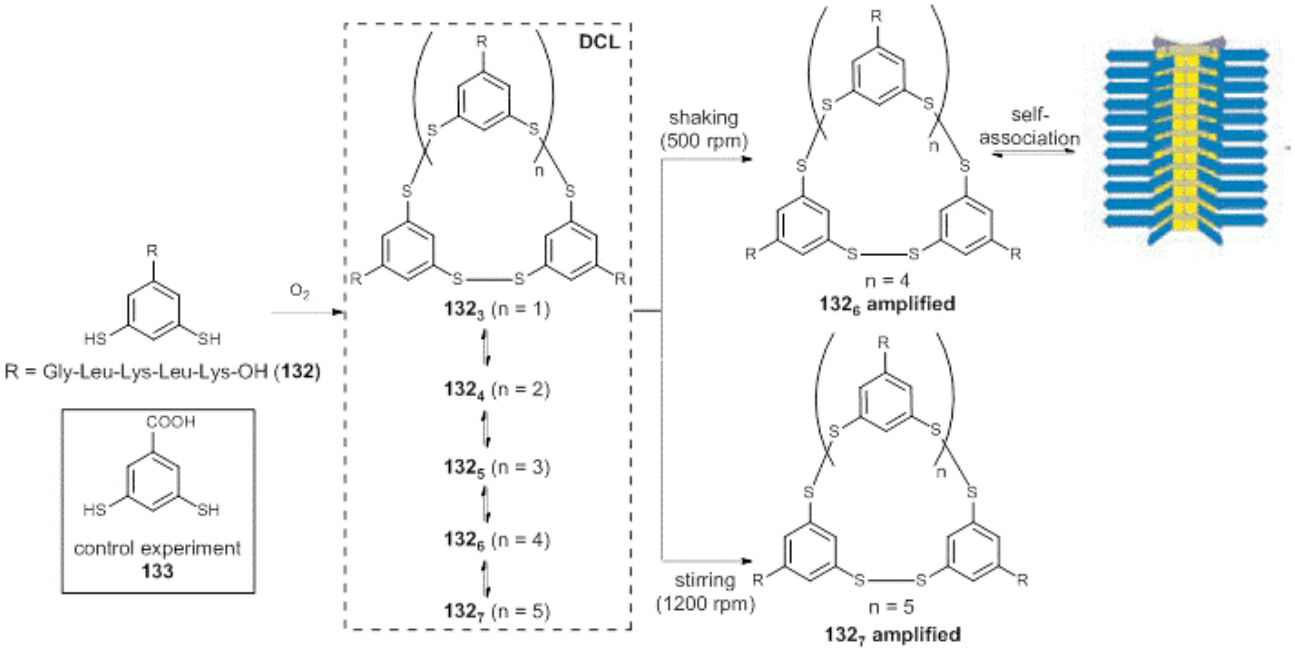

Fig. 31 $\mathbf{132_6}$ and $\mathbf{132_7}$ are amplified upon shaking and stirring respectively from a DCL based on dithiol building blocks. The association of peptide chains into elongated cross-β sheets drove the self-replication of $\mathbf{132_6}$ and $\mathbf{132_7}$. The self-organisation into fibres is represented for $\mathbf{132_6}$ but the same process occurred for $\mathbf{132_7}$. (The schematic representation of the fibres is reprinted with permission from ref. 591. Copyright 2010. American Association for the Advancement of Science).

imine,[560,574–576] a Diels–Alder reaction,[568,570,577–583] a 1,3-dipolar cycloaddition reaction,[584–589] and the formation of a S–S bond.[590–592] Excellent reviews exist which focus specifically on that topic and we will provide here only didactic examples for the non-expert readers.[336,569,593–609]

More elaborated systems are composed of several components: (i) reciprocal replication systems where cross-catalysis (and not autocatalysis) is at the origin of the rate enhancement,[586,610–612] (ii) dynamic combinatorial libraries composed of several molecules interacting with each other and by which self-replicating components can be amplified.[605,608,609] A potential perfect cross-catalytic example is represented in **Fig. 27** where templates T_{AB} and T_{CD} copy one another. Rebek and co-workers first attempted to build an artificial multi-component system with the idea to perform reciprocal replication cycles. First, they independently showed that products **110** and **111** are templates for the replication of each other (**Fig. 28**).[610,611] Indeed, a ten-fold increase of the initial reaction rate is observed when the reaction between **108** and **109** is performed with 0.05 mM of template **110**. Similarly, the reaction between **112** and **113** is enhanced 5 times in the presence of 0.05 mM of template **111**. However, a perfect reciprocal cross-catalytic system (*i.e.* the observation of cross-catalytic reactions in a system containing **108**, **109**, **112** and **113** as the four starting components) is not possible due to fast "side reactions" between **108** and **113** and between **109** and **112**.

Inspired by the work of Rebek, Giuseppone and co-workers studied a DCL composed of components **114–118** able to form reversible imine bonds yielding a possible mixture of six compounds.[575] Product **119** is both kinetically and thermodynamically amplified compared to the other imine products. This amplification is the result of the self-replication properties of product **119**, probably mainly through the formation of the hydrogen-bonded termolecular complex **[119•114•117]** shown in **Fig. 29**.

Philp and co-workers used a different approach to demonstrate that a self-replication reaction can bias the product distribution of a DCL.[588] Compounds **120** and **121** are in equilibrium with **126** and **127** through the reversible formation of the covalent imine and nitrone functions (**Fig. 30**). Upon addition of maleimide ester **128**, irreversible 1,3-dipolar cycloaddition with the nitrones yields the corresponding cycloadducts in low yield (21%) and poor selectivity (in terms both of the diastereoselectivity of the final cycloadduct and of the respective reactivity of the starting nitrones). However, in the presence of maleimide acid **129**, which possesses the complementary site of the amidopyridine group of nitrone **126**, formation of ***trans*-131** is clearly favoured (48% overall yield for the cycloadducts; almost 80% selectivity in ***trans*-131** compared to other cycloadducts) and **127** accumulated in the DCL exchanging pool. In the presence of both **129** and cycloadduct ***trans*-131** (*i.e.* that the DCL exchanging pool is seeded with a small amount of cycloadduct ***trans*-131**), the overall yield in cycloadducts is now 64% and cycloadduct ***trans*-131** represent 88% of the product mixture. The self-replicating behaviour of ***trans*-131** is at the origin of this product selectivity and of the amplification observed in the exchanging DCL. Self-replication goes through the catalytic termolecular complex **[*trans*-131•126•-129]** shown in **Fig. 30**.

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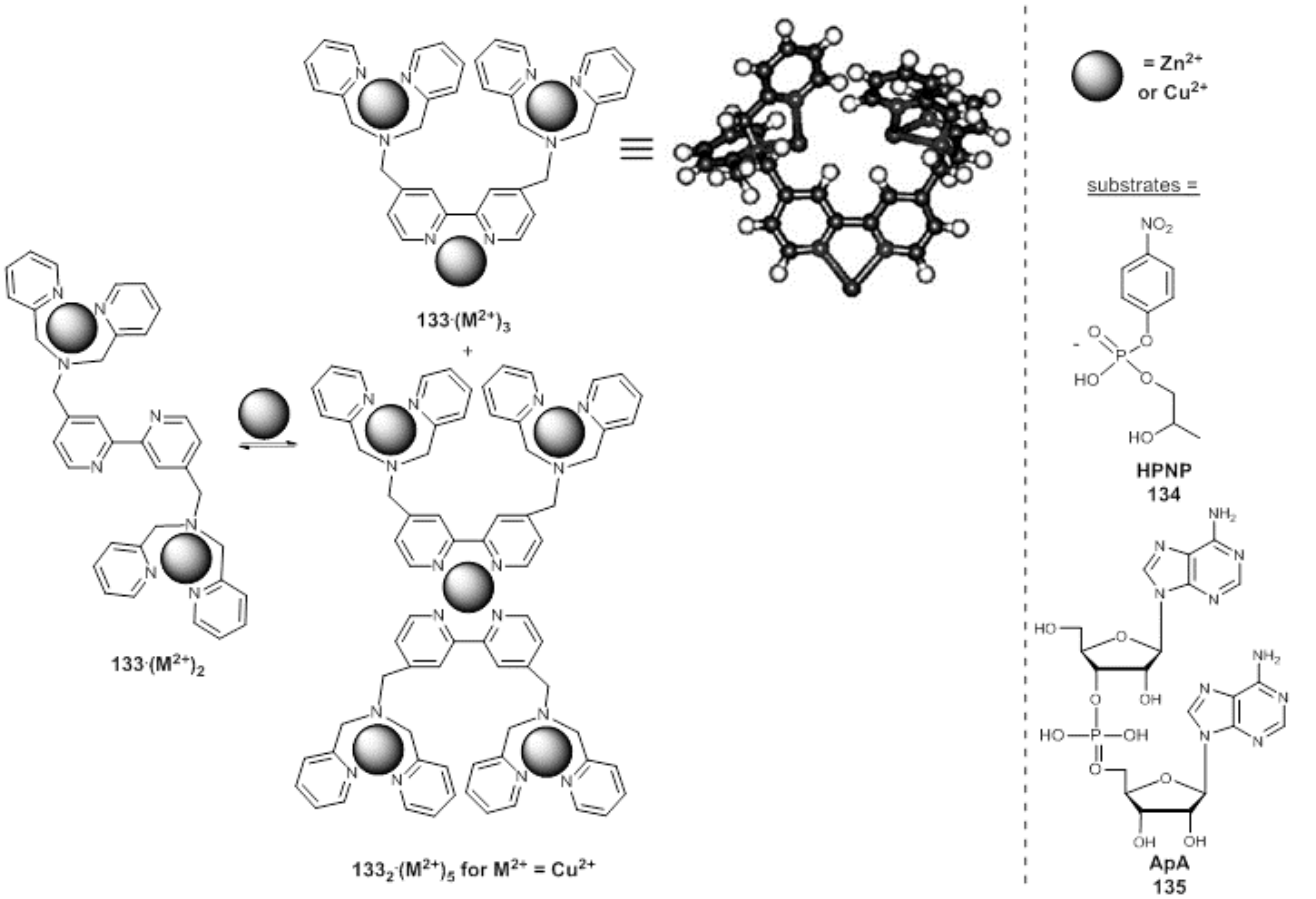

Fig. 32 Coordination of a third Zn or Cu cation to **133•$(M^{2+})_2$** (M = Zn or Cu) strongly alters the catalytic efficiency of the resulting complexes towards the hydrolysis of HPNP (**134**) and ApA (**135**). HPNP = 2-hydroxypropyl-*p*-nitrophenyl phosphate, ApA is a RNA dinucleotide. (The molecular model of **133•$(M^{2+})_3$** is reprinted with permission from ref. 647. Copyright 2008. The Royal Society of Chemistry). Refs: see the text.

Otto and co-workers studied the oxidation of compound **132** which potentially forms several macrocyclic oligomers **132_3**, **132_4**, **132_5**, **132_6** and **132_7**. The macrocycles are in equilibrium due to the reversible formation of the S–S bonds (**Fig. 31**).[591] Compared to the reference compound **133** which yields a mixture of trimer and tetramer, **132** gave dominantly the hexamer **132_6** upon shaking and the heptamer **132_7** upon stirring after 20 and 15 days respectively. **132_6** and **132_7** catalyse their own formation as it can be deduced from their sigmoidal concentration-time profiles and their increased rate of formation when the starting reaction mixture is seeded with a small amount of **132_6** or **132_7**. Several analyses revealed that the autocatalysis is driven by the assembly of the peptide chains into elongated cross-β-sheets. The formation of fibres precludes further equilibration of the hexamer and the heptamer into different macrocycles. The influence of the shear stress on the nature of the oligomer obtained can be explained by the mode of elongation of the hexamer and heptamer fibres. In both cases, the linear growth of the fibres is enhanced by fragmentation because it increases the number of fibre ends. Upon stirring, both hexamer and heptamer fibres are fragmented and the respective growing rate of both types of fibre favours the formation of the heptamer. Upon shaking, only the hexamer is consistently fragmented enhancing its own formation.

The field of self-replication has evolved from the duplication of small nucleotide sequences[547–553, 613] to anabolic autocatalysis, *e.g.* RNA enzymes undergo self-sustained replications in the absence of proteins.[614–617] Advances in self-replicating peptides[612,618–621] and fatty acids[622,623] also provide hints for a better understanding of the origin of life on earth and early molecular evolution. In parallel, the replication properties of synthetic molecules are of interest in order to control the dynamic behaviour of complex chemical reaction systems.[590] Recent results indicate that selectivity can be achieved by a suitable control of the replication processes.[583,588]

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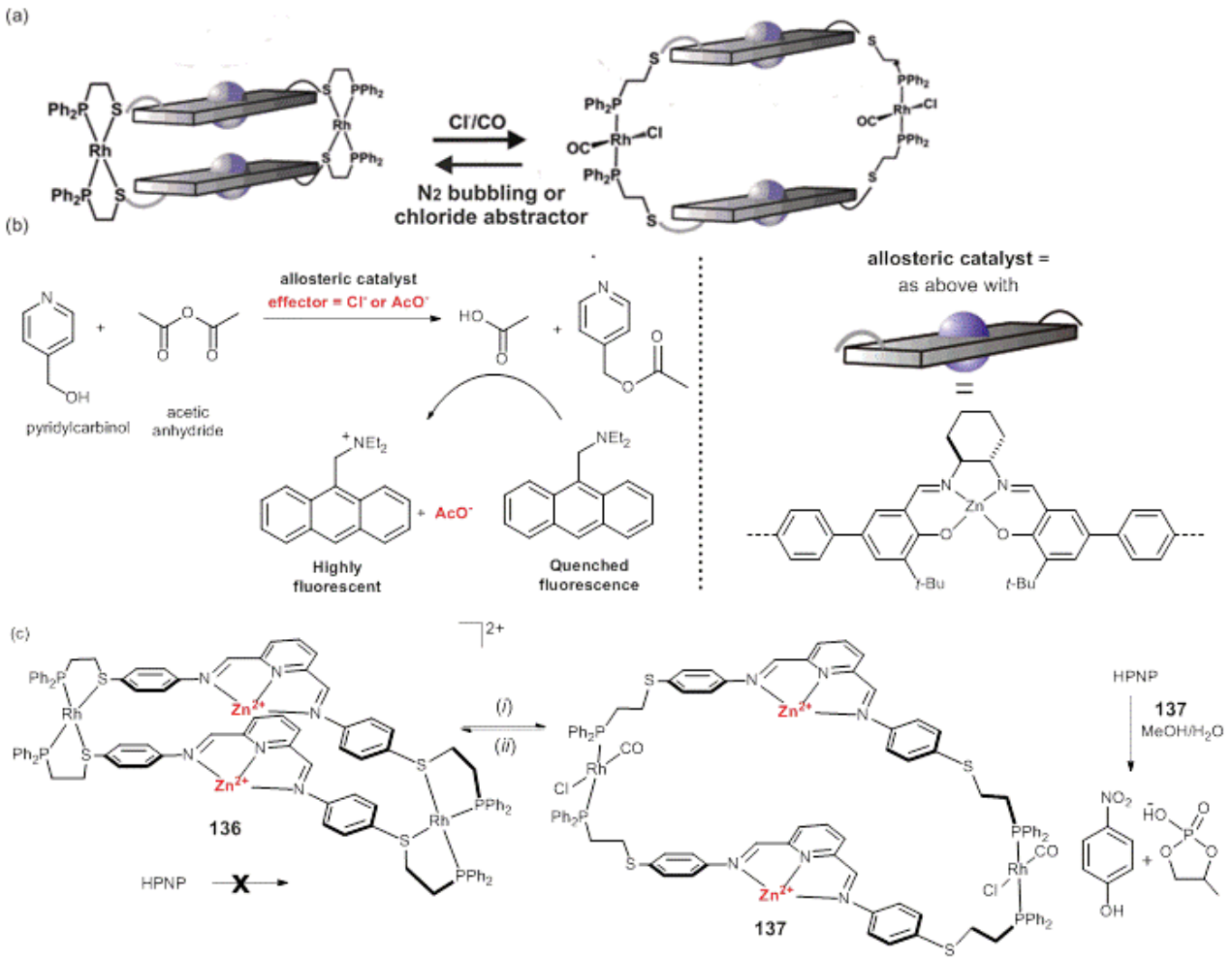

Fig. 33 (a) First series of allosteric catalysts developed by Mirkin and co-workers. The nature of the complex, *i.e.* a condensed state (closed-form, left) or open-form (right) can be controlled by the addition of small molecules. The catalytic centre can be a Cr^{III} salen complex (for the ring-opening of epoxides), Zn^{II} salen or porphyrin complex (for acyl transfer reactions) or Zn^{II} N,N,N pincer (for the hydrolysis of HPNP). (Representation of the allosteric catalyst is reprinted with permission from ref. 660. Copyright 2006. American Chemical Society). (b) The acylation of pyridylcarbinol is catalysed by the open-form of an allosteric catalyst (the catalytic centre is a Zn^{II} salen complex). Chloride anions are effectors for the generation of this open-form. At a given catalyst loading, the minimum observable amount of acylation product formed (4-acetoxymethylpyridine) depends on the concentration of chloride. The greatest amplification measurable as 4-acetoxymethylpyridine formed per mole of Cl^- occurring to lower Cl^- to catalyst ratio. The system can be used for the detection of chloride anions. To this end, an acid-sensitive fluorophore was used for the detection of acetic acid (the second product of the reaction) and concentration of Cl^- as low as 800 nM was detected. The same strategy works with acetate anions used as effectors. Because AcO^- is generated by the fluorophore, the reaction is autocatalytic and presents some analogy with the self-replicators presented in section 4. Refs: see the text. (c) Allosteric regulation of the hydrolysis of HPNP (**134**, see formula in **Fig. 32**): the closed-form **136** is inactive whereas the open one **137** is extremely active. The AcO^- ligands and counterions of the complexes are omitted for clarity. (i) tetrabutylammonium chloride/CO, CD_2Cl_2; (ii) N_2 bubbling or addition of 2 equiv. of $AgBF_4$. Refs: see the text.

5. Allosteric catalysis

In enzymes, the catalytic activity can be triggered by the binding of a molecule to a regulatory site different and usually remote from the active/catalytic site. The allosteric effector/modulator can be the substrate itself (homotropic activator) or a different molecule (heterotropic activator). The coordination of the activator/effector to the regulatory site alters the geometry of the active site through a conformational change of the enzyme structure. An effector can either enhance or diminish the catalytic activity. The presence of a small amount of a molecule (the allosteric effector) in the cell is translated to the formation of other activators through cascade reactions. The synthetic

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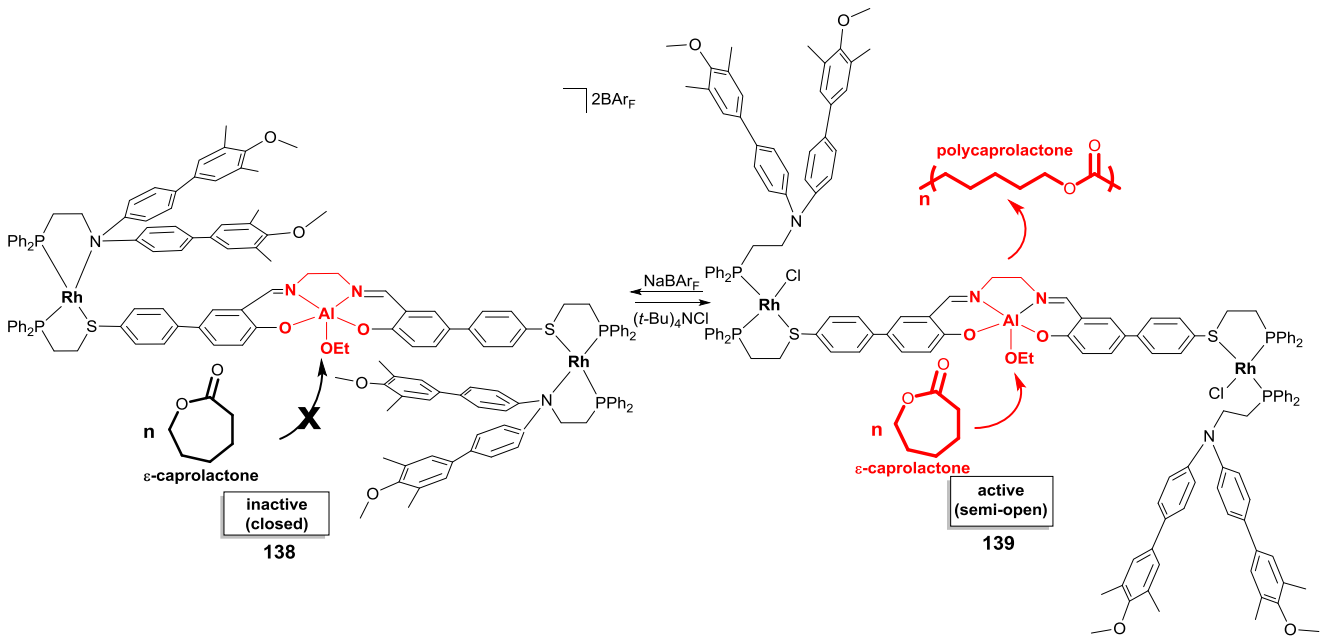

Fig. 34 Allosteric supramolecular triple-layer catalyst. The semi-open form **139** is highly active for the polymerization of ε-caprolactone whereas the closed-form **138** is almost completely inactive. Regulation of catalysis with time is achieved by going from one complex to another through the simple addition of $NaBAr_F$ or $(t\text{-Bu})_4NCl$. Ref: see the text.

modification of the regulatory site of a biomolecule (enzymes, proteins…) allows for the comprehension of the allosteric reaction and the development of different *in vivo*/*in vitro* enzymatic reactions.[624,625]

At the molecular level, the allosteric effect has been mostly considered in terms of binding properties. The allosteric receptors that have mainly been studied are those in which the coordination of the allosteric effector to the first binding site alters positively (or negatively) the binding of the same or a different molecule to the second receptor binding site. Synthetic allosteric catalysts allow not only for a better understanding of enzymatic processes and the development of catalysts for enzymatic reactions but also for new catalysts for "non-natural" reactions in which the activity/selectivity can be switched by the activator.[376,626–628] Earlier examples described how an intramolecular reaction can be modulated by the addition of well-chosen effectors.[33,629–634] Mirkin and co-workers[376] recently reviewed allosteric catalysts including several examples of allosteric enzyme mimics (NAD(P)H mimic,[631,632] Flavin coenzyme mimics[635–637] and several nuclease mimics.[42,638–647]

We already mentioned in the **Part 1** of this review[315] how ions can alter the chiral ability[648,649] or the coordination mode of classical covalent ligands.[650,651] Very recently, Vidal and co-workers showed that the addition of Cs^+ could trigger the bidentate coordination of a ligand in which the phosphite functions are separated by a polyethyleneoxy linker.[652] Without Cs^+, only monodentate coordination was observed and the resulting catalyst was poorly selective. Upon addition of 1.3 equiv. of $CsBAr_F$, a far more selective catalyst was generated in which the chiral phosphite ligands adopt an equatorial-equatorial coordination mode (up to 90% ee for the asymmetric hydroformylation of vinyl acetate).

Nuclease enzymes as well as their synthetic mimics usually benefit from cooperative effects between two or more catalytic metal centres.[653] In allosteric catalysis, activators (usually metal ions) are used to arrange the catalytic centres in close proximity through coordination to the regulatory site and subsequent induced conformational change. Comparison of the hydrolysis rates of the phosphodiester bond by the catalyst with and without the allosteric effector reveals the efficiency of the approach. For example, Takebayashi et al. examined the ability of ligands **133**, in presence of 3 equiv. of Cu^{2+} or Zn^{2+} ions, to catalyse the hydrolysis of 2-hydroxypropyl-*p*-nitrophenyl phosphate (HPNP, **134**) and ApA **135**, a RNA dinucleotide (**Fig. 32**). For HPNP, a 55 and 4.1-fold increase of the reaction rate were observed for the trinuclear complexes **133**•$(Cu^{2+})_3$ and **133**•$(Zn^{2+})_3$ compared to the binuclear complexes **133**•$(Cu^{2+})_2$ and **133**•$(Zn^{2+})_2$ respectively. ApA is also more efficiently hydrolyzed by these species (a 33-fold increase of the reaction rate is observed for **133**•$(Zn^{2+})_3$ compared to **133**•$(Zn^{2+})_2$). The molecular models of **133**•$(Zn^{2+})_2$ and **133**•$(Zn^{2+})_3$ (**Fig. 32**) help to understand these rate enhancements; in the dinuclear complex the two metals are located on two different half-spaces related to the bipyridine ligand whereas in the trinuclear complexes the two metals are

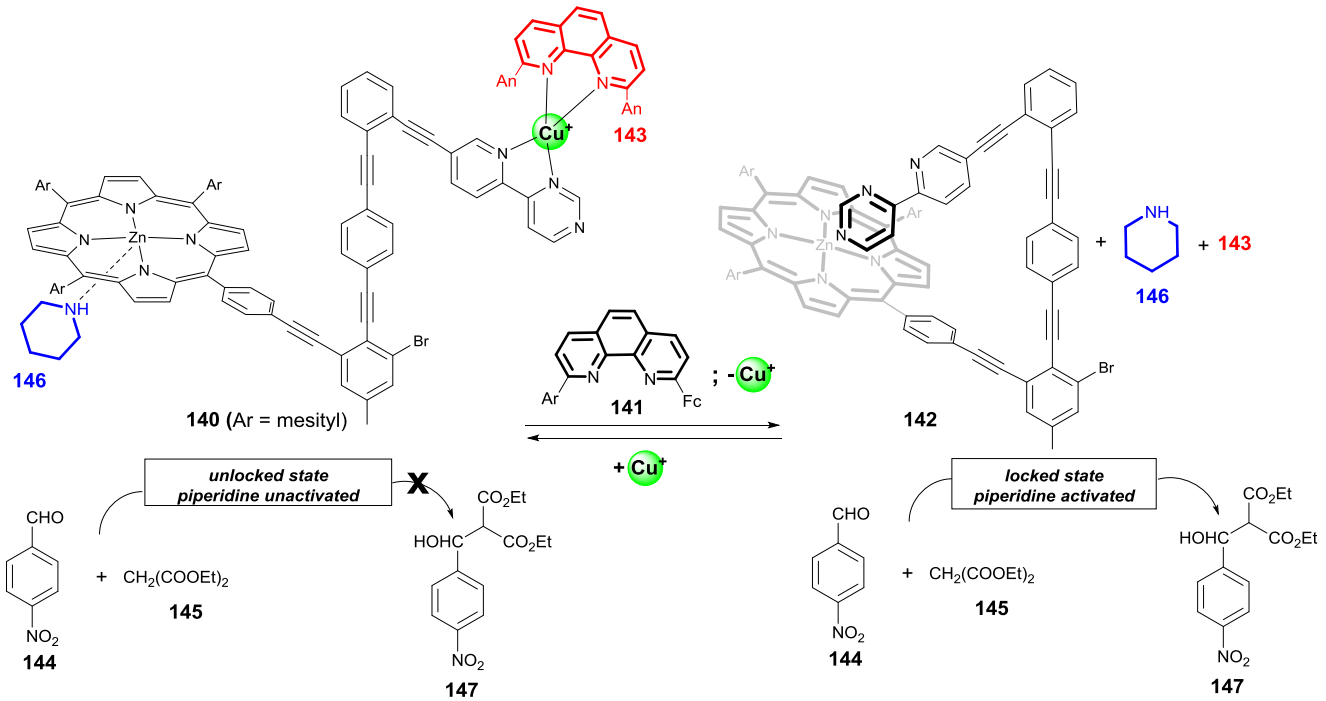

Fig. 35 The activity of the organocatalyst piperidine (**146**) is regulated by its reversible coordination to the zinc porphyrin unit of **140** and **142**. In the locked state, **142** is unable to interact with piperidine and so the organocatalysed Knoevenagel reaction occurs in solution. Upon addition of Cu^+, the pyrimidine unit moves from the zinc centre to the Cu^+, **143** completing the coordination sphere of the copper centre. The state is now unlocked, the piperidine can coordinate the zinc and catalysis is inhibited. The system is reversible and addition of phenanthroline **141** to the unlocked state restarts the catalytic reaction. An = anthracene. Ref: see the text.

close each other. The two different binding sites in **133** allow for an allosteric regulation of the hydrolysis reaction by the metal ions; the reaction can be switched "on" (addition of an excess of metal ions to favour the formation of the trinuclear complex) and "off" (removal of the metal ion with EDTA), although not perfectly (the "background" reaction with the dinuclear complex is not negligible).[644,647]

As stressed by Mirkin,[376] an efficient allosteric enzyme mimic must involve a reversible binding of the effector to the regulatory site. Such reversibility is required to regulate the catalysis, *i.e.* modify the activity or selectivity of the catalyst along the time. Also, the catalysts will be considered as really supramolecular only if the binding of the effector is reversible. Mirkin developed the weak-link approach (WLA), *i.e.* the use of hemilabile ligands[654] to construct flexible supramolecular macrocyclic and tweezers-like complexes.[655,656] The geometry of these structures can be easily modified by adding small molecules (such as chloride anions and CO) that interact with the metal centre, displace the hemilabile ligand, and alter/control the general architecture of the supramolecule. Since the reaction is reversible (purging with nitrogen gas restores the first catalyst state) control of the geometry of the catalyst over the time is conceivable.

Mirkin reported a first series of ligands containing a Zn^{II} or Cr^{III} catalytic metal centres in its core appended with one or two ether or thioether phosphine hemilabile ligands (**Fig. 33, a**). Rh or Cu cations were used to bind the hemilabile ligands and generated a closed or semi-closed structure. The open structure of the catalysts was obtained by simple addition of chloride anion and CO. The proximity of the catalytic centres in the closed/condensed form was translated into a higher activity for these complexes in the ring-opening of epoxides compared to the open-form.[657,658] On the contrary, the open-forms were more active for acyl transfer reactions.[659–662] The reaction between pyridylcarbinol and acetic anhydride yields acetoxymethylpyridine and acetic acid (**Fig. 33, b**). In presence of Mirkin complex, chloride anions can be used as effectors for this reaction. The minimum amount of chloride anions requires to observe product formation (or signal amplification) can be determined. Interestingly, optimal signal amplification occurs at the lower $[Cl^-]$/[catalyst] ratio. The catalytic system was coupled with an acid-sensitive fluorophore (acetic acid being the second product of the reaction) and chloride concentration as low as 800 nM can be detected.[659,661] Acetate anions can be used as effectors instead of chloride and their detection was achieved following the same strategy. However in this case, the acetate anions generated by the acid-base reaction between the fluorophore and the acetic acid product can also act as effectors and the whole reaction becomes autocatalytic (**Fig. 33, b**).[662]

A limitation of these systems was that the catalytic activity was not totally suppressed in their less active forms and thus the catalytic experiment was not perfectly controlled. This problem was solved when complexes **136** and **137** were used for the hydrolysis of HPNP. The closed-form **136** was totally inactive whereas the open-form **137** hydrolyzed HPNP quantitatively in less than 40 min (**Fig. 33, c**).[663]

An even more striking example was jointly reported by Kuwabara and Mirkin groups recently.[664] They described a triple-layer complex that exists in a semi-open and a closed-form, both

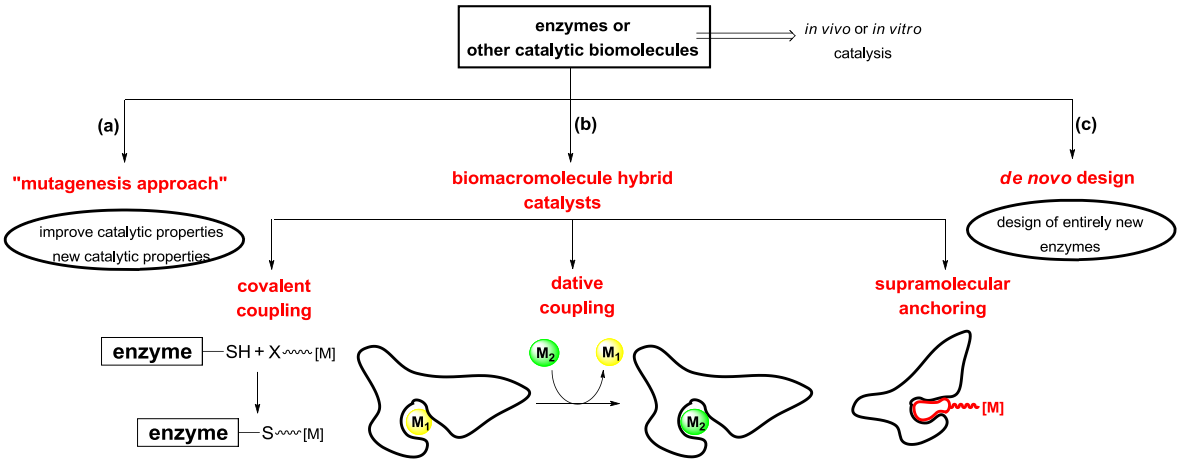

Fig. 36 Schematic representation of the different approaches used in the construction of new catalysts based on enzyme scaffolds: a) site-directed modification of the wild enzyme structure, b) hybridization of enzymes with small molecule homogeneous catalyst and c) *de novo* design of new enzymes.

of them can be reversibly obtained by adding small molecules (**Fig. 34**). The semi-open form **139** proved to be highly active for the polymerization of ε-caprolactone (quantitative conversion of the monomer after 40 min) whereas the closed-form **138** was inactive (although activity is observed over 100 h due to decomposition). The lack of activity of the closed-form was explained by the folding of the upper and lower layers, above and below the Al-salen group, preventing the coordination of the substrate to the Al catalytic centre. Finally, the authors demonstrated that the catalytic experiment could be switched "on" and "off" without loss of activity and thus the polymerization number and the polydispersity of the resulting polymer could be controlled over the time.

Very recently, Schmittel et al. used a different approach to control the activity of an organocatalyst (piperidine **146**, **Fig. 35**) for the Knoevenagel reaction between **144** and **145**.[665] The reaction occurs in solution but can be stopped if the piperidine is coordinated to a Lewis acid centre, an unsaturated zinc atom in this case. They designed the complex **142** where the pyrimidine is intramolecularly coordinated to the apical position of the zinc porphyrin. In this locked state, the piperidine was activated and catalysis occurred in solution. Upon addition of Cu^+ and phenanthroline derivative **143**, the system switched from the locked to the unlocked state **140** in which the phenanthroline and the pyridine-pyrimidine units coordinated to the copper liberating a coordination site of the zinc metal. The coordination of piperidine to the Zn atom of the porphyrin inhibits the catalytic reaction. The system is reversible and the unlocked state is totally catalytically inactive (no background reaction reported in this case). However, it is worth noting that the effectors used in this allosteric system (*i.e.* Cu^+, and the phenanthroline derivatives **141** and **143**) accumulate in the reaction media during the locked/unlocked cycles.

These allosteric catalysts constitute encouraging attempts towards the development of catalysts for which the activity and selectivity can be controlled reversibly along the course of the catalytic reaction. In the examples mentioned above, non-covalent interactions play an important role in the control of the process[666] and the strategy is complementary to the switchable catalysts developed so far in which the activity is controlled by acid/base addition,[667–669] by modifying the temperature,[670–673] the magnetic force,[674,675] the wavelength,[109,147,312,676–683] the redox potential[684–688] and other parameters.[689] Feringa and co-workers recently reported a system in which both the activity and enantioselectivity of an organocatalytic reaction is tuned by the motion of a molecular motor.[690]

6. Biomacromolecule and peptide hybrids as organic and inorganic catalysts

Overcoming the limitations of enzyme catalysis in terms of its restricted reaction and substrate scope, stability, and diversity is the subject of intense research. Several approaches (**Fig. 36**) have been developed using the knowledge accumulated on enzyme structure, these include: (a) "the mutagenesis approach" in which site specific modification of the enzyme structure allows for a better control of its activity and properties,[691–694] (b) "the preparation of biomacromolecule and peptide hybrids" by covalent and supramolecular anchoring of organic or inorganic catalysts to enzymes or peptides, and (c) "the *de novo* approach" for the design of entirely new enzymes. Supramolecular interactions are obvious in all cases due to the enzyme-like structure of these catalysts. We will only focus on the design of efficient biomacromolecule and peptide hybrid catalysts. In this case, non-covalent interactions are not only inherent to the presence of the enzyme part but are also present in the anchoring strategy used to link the enzymes with the inorganic or organic catalysts.

A great effort has been made recently to design biomacromolecule and peptide hybrids of organic and inorganic catalysts. The main idea is to conjugate a catalytic metal centre or an organocatalyst with a biomacromolecule (RNA, DNA, protein or enzymes) or with a designed peptide without substantially altering its overall structure. Such a conjugation process affords hybrid catalysts with new features, by combining the molecular recognition and shape selectivity of biomolecules with the metal-

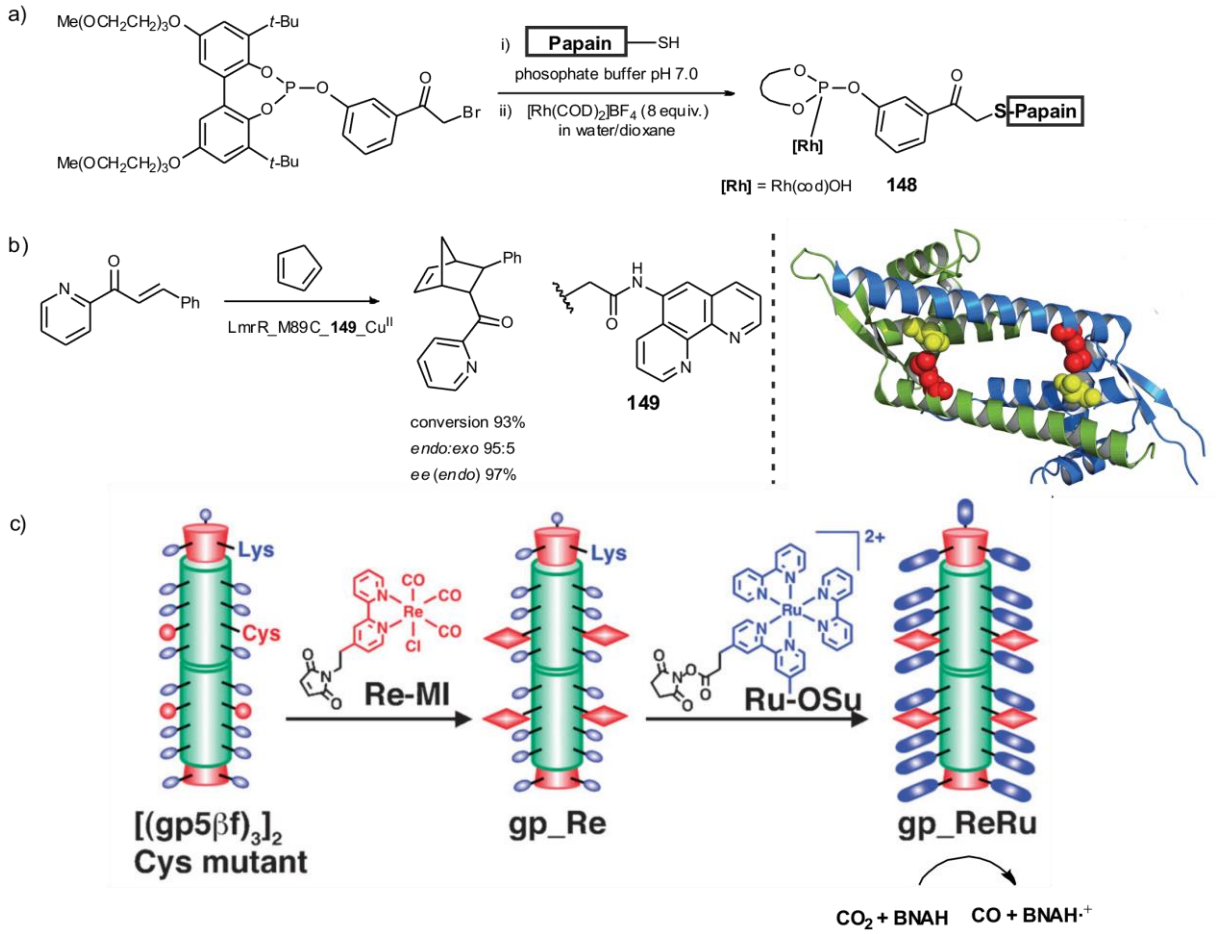

Fig. 37 Examples of covalent linking between an enzyme and a homogeneous catalyst. (a) Conjugation of a phosphite ligand to the thiol function of a cysteine residue of papain enables the preparation of the hybrid catalyst **148**. **148** catalyses the hydrogenation of methyl 2-acetamidoacrylate but no enantioselectivity is observed. (b) Left: Diels–Alder reaction catalysed by LmrR_M89C_**149**_Cu^{II}. Right: Pymol representation of dimeric Lactococcal multidrug resistance Regulator LmrR in a ribbon model. Either position 89 (red) or 19 (yellow) were used for the covalent attachment of ligand **149**. (The representation of the protein dimer is reprinted with permission from ref 720. Copyright 2012. John Wiley and Sons). (c) Covalent modification of a triple-strand β-helix nanotube $[(gp5\beta f)_3]_2$ Cys mutant with a Re and a Ru complexes using the complementarities between Lys and Cys as anchoring groups. The hybrid heteronuclear complex catalyses the reduction of CO_2 into CO. BNAH = 1-benzyl-1,4-dihydronicotinamide. (The synthetic scheme is reprinted with permission from ref. 718. Copyright 2011. The Royal Society of Chemistry). Refs: see the text.

ligand properties of a homogeneous catalyst or the inherent activity of an organocatalyst. Three different approaches for anchoring the catalytic moiety are used: (a) covalent, (b) dative or (c) supramolecular (see schematic representation of these approaches in **Fig. 36**). The different approaches will be briefly described with a special focus on supramolecular anchoring.[695–707]

In the covalent approach, the nucleophilic thiol function of cysteine is usually employed to attach covalently the protein scaffold to ligands for metal catalysis.[708–720] In this manner, papain can be conjugated to a phosphite ligand by means of a nucleophile substitution reaction between the thiol of a cysteine residue and a carbon-bromine bond present in the backbone of the phosphite. In the presence of Rh(I), the hybrid molecule is an active hydrogenation catalyst (**148**, **Fig. 37, a**).[708] Usually, the catalyst is incorporated within an existing binding pocket of the enzyme, comprising enough space for subsequent substrate binding and reaction. Roelfes and co-workers recently demonstrated that such a binding site can be created at the interface of a protein dimer. They used site-directed mutagenesis to introduce cysteine residues at the 19 and 89 positions of Lactococcal multidrug resistance Regulator (LmrR). The mutant called LmrR_M89C_**149**_Cu^{II} (where **149** is the phenanthroline ligand covalently linked to the enzyme, **Fig. 37, b**) catalysed asymmetric Diels–Alder reactions with ee up to 97%.[720] The reaction takes place within the chiral environment provided by the hydrophobic pocket at the interface of the protein dimer. Recently, the thiol group of cysteine and the amino group of lysine were used to orthogonally anchor a Re catalyst and a Ru photosensitizer on a $[(gp5\beta f)_3]_2$ Cys mutant. The resulting photocatalyst reduces CO_2 into CO under visible light using 1-benzyl-1,4-dihydronicotinamide (BNAH) as a sacrificial reagent (**Fig. 37, c**).[718]

The covalent approach is not limited to coupling with enzymes as oligopeptides and even small sequences of α-amino acids can be functionalized with an organic or inorganic catalytic centre.[721–732] As an example, Ball and co-workers used the carboxylate functions of glutamate or aspartate of a natural nonapeptide

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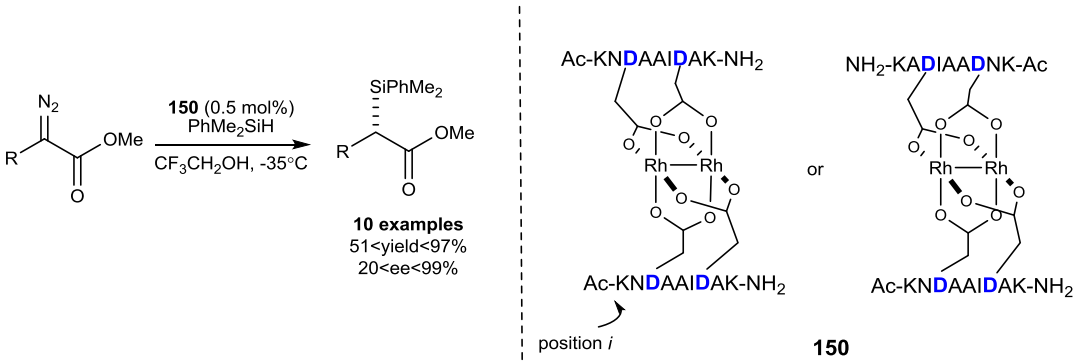

Fig. 38 Metallopeptide **150** is obtained by coupling the carboxylate functions of the aspartate residues of a nonapeptide with $[Rh_2(OAc)_2(tfa)_2]$. One of the isomer of **150** (not assigned but separated by HPLC) gave up to 99% ee for the asymmetric insertion of diazoacetates into Si-H bonds. Surprisingly, depending on the substrates, both isomers can give comparable or markedly different ee. K = Lysine, N = Asparagine, D = Aspartic acid, A = Alanine and I = Isoleucine. Ref: see the text.

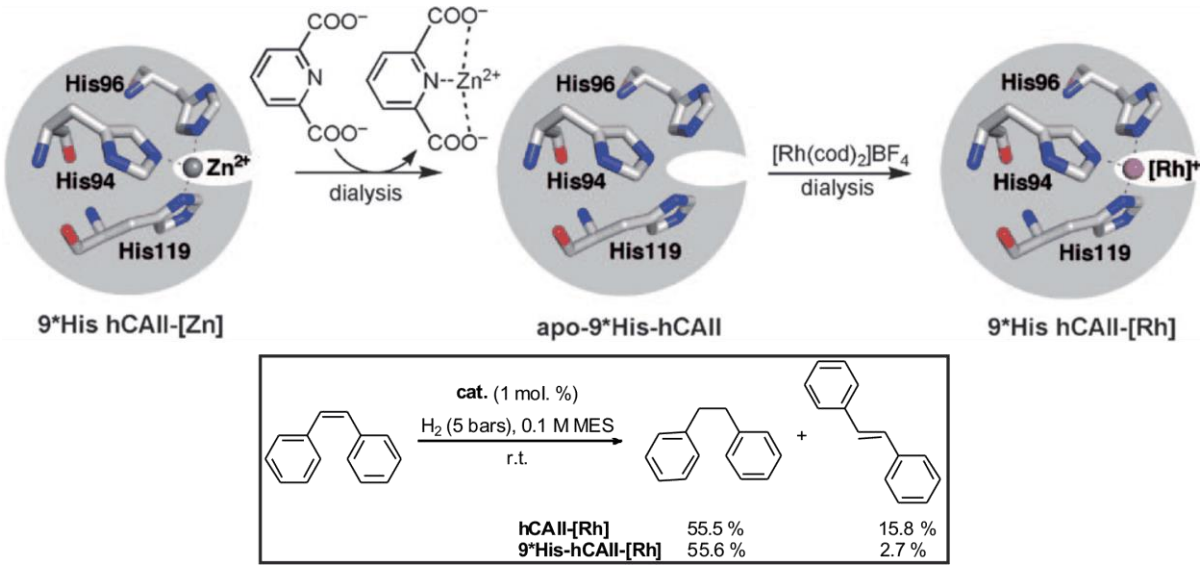

Fig. 39 Example of a dative approach for the preparation of a rhodium-substituted carbonic anhydrase. Above: Procedure for the preparation of **9*His hCAII-[Rh]**. Firstly, 2,6-pyridinedicarboxylate is used to remove the zinc active-site. Then, dialysis of the apoenzyme against a solution of $[Rh(cod)_2]BF_4$ yields **9*His hCAII-[Rh]**. Below: Comparison of the activity of **9*His hCAII-[Rh]** and **hCAII-[Rh]** for the hydrogenation of *cis*-stilbene. **hCAII-[Rh]** has 6.5 extra Rh, probably presents on its surface, whereas **9*His hCAII-[Rh]** only has one. **9*His hCAII** is a variant of human carbonic anhydrase isoenzyme II (**hCAII**), in which site-directed mutagenesis replaced nine of the histidine residues on the surface by arginine, alanine, or phenylalanine residues. MES = 2-(N-morpholino)ethanesulfonic acid. (Synthetic scheme for the preparation of **9*His hCAII-[Rh]** is reprinted with permission from ref. 744. Copyright 2009. John Wiley and Sons). Ref: see the text.

sequence as ligands for Rh(II) and the resulting catalyst performed the asymmetric reduction of a diazoacetate substrates.[733] Based on a computed structure, a library of 22 metallopeptides was investigated and the best catalytic result (92% ee) was obtained with **150** (**Fig. 38**). The presence of a bulky group at the *i*+3 position (where *i* is the first aspartic acid of the sequence) is important to achieve good enantioselectivity. Recently, the metallopeptide catalysts were supported "on beads" and the catalytic reaction was extended to asymmetric cyclopropanation.[734] The same group employed a single peptide chain as ligand for a dirhodium precursor. The hybrid combined peptide sequence for molecular recognition and a catalytic moiety for site-directed transformation. The resulting metallopeptide was used as a catalyst to modify regioselectively remote unreactive groups of complementary oligopeptides or proteins.[735–738]

In the dative approach, a catalytic site is conjugated to a protein by means of non-covalent interactions. Metal cations or complexes are incorporated within the binding pocket of enzymes as a result of Lewis acid – Lewis base interactions, electrostatic interactions and hydrogen bond interactions occurring between α-

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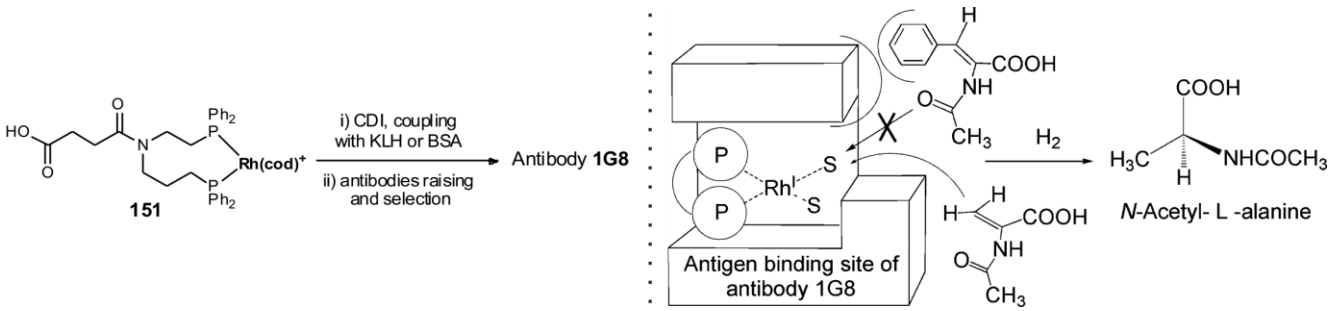

Fig. 40 Asymmetric and substrate-size selective hydrogenation with antibody-achiral rhodium complex. Left: Preparation of antibody **1G8** (CDI = 1,1′-carbonyldiimadazole; KLH = keyhole limpet hemocyanin; BSA = bovine serum albumin). Right: Hydrogenation of 2-acetamidoacrylic acid is achieved with 98% ee whereas 2-acetamidocinnamic acid is not hydrogenated because it does not fit the binding pocket of **1G8**. The asymmetric hydrogenation is performed in buffer (pH 7.4); the low conversion is a consequence of the low solubility of the substrate in this medium. (The schematic representation of the complex is reprinted with permission from ref. 783. Copyright 2006. The Royal Society of Chemistry).

amino acid chain residues and the metal ion. The preparation usually requires the removal of the prosthetic group which is replaced by introducing a synthetic metal complex within the active site of the apoenzyme.[739] Metal ions and organometallic catalysts were successfully incorporated into the active site of phytase,[740,741] carbonic anhydrase,[742–745] myoglobin,[739,746–750] streptavidin,[751,752] Xylanase A[753–755] and within the ferritin cage.[756–760] In these artificial metalloenzymes, the chemical mutation of the prosthetic group can improve the efficiency of the enzyme for its catalysed reaction or totally change the reactivity of the enzyme. Thus, Kazlauskas and co-workers replaced zinc in various mutants of bovine or human carbonic anhydrase isoenzyme II by rhodium.[744] For the best mutant (**9*His hCAII-[Rh],** **Fig. 39**), only one extra rhodium is present *i.e.* one of the rhodium is bound to the active site and the other on the surface. The rhodium centre within the active site of the artificial biocatalyst catalyses the hydrogenation of *cis*-stilbene, but with a lower activity compared to a "naked" rhodium precursor, while the rhodium atom on the surface catalyses the isomerisation reaction. Because *cis*-stilbene fits better in the active site of the metalloenzyme than *trans*-stilbene, selective hydrogenation of *cis*- over *trans*-stilbene is observed.[744] Serum albumin is another protein medium used for catalytic reaction, although the nature of the active site is less well-defined than that in the other proteins mentioned above.[761–777] Mahammed et al. reported that the chirality present in the serum albumin can be transferred, to some extent, to the corrole metal complex incorporated. In the sulfoxidation of sulfides, the albumin-conjugated metal complex outperforms the serum albumin alone and at good conversion (>75%), enantioselectivity up to 68% was obtained.[771] Nolte and co-workers also used the dative approach (or cofactor reconstitution method) to create giant amphiphiles and perform reactions within their confined and protected space.[778–781]

In addition to the covalent and dative strategies, supramolecular anchoring of a metal complex to enzyme biomolecules was also accomplished by means of: (i) antibodies incorporating transition metal complex, (ii) embedding metal complexes in double-strand DNA, and (iii) use of the biotin-(strept)avidin technology.

Antibodies can be elicited against transition-metal complexes which resemble the transition state of a given catalytic reaction and subsequently evaluated as catalytic hosts.[782–786] Even though catalytic activity inside these antibodies was successfully achieved, the chemoselectivity and enantioselectivity were lower than those observed with other artificial metalloenzymes. However, Harada and co-workers showed that monoclonal antibody **1G8** elicited against the achiral rhodium complex **151**, beforehand conjugated to a keyhole limpet hemocyanin (KLH) or bovine serum albumin (BSA), are able to catalyse the asymmetric hydrogenation of 2-acetamidoacrylic acid with ee up to 98% (however, at a modest 23% yield, **Fig. 40**).[783]

Engineered RNA[787–790] and DNA[791–794] biomolecules found far less application in catalysis than synthetic enzymatic proteins.

However, Roelfes and Feringa revitalized the field by intercalating achiral metal complexes within DNA duplex and thus performing DNA-based asymmetric catalysis (**Fig. 41, a**).[795,796] They first used a 9-aminoacridine spacer to separate the intercalating group from the nitrogen donor atoms (1st generation ligand) but simple derivatives of 4,4'-bipyridine (2nd generation ligand) also proved to be effective. The authors reported a large number of examples where the chirality of the DNA is successfully transferred to the copper(II) catalytic centre for Diels–Alder reactions,[797–804] Michael addition reaction,[802,805–807] Friedel–Crafts reaction,[802,804,806] hydration of enones,[803,808] hydrolytic kinetic resolution of epoxides,[809] and the α-fluorination of carbonyl compounds[810] in water. The DNA backbone not only provided the chirality but also constitutes a stable host for the organometallic copper complex, the resulting conjugated biocatalyst exhibiting higher activity than the copper complex alone. As an illustration of the success of this approach, Cu(II) complex of 4,4'-dimethyl-2,2'-bipyridine **154** in combination with salmon testes DNA (st-DNA) were found to

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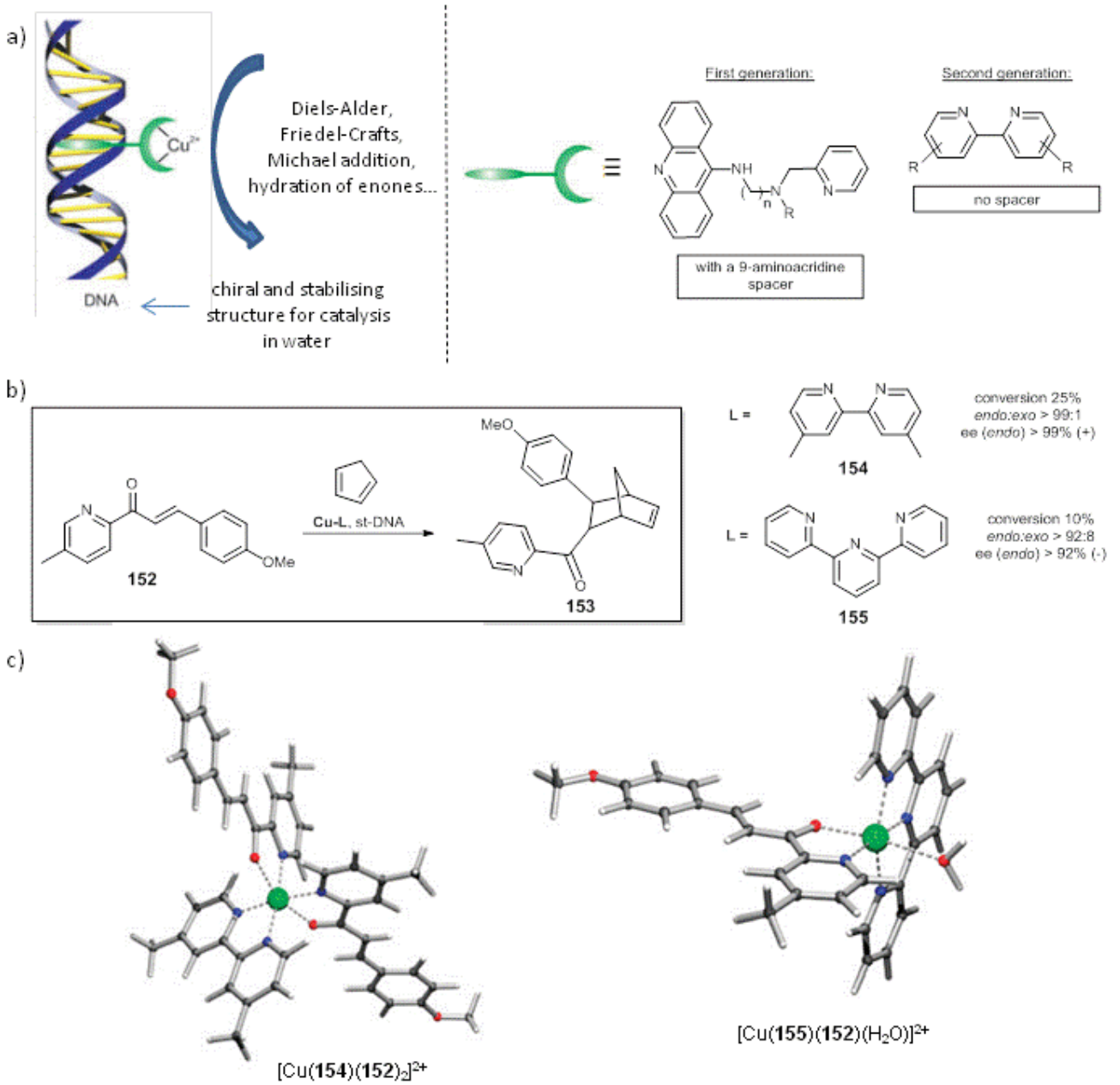

Fig. 41 a) General scheme of the strategy developed by Roelfes and Feringa for the development of DNA-based asymmetric catalysts. (Schematic representation of the DNA-Cu catalyst is reprinted with permission from ref.797. Copyright 2005. John Wiley and Sons). b) **Cu-154** and **Cu-155**/st-DNA catalysed the Diels–Alder reaction between **152** and Cp giving **153** with 99% and 92% ee respectively but as different enantiomers. The enantiomeric preference can be explained by the different coordination mode of the ligand. c) Optimized DFT geometries of $[Cu(\mathbf{154})(\mathbf{152})_2]^{2+}$ and $[Cu(\mathbf{155})(\mathbf{152})(H_2O)]^{2+}$ (in the absence of st-DNA). st-DNA = salmon testes DNA. Ref: see the text. (Optimized geometries were reprinted with permission from ref. 804. Copyright 2012. The Royal Society of Chemistry).

catalyse Diels–Alder and Friedel–Crafts reactions with 99% and 83% ee respectively at full conversion.[804] Interestingly, even though the DNA adopts a right handed helical conformation only, the denticity of the ligand (*i.e.* the use of a bidentate ligand as **154** or a tridentate ligand as **155**) influenced the absolute configuration of the major enantiomer obtained (**Fig. 41, b and c**). In the same vein, G-quadruplexes were recently used as a support for organocatalysis[811] and transition metal catalysis.[812–814]

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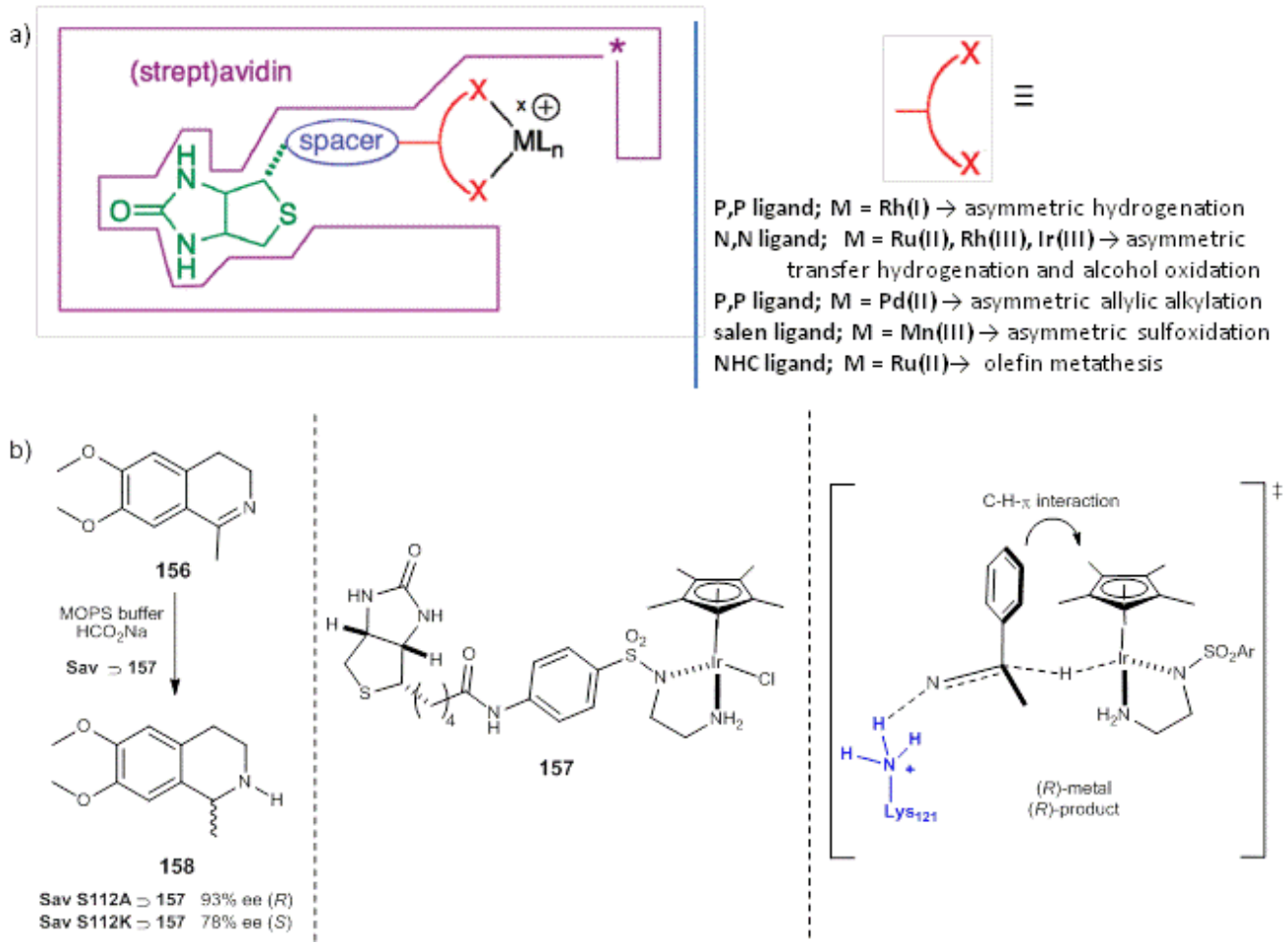

Fig. 42 a) Schematic representation of the biotin-(strept)avidin technology developed by the group of Ward. (The scheme is reprinted with permission from ref. 704. Copyright 2011. American Chemical Society). b) Selected example for the enantioselective reduction of imine **156**. Depending on the streptavidin mutant, both enantiomers can be obtained with good ee. Right: transition state proposed for the reaction involving Sav **S112A ⊃ 157**. Refs: see the text.

Inspired by the seminal works of Whitesides[815] and later Chan,[816] Ward group used the high affinity (K_a *ca.* 10^{14} M^{-1}) between chiral streptavidin and achiral biotin for the construction of asymmetric catalysts.[697,699,704] The system is extremely versatile and was successfully employed for asymmetric hydrogenation (Rh),[817–822] asymmetric transfer hydrogenation (Rh, Ir, Ru),[699,823–827] asymmetric allylic alkylation (Pd),[828] oxidation of alcohols (Rh, Ir, Ru),[829] enantioselective sulfoxidation (Mn),[830] and olefin metathesis[831] in water or aqueous solution (**Fig. 42**). For the asymmetric transfer hydrogenation of imine **156**, both chemical optimization (variation of the nature of the biotin metal complex) and genetic optimization (saturation mutagenesis) were employed to obtain a very efficient catalytic system.[827] Depending on the streptavidin mutant used, the nature of the major enantiomer can be shifted from (*R*) (with 93% ee, **S112A ⊃ 157**) to (*S*) (with 78% ee, **S112K ⊃ 157**). Based on X-ray structural data of **S112A ⊃ 157** and control mutagenesis experiments, the authors proposed a non-concerted transition state with a C–H-π interaction between the substrate and the Cp* ligand, and one hydrogen bond interaction between the substrate and the Lysine 121 of the streptavidin host (**Fig. 42**). This latter contact can replace the protonation step occurring between the amine of the ligand and the substrate in the concerted mechanism. The biotin-streptavidin technology is not limited to hydrogenation or oxidation reactions. Very recently, a Rh(III) complex modified with a biotin side chain was coupled with streptavidin to catalyse an asymmetric C–H activation reaction. Site-directed mutagenesis was used to introduce a basic moiety (an aspartate residue) in the proximity of the rhodium complex. The synergetic action of both this

carboxylate side chain and the chiral cavity inside the metalloenzyme can explain the excellent catalytic performance of this mutant (95% yield, 82% ee, benzannulation reaction between pivaloyl protected benzhydroxamic acid and methyl acrylate).[832]

In its simplest form, the directed evolution approach uses a sequence comprising site-directed mutagenesis and subsequent evaluation of the catalytic performance of the modified catalyst; the best mutant being selected through trial-and-error cycles. By means of this method, the groups of Ward[833,834] and Reetz[835,836] improved the efficiency of biomacromolecule hybrid catalysts issued form the streptavidin-biotin technology and the dative approaches mentioned above.

The design of totally synthetic proteins and their use as catalysts is driven by the improvements experienced in computational chemistry (*de novo* approach) and protein preparation (syntheses of the genes expressing the designed proteins followed by expression of the proteins in microorganisms and their purification; automated solid-phase synthesis).[837–842] While this approach has already been applied with success for organocatalytic reactions, such as retro-aldolisation,[843] Kemp elimination[844] and Diels–Alder reaction,[845] the preparation of *de novo* metalloenzymes[846,847] for non-natural reactions is still a challenge.[848–850] Finally, an approach consisting in the chemical design of small peptide catalysts (usually constituted of less than 50 amino acids), potentially incorporating non-natural amino-acids, has been reported.[23,851,852]

7. Conclusions

In this part, we reviewed the application of supramolecular concepts to catalysis targeted from different biomimetic approaches. Examples of the use of biomolecules as molecular components in supramolecular catalysts have also been outlined. Self-assembled reaction vessels based on hydrogen bond interactions, coordination bonds or other reversible interactions can be considered as a new phase of matter in which chemical reactions can be performed. In general, the physicochemical properties of the molecules and ions contained in the "molecular flasks" are considerably modified with respect to those exhibited in the solid, liquid or in gas phase. Consequently, new reactivity and reaction pathways have emerged from molecules included in the interior of these containers. The kinetics and thermodynamics (regio- and stereoselectivity) of the reactions occurring in the bulk are modified by molecular encapsulation or inclusion of the substrates in confined spaces of similar size. The resulting supramolecular systems mediate the reaction between substrates or substrate and catalytic centre by bringing them in close proximity and increasing the effective molarity of the reaction (*EM*). This is probably the main factor governing the kinetics of the highlighted examples of catalysis in water and self-replicating systems. In addition, the required total or partial desolvation of the substrates due to the encapsulation process tends to eliminate or reduce the entropic costs caused by solvent reorganisation in the transition state. The transition state developed within the capsular assembly can also reduce its activation energy by different mechanism (stabilisation or increase in the energy of the reactants). We have presented several examples of the modification of the catalytic properties typically expressed by metal centres in the bulk solution not only by supramolecular inclusion or encapsulation processes but also through the use of biomimetic supramolecular approaches *i.e.* allosterism. To conclude, we have described selected examples of the possibilities offered by the combination of biomolecules with synthetic catalyst. Significant advances have been achieved in the different fields reviewed, which augurs well for future realistic application of these supramolecular approaches in solving catalytic problems. Likewise, a sound and wide knowledge of the use of different supramolecular concepts in catalysis have been accomplished with all these investigations. Nevertheless, we are far from being capable to predict the expected outcomes of chemical reactions when altered through the use of supramolecular approaches. Supramolecular catalysis involving enzyme mimics is by no means a mature area of chemical research. Most likely, this is due because it deals with the molecular recognition of an energetic stabilisation of an elusive target, the transition state.

Notes and references

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References

1. A. J. Kirby and F. Hollfelder, *From Enzyme Models to Model Enzymes*, RSC Publishing, Cambridge, 2009.
2. L. Pauling, *Chem. Eng. News*, 1946, **161**, 707-709.
3. L. Pauling, *Nature*, 1948, **161**, 707-709.
4. L. Pauling, *Am. Sci.*, 1948, **36**, 51-58.
5. R. Breslow and L. E. Overman, *J. Am. Chem. Soc.*, 1970, **92**, 1075-1077.
6. I. Tabushi, N. Shimizu, T. Sugimoto, M. Shiozuka and K. Yamamura, *J. Am. Chem. Soc.*, 1977, **99**, 7100-7102.
7. I. Tabushi, N. Shimizu, Cyclodextrin metal complexes, 1978, Jpn. Kokai Tokkyo Koho (to Showa), JP 53102986.
8. I. Tabushi, *Acc. Chem. Res.*, 1982, **15**, 66-72.
9. I. Tabushi, *Tetrahedron*, 1984, **40**, 269-292.
10. R. Breslow, *Acc. Chem. Res.*, 1995, **28**, 146-153.
11. R. Breslow and S. D. Dong, *Chem. Rev.*, 1998, **98**, 1997-2011.
12. J. Bjerre, C. Rousseau, L. Marinescu and M. Bols, *Appl. Microbiol. Biotechnol.*, 2008, **81**, 1-11.
13. L. Marinescu and M. Bols, *Trends in Glycoscience and Glycotechnology*, 2009, **21**, 309-323.
14. D. J. Cram, *Angew. Chem. Int. Ed. Engl.*, 1988, **27**, 1009-1112.
15. D. Astruc, *Nature Chem.*, 2012, **4**, 255-267.
16. G. Wulff, *Chem. Rev.*, 2002, **102**, 1-27.
17. C. Alexander, L. Davidson and W. Hayes, *Tetrahedron*, 2003, **59**, 2025-2057.
18. G. Wulff and J. Liu, *Acc. Chem. Res.*, 2012, **45**, 239-247.
19. D. Chappell, B. W. Greenland and W. Hayes, in *Supramolecular Chemistry: From Molecules to Nanomaterials*, eds. J. W. Steed and P. A. Gale, John Wiley & Sons, Ltd., 2012, DOI: 10.1002/9780470661345.smc9780470661165.
20. M. M. Mader and P. A. Bartlett, *Chem. Rev.*, 1997, **97**, 1281-1301.
21. J. K. M. Sanders, *Chem. Eur. J.*, 1998, **4**, 1378-1383.

22. Y. Z. Yin, Z. Y. Dong, Q. Luo and J. Q. Liu, *Prog. Polym. Sci.*, 2012, **37**, 1476-1509.
23. B. Geibel, M. Merschky, C. Rether and C. Schmuck, in *Supramolecular Chemistry: From Molecules to Nanomaterials*, eds. J. W. Steed and P. A. Gale, John Wiley & Sons, Ltd, 2012, DOI: 10.1002/9780470661345.smc9780470661159.
24. M. Yoshizawa and M. Fujita, *Pure Appl.Chem.*, 2005, **77**, 1107-1112.
25. M. Yoshizawa, J. K. Klosterman and M. Fujita, *Angew. Chem. Int. Ed.*, 2009, **48**, 3418-3438.
26. M. D. Pluth, R. G. Bergman and K. N. Raymond, *Acc. Chem. Res.*, 2009, **42**, 1650-1659.
27. L. Ma, C. Abney and W. Lin, *Chem. Soc. Rev.*, 2009, **38**, 1248-1256.
28. J. Lee, O. K. Farha, J. Roberts, K. A. Scheidt, S. T. Nguyen and J. T. Hupp, *Chem. Soc. Rev.*, 2009, **38**, 1450-1459.
29. A. Corma, H. García and F. X. Llabrés i Xamena, *Chem. Rev.*, 2010, **110**, 4606-4655.
30. M. Yoon, R. Srirambalaji and K. Kim, *Chem. Rev.*, 2012, **112**, 1196-1231.
31. T. R. Cook, Y. R. Zheng and P. J. Stang, *Chem. Rev.*, 2013, **113**, 734-777.
32. T. Tjivikua, P. Ballester and J. Rebek, Jr., *J. Am. Chem. Soc.*, 1990, **112**, 1249-1250.
33. J. Rebek, Jr., *Acc. Chem. Res.*, 1984, **17**, 258-264.
34. For recent reviews that deal with several strategies applied for the design of enzyme mimics see references 34-35: Z. Y. Dong, Y. G. Wang, Y. Z. Yin and J. Q. Liu, *Curr. Opin. Colloid Interface Sci.*, 2011, **16**, 451-458.
35. Z. Y. Dong, Q. Luo and J. Q. Liu, *Chem. Soc. Rev.*, 2012, **41**, 7890-7908.
36. J. Yang, B. Gabriele, S. Belvedere, Y. Huang and R. Breslow, *J. Org. Chem.*, 2002, **67**, 5057-5067.
37. F. Cuevas, S. Di Stefano, J. O. Magrans, P. Prados, L. Mandolini and J. de Mendoza, *Chem. Eur. J.*, 2000, **6**, 3228-3234.
38. J. de Mendoza, V. Alcázar, E. Botana, A. Galán, G. Lu, J. O. Magrans, M. Martín-Portugués, P. Prados, A. Salmerón, J. Sánchez-Quesada, C. Seel and M. Segura, *Pure Appl. Chem.*, 1997, **69**, 577-582.
39. J. O. Magrans, A. R. Ortiz, A. Molins, P. H. P. Lebouille, J. Sánchez-Quesada, P. Prados, M. Pons, F. Gago and J. de Mendoza, *Angew. Chem. Int. Ed. Engl.*, 1996, **35**, 1712-1715.
40. D. J. Cram, P. Y.-S. Lam and S. P. Ho, *J. Am. Chem. Soc.*, 1986, **108**, 839-841.
41. Y. Chao and D. J. Cram, *J. Am. Chem. Soc.*, 1976, **98**, 1015-1017.
42. P. Scrimin, P. Tecilla, U. Tonellato and N. Vignaga, *J. Chem. Soc., Chem. Commun.*,, 1991, **7**, 449-451.
43. R. Cacciapaglia, S. Di Stefano and L. Mandolini, *Acc. Chem. Res.*, 2004, **37**, 113-122.
44. B. L. Tsao, R. J. Pieters and J. Rebek, Jr., *J. Am. Chem. Soc.*, 1995, **117**, 2210-2213.
45. P. Mattei and F. Diederich, *Helv. Chim. Acta*, 1997, **80**, 1555-1588.
46. J. Wolfe, D. Nemeth, A. Costero and J. Rebek, Jr., *J. Am. Chem. Soc.*, 1988, **110**, 983-984.
47. T. R. Kelly, C. Zhao and G. J. Bridger, *J. Am. Chem. Soc.*, 1989, **111**, 3744-3745.
48. T. R. Kelly, G. J. Bridger and C. Zhao, *J. Am. Chem. Soc.*, 1990, **112**, 8024-8034.
49. P. Tecilla, S.-K. Chang and A. D. Hamilton, *J. Am. Chem. Soc.*, 1990, **112**, 9586-9590.
50. For the binding properties of cyclodextrins see the following review: M. V. Rekharsky and Y. Inoue, *Chem. Rev.*, 1998, **98**, 1875-1917.
51. For the complexation properties of cyclodextrins and other hosts see the following review: K. N. Houk, A. G. Leach, S. P. Kim and X. Zhang, *Angew. Chem. Int. Ed.*, 2003, **42**, 4872-4897.
52. A. J. Kirby, *Angew. Chem. Int. Ed. Engl.*, 1996, **35**, 707-724.
53. R. Cacciapaglia, S. Di Stefano and L. Mandolini, in *Supramolecular Cataysis.*, ed. P. W. N. M. van Leeuwen, Wiley-VCH, Weinheim, 2008, pp. 113-142.
54. F. M. Menger, *Acc. Chem. Res.*, 1985, **18**, 128-134.
55. H. Ye, W. Tong and V. T. D'Souza, *J. Am. Chem. Soc.*, 1992, **114**, 5470-5472.
56. H. Ye, W. Tong and V. T. D'Souza, *J. Chem. Soc., Perkin Trans. 2*, 1994, 2431-2437.
57. Y. Murakami, J.-I. Kikuchi, Y. Hisaeda and O. Hayashida, *Chem. Rev.*, 1996, **96**, 721-758.
58. K. Takahashi, *Chem. Rev.*, 1998, **98**, 2013-2033.
59. J.-P. Behr and J.-M. Lehn, *J. Chem. Soc., Chem. Commun.,*, 1978, 143-146.
60. T. Matsui and K. Koga, *Tetrahedron Lett.*, 1978, **19**, 1115-1118.
61. D. J. Cram and G. D. Y. Sogah, *J. Chem. Soc., Chem. Commun.,*, 1981, 625-628.
62. M. W. Hosseini, J. M. Lehn, K. C. Jones, K. E. Plute, K. B. Mertes and M. P. Mertes, *J. Am. Chem. Soc.*, 1989, **111**, 6330-6335.
63. H.-D. Lutter and F. Diederich, *Angew. Chem. Int. Ed. Engl.*, 1986, **25**, 1125-1127.
64. F. Diederich and H.-D. Lutter, *J. Am. Chem. Soc.*, 1989, **111**, 8438-8446.
65. S.-W. Tam-Chang, L. Jimenez and F. Diederich, *Helv. Chim. Acta*, 1993, **76**, 2616-2639.
66. T. Habicher and F. Diederich, *Helv. Chim. Acta*, 1999, **82**, 1066-1095.
67. M. C. Feiters, A. E. Rowan and R. J. M. Nolte, *Chem. Soc. Rev.*, 2000, **29**, 375-384.
68. W. B. Motherwell, M. J. Bingham and Y. Six, *Tetrahedron*, 2001, **57**, 4663-4686.
69. E. E. Karakhanov, A. L. Maksimov, E. A. Runova, Y. S. Kardasheva, M. V. Terenina, T. S. Buchneva and A. Y. Guchkova, *Macromol. Symp.*, 2003, **204**, 159-173.
70. D. M. Vriezema, M. C. Aragones, J. A. A. W. Elemans, J. J. L. M. Cornelissen, A. E. Rowan and R. J. M. Nolte, *Chem. Rev.*, 2005, **105**, 1445-1489.
71. F. Bellia, D. La Mendola, C. Pedone, E. Rizzarelli, M. Saviano and G. Vecchio, *Chem. Soc. Rev.*, 2009, **38**, 2756-2781.
72. D. T. Schuhle, J. A. Peters and J. Schatz, *Coord. Chem. Rev.*, 2011, **255**, 2727-2745.
73. G. L. Trainor and R. Breslow, *J. Am. Chem. Soc.*, 1981, **103**, 154-158.
74. D.-Q. Yuan, Y. Kitagawa, K. Aoyama, T. Douke, M. Fukudome and K. Fujita, *Angew. Chem. Int. Ed.*, 2007, **46**, 5024-5027.
75. N. M. Milović, J. D. Badjić and N. M. Kostić, *J. Am. Chem. Soc.*, 2004, **126**, 696-697.
76. M. Kunishima, K. Yoshimura, H. Morigaki, R. Kawamata, K. Terao and S. Tani, *J. Am. Chem. Soc.*, 2001, **123**, 10760-10761.
77. C. Rousseau, B. Christensen and M. Bols, *Eur. J. Org. Chem.*, 2005, 2374-2739.
78. C. Rousseau, B. Christensen, T. E. Petersen and M. Bols, *Org. Biomol.Chem.*, 2004, **2**, 3476-3482.
79. L. Marinescu, M. Mølbach, C. Rousseau and M. Bols, *J. Am. Chem. Soc.*, 2005, **127**, 17578-17579.
80. L. G. Marinescu and M. Bols, *Angew. Chem. Int. Ed.*, 2006, **45**, 4590-4593.
81. J. Bjerre and M. Bols, *J. Inclusion Phenom. Macrocyclic Chem.*, 2011, **69**, 417-423.
82. T. H. Fenger, L. G. Marinescu and M. Bols, *Eur. J. Org.Chem.*, 2011, 2339-2345.
83. T. H. Fenger, L. G. Marinescu and M. Bols, *Org. Biomol.Chem.*, 2009, **7**, 933-943.
84. T. H. Fenger, J. Bjerre and M. Bols, *ChemBioChem*, 2009, **10**, 2494-2503.
85. S. Hu, J. Li, J. Xiang, J. Pan, S. Luo and J.-P. Cheng, *J. Am. Chem. Soc.*, 2010, **132**, 7216-7228.
86. Y. Inoue, F. Dong, K. Yamamoto, L.-H. Tong, H. Tsuneishi, T. Hakushi and A. Tai, *J. Am. Chem. Soc.*, 1995, **117**, 11033-11034.
87. G. Fukuhara, T. Mori, T. Wada and Y. Inoue, *Chem. Commun.*, 2005, 4199-4201.
88. G. Fukuhara, T. Mori, T. Wada and Y. Inoue, *J. Org. Chem.*, 2006, **71**, 8233-8243.
89. C. Yang, W. Liang, M. Nishijima, G. Fukuhara, T. Mori, H. Hiramatsu, Y. Dan-Oh, K. Tsujimoto and Y. Inoue, *Chirality*, 2012, **24**, 921-927.

90. Y. Inoue, T. Wada, N. Sugahara, K. Yamamoto, K. Kimura, L.-H. Tong, X.-M. Gao, Z.-J. Hou and Y. Liu, *J. Org. Chem.*, 2000, **65**, 8041-8050.
91. R. Lu, C. Yang, Y. Cao, Z. Wang, T. Wada, W. Jiao, T. Mori and Y. Inoue, *Chem. Commun.*, 2008, 374-376.
92. R. Lu, C. Yang, Y. Cao, L. Tong, W. Jiao, T. Wada, Z. Wang, T. Mori and Y. Inoue, *J. Org. Chem.*, 2008, **73**, 7695-7701.
93. C. Yang, T. Mori, T. Wada and Y. Inoue, *New J. Chem.*, 2007, **31**, 697-702.
94. H. Qiu, C. Yang, Y. Inoue and S. Che, *Org. Lett.*, 2009, **11**, 1793-1796.
95. G. Fukuhara, T. Mori, T. Wada and Y. Inoue, *Chem. Commun*., 2006, 1712-1714.
96. G. Fukuhara, T. Mori and Y. Inoue, *J. Org. Chem.*, 2009, **74**, 6714-6727.
97. A. L. Koner, C. Márquez, M. H. Dickman and W. M. Nau, *Angew. Chem. Int. Ed.*, 2011, **50**, 545-548.
98. For reviews dealing with the properties (including catalytic properties) of cucurbiturils see references 98-104: J. W. Lee, S. Samal, N. Selvapalam, H.-J. Kim and K. Kim, *Acc. Chem. Res.*, 2003, **36**, 621-630.
99. J. Lagona, P. Mukhopadhyay, S. Chakrabarti and L. Isaacs, *Angew. Chem. Int. Ed.*, 2005, **44**, 4844-4870.
100. W. M. Nau, M. Florea and K. I. Assaf, *Isr. J. Chem.*, 2011, **51**, 559-577.
101. G. Parvari, O. Reany and E. Keinan, *Isr. J. Chem.*, 2011, **51**, 646-663.
102. E. Masson, X. X. Ling, R. Joseph, L. Kyeremeh-Mensah and X. Y. Lu, *RSC Advances*, 2012, **2**, 1213-1247.
103. B. C. Pemberton, R. Raghunathan, S. Volla and J. Sivaguru, *Chem. Eur. J.*, 2012, **18**, 12178-12190.
104. J. Lu, J. X. Lin, M. N. Cao and R. Cao, *Coord. Chem. Rev.*, 2013, **257**, 1334-1356.
105. L. Jiang, Z. Liu, Z. Liang and Y. Gao, *Biiorg. Med. Chem.*, 2005, **13**, 3673-3680.
106. P. Molenveld, J. F. J. Engbersen, H. Kooijman, A. L. Spek and D. N. Reinhoudt, *J. Am. Chem. Soc.*, 1998, **120**, 6726-6737.
107. R. Cacciapaglia, A. Casnati, L. Mandolini, D. N. Reinhoudt, R. Salvio, A. Sartori and R. Ungaro, *J. Org. Chem.*, 2005, **70**, 5398-5402.
108. R. Cacciapaglia, S. Di Stefano and L. Mandolini, *J. Org. Chem.*, 2001, **66**, 5926-5928.
109. R. Cacciapaglia, S. Di Stefano and L. Mandolini, *J. Am. Chem. Soc.*, 2003, **125**, 2224-2227.
110. R. Cacciapaglia, A. Casnati, S. Di Stefano, L. Mandolini, D. Palolemili, D. N. Reinhoudt, A. Sartori and R. Ungaro, *Chem. Eur. J.*, 2004, **10**, 4436-4442.
111. R. Paciello, L. Siggel and M. Röper, *Angew. Chem. Int. Ed.*, 1999, **38**, 1920-1923.
112. F. J. Parlevliet, M. A. Zuideveld, C. Kiener, H. Kooijman, A. L. Spek, P. C. J. Kamer and P. W. N. M. van Leeuwen, *Organometallics*, 1999, **18**, 3394-3405.
113. C. J. Cobley, D. D. Ellis, A. G. Orpen and P. G. Pringle, *J. Chem. Soc., Dalton Trans.*, 2000, 1109-1112.
114. F. J. Parlevliet, C. Kiener, J. Fraanje, K. Goubitz, M. Lutz, A. L. Spek, P. C. J. Kamer and P. W. N. M. van Leeuwen, *J. Chem. Soc., Dalton Trans.*, 2000, 1113-1122.
115. C. Dieleman, S. Steyer, C. Jeunesse and D. Matt, *J. Chem. Soc., Dalton Trans.*, 2001, 2508-2517.
116. S. Steyer, C. Jeunesse, D. Matt, R. Welter and M. Wesolek, *J. Chem. Soc., Dalton Trans.*, 2002, 4264-4274.
117. M. Lejeune, D. Sémeril, C. Jeunesse, D. Matt, F. Peruch, P. J. Lutz and L. Ricard, *Chem. Eur. J.*, 2004, **10**, 5354-5360.
118. C. Gaeta, M. De Rosa, M. Fruilo, A. Soriente and P. Neri, *Tetrahedron: Asymmetry*, 2005, **156**, 2333-2340.
119. C. Jeunesse, D. Armspach and D. Matt, *Chem. Commun.*, 2005, 5603-5614.
120. D. Sémeril, C. Jeunesse, D. Matt and L. Toupet, *Angew. Chem. Int. Ed.*, 2006, **45**, 5810-5814.
121. A. Marson, J. E. Ernsting, M. Lutz, A. L. Spek, P. W. M. N. van Leeuwen and P. C. J. Kamer, *Dalton Trans.*, 2009, 621-633.
122. S. Sameni, M. Lejeune, C. Jeunesse, D. Matt and R. Welter, *Dalton Trans.*, 2009, 7912-7923.
123. S. Sameni, C. Jeunesse, D. Matt and L. Toupet, *Chem. Eur. J.*, 2009, **15**, 10446-10456.
124. L. Monnereau, D. Sémeril, D. Matt and L. Toupet, *Chem. Eur. J.*, 2010, **16**, 9237-9247.
125. L. Monnereau, D. Semeril and D. Matt, *Chem. Commun.*, 2011, **47**, 6626-6628.
126. M. T. Reetz and S. R. Waldvogel, *Angew. Chem. Int. Ed. Engl.*, 1997, **36**, 865-867.
127. F. Hapiot, S. Tilloy and E. Monflier, *Chem. Rev.*, 2006, **106**, 767-781.
128. C. Machut-Binkowski, F.-X. Legrand, N. Azaroual, S. Tilloy and E. Monflier, *Chem. Eur. J.*, 2010, **6**, 10195-10201.
129. R. Gramage-Doria, D. Armspach, D. Matt and L. Toupet, *Angew. Chem. Int. Ed.*, 2011, **50**, 1554-1559.
130. F. X. Legrand, N. Six, C. Slomianny, H. Bricout, S. Tilloy and E. Monflier, *Adv. Synth. Catal.*, 2011, **353**, 1325-1334.
131. R. Gramage-Doria, D. Armspach, D. Matt and L. Toupet, *Dalton Trans.*, 2012, **41**, 8786-8796.
132. F. Hapiot, H. Bricout, S. Tilloy and E. Monflier, *Eur. J. Inorg. Chem.*, 2012, 1571-1578.
133. R. R. French, P. Holzer, M. G. Leuenberger and W.-D. Woggon, *Angew. Chem. Int. Ed.*, 2000, **39**, 1267-1269.
134. D. Armspach, D. Matt, F. Peruch and P. Lutz, *Eur. J. Inorg. Chem.*, 2003, 805-809.
135. A. Schlatter and W. D. Woggon, *Adv. Synth. Catal.*, 2008, **350**, 995-1000.
136. D. M. Homden and C. Redshaw, *Chem. Rev.*, 2008, **108**, 5086-5130.
137. R. Gramage-Doria, D. Armspach and D. Matt, *Coord. Chem. Rev.*, 2013, **257**, 776-816.
138. For selected recent examples of cyclodextrins with appended catalytic functions used as enzyme mimics see references 138-149: Z. Dong, J. Liu, S. Mao, X. Huang, B. Yang, X. Ren, G. Luo and J. Shen, *J. Am. Chem. Soc.*, 2004, **126**, 16395-16404.
139. F. Ortega-Caballero, C. Rousseau, B. Christensen, T. E. Petersen and M. Bols, *J. Am. Chem. Soc.*, 2005, **127**, 3238-3239.
140. C. Rousseau, F. Ortega-Caballero, L. U. Nordstrøm, B. Christensen, T. E. Petersen and M. Bols, *Chem. Eur. J.*, 2005, **11**, 5094-5101.
141. F. Ortega-Caballero, J. Bjerre, L. S. Laustsen and M. Bols, *J. Org. Chem.*, 2005, **70**, 7217-7226.
142. Z. Dong, X. Li, K. Liang, S. Mao, X. Huang, B. Yang, J. Xu, J. Liu, G. Luo and J. Shen, *J. Org. Chem.*, 2007, **72**, 606-609.
143. J. Bjerre, E. H. Nielsen and M. Bols, *Eur. J. Org.Chem.*, 2008, 745-752.
144. Y.-H. Zhou, M. Zhao, Z.-W. Mao and L.-N. Ji, *Chem. Eur. J.*, 2008, **14**, 7193-7201.
145. V. Mojr, V. Herzig, M. Buděšínsky, R. Cibulka and T. Kraus, *Chem. Commun.*, 2010, **46**, 7599-7601.
146. V. Mojr, M. Buděšínsky, R. Cibulka and T. Kraus, *Org. Biomol.Chem.*, 2011, **9**, 7318-7326.
147. L. L. Zhu, H. Yan, C. Y. Ang, K. T. Nguyen, M. H. Li and Y. L. Zhao, *Chem. Eur. J.*, 2012, **18**, 13979-13983.
148. Y. Zhou, E. Lindbäck, L. G. Marinescu, C. M. Pedersen and M. Bols, *Eur. J. Org.Chem.*, 2012, 4063-4070.
149. E. Lindbäck, Y. Zhou, C. M. Pedersen and M. Bols, *Tetrahedron Lett.*, 2012, **53**, 5023-5026.
150. R. P. Sijbesma, A. P. M. Kentgens, E. T. G. Lutz, J. H. van der Maas and R. J. M. Nolte, *J. Am. Chem. Soc.*, 1993, **115**, 8999-9005.
151. H. K. A. C. Coolen, P. W. N. M. van Leeuwen and R. J. M. Nolte, *Angew. Chem. Int. Ed. Engl.*, 1992, **31**, 905-907.
152. H. K. A. C. Coolen, J. A. M. Meeuwis, P. W. M. N. van Leeuwen and R. J. M. Nolte, *J. Am. Chem. Soc.*, 1995, **117**, 11906-11913.
153. V. S. I. Sprakel, M. C. Feiters, W. Meyer-Klaucke, M. Klopstra, J. Brinksma, B. L. Feringa, K. D. Karlin and R. J. M. Nolte, *Dalton Trans.*, 2005, 3522-3534.
154. C. F. Martens, R. J. M. K. Gebbink, M. C. Feiters and R. J. M. Nolte, *J. Am. Chem. Soc.*, 1994, **116**, 5667-5670.

155.J. A. A. W. Elemans, E. J. A. Bijsterveld, A. E. Rowan and R. J. M. Nolte, *Chem. Commun.*, 2000, 2443-2444.
156.P. Thordarson, E. J. A. Bijsterveld, A. E. Rowan and R. J. M. Nolte, *Nature*, 2003, **424**, 915-918.
157.R. G. E. Coumans, J. A. A. W. Elemans, R. J. M. Nolte and A. E. Rowan, *Proc. Natl. Acad. Sci. U.S.A.*, 2006, **103**, 19647-19651.
158.J. A. A. W. Elemans, E. J. A. Bijsterveld, A. E. Rowan and R. J. M. Nolte, *Eur. J. Org. Chem.*, 2007, 751-757.
159.P. H. Ramos, R. G. E. Coumans, A. B. C. Deutman, J. M. M. Smits, R. de Gelder, J. A. A. W. Elemans, R. J. M. Nolte and A. E. Rowan, *J. Am. Chem. Soc.*, 2007, **129**, 5699-5702.
160.A. B. C. Deutman, C. Monnereau, J. A. A. W. Elemans, G. Ercolani, R. J. M. Nolte and A. E. Rowan, *Science*, 2008, **322**, 1668-1671.
161.C. Monnereau, P. H. Ramos, A. B. C. Deutman, J. A. A. W. Elemans, R. J. M. Nolte and A. E. Rowan, *J. Am. Chem. Soc.*, 2010, **132**, 1529-1531.
162.B. W. Purse and J. Rebek, Jr., *Proc. Nat. Acad. Sci. U. S. A.*, 2005, **102**, 10777-10782.
163.R. J. Hooley and J. Rebek, Jr., *Chem. Biol.*, 2009, **16**, 255-264.
164.M. P. Schramm and J. Rebek, Jr., *Chem. Eur. J.*, 2006, **12**, 5924-5933.
165.S. Xiao, D. Ajami and J. Rebek, Jr., *Chem. Commun.*, 2010, **46**, 2459-2461.
166.A. Gissot and J. Rebek, Jr., *J. Am. Chem. Soc.*, 2004, **126**, 7424-7425.
167.S. Richeter and J. Rebek, Jr., *J. Am. Chem. Soc.*, 2004, **126**, 16280-16281.
168.F. H. Zelder and J. Rebek, Jr., *Chem. Commun.*, 2006, 753-754.
169.F. H. Zelder, R. Salvio and J. Rebek, Jr., *Chem. Commun.*, 2006, 1280-1282.
170.T. Iwasawa, R. J. Hooley and J. Rebek, Jr., *Science*, 2007, **317**, 493-496.
171.R. J. Hooley, T. Iwasawa and J. Rebek, Jr., *J. Am. Chem. Soc.*, 2007, **129**, 15330-15339.
172.S. R. Shenoy, F. R. P. Crisóstomo, T. Iwasawa and J. Rebek, Jr., *J. Am. Chem. Soc.*, 2008, **130**, 5658-5659.
173.F. R. Pinacho Crisostomo, A. Lledo, S. R. Shenoy, T. Iwasawa and J. Rebek, Jr., *J. Am. Chem. Soc.*, 2009, **131**, 7402-7410.
174.P. Restorp and J. Rebek, Jr., *J. Am. Chem. Soc.*, 2008, **130**, 11850-11851.
175.L. Xu, S. G. Hua and S. H. Li, *Chem. Commun.*, 2013, **49**, 1542-1544.
176.P. D. Frischmann and M. J. MacLachlan, *Chem. Soc. Rev.*, 2013, **42**, 871-890.
177.B. Kersting, *Z. Anorg. Allg. Chem.*, 2004, **630**, 765-780.
178.B. Kersting and U. Lehmann, *Adv. Inorg. Chem.*, 2009, **61**, 407-470.
179.G. Steinfeld, V. Lozan and B. Kersting, *Angew. Chem. Int. Ed.*, 2003, **42**, 2261-2263.
180.S. Käss, T. Gregor and B. Kersting, *Angew. Chem. Int. Ed.*, 2006, **45**, 101-104.
181.A. Martinez and J. P. Dutasta, *J. Catal.*, 2009, **267**, 188-192.
182.Y. Makita, K. Sugimoto, K. Furuyoshi, K. Ikeda, S. Fujiwara, T. Shin-ike and A. Ogawa, *Inorg. Chem.*, 2010, **49**, 7220-7222.
183.Y. Makita, K. Ikeda, K. Sugimoto, T. Fujita, T. Danno, K. Bobuatong, M. Ehara, S. Fujiwara and A. Ogawa, *J. Organomet. Chem.*, 2012, **706**, 26-29.
184.O. Perraud, A. B. Sorokin, J. P. Dutasta and A. Martinez, *Chem. Commun.*, 2013, **49**, 1288-1290.
185.S. J. Rowan and J. K. M. Sanders, *Curr. Opin. Chem. Biol.*, 1997, **1**, 483-490.
186.T. S. Koblenz, J. Wassenaar and J. N. H. Reek, *Chem. Soc. Rev.*, 2008, **37**, 247-262.
187.R. Chakrabarty, P. S. Mukherjee and P. J. Stang, *Chem. Rev.*, 2011, **111**, 6810-6918.
188.D. J. Cram, M. E. Tanner and R. Thomas, *Angew. Chem. Int. Ed. Engl.*, 1991, **30**, 1024-1027.
189.R. Warmuth, *Angew. Chem. Int. Ed. Engl.*, 1997, **36**, 1347-1350.
190.R. Warmuth and M. A. Marvel, *Angew. Chem. Int. Ed.*, 2000, **39**, 1117-1119.
191.M. Yoshizawa, T. Kusukawa, M. Fujita and K. Yamaguchi, *J. Am. Chem. Soc.*, 2000, **122**, 6311-6312.
192.R. Warmuth and M. A. Marvel, *Chem. Eur. J.*, 2001, **7**, 1209-1220.
193.M. Yoshizawa, T. Kusukawa, M. Fujita, S. Sakamoto and K. Yamaguchi, *J. Am. Chem. Soc.*, 2001, **123**, 10454-10459.
194.X. Liu, G. Chu, R. A. Moss, R. R. Sauers and R. Warmuth, *Angew. Chem. Int. Ed.*, 2005, **44**, 1994-1997.
195.V. M. Dong, D. Fiedler, B. Carl, R. G. Bergman and K. N. Raymond, *J. Am. Chem. Soc.*, 2006, **128**, 14464-14465.
196.P. Mal, B. Breiner, K. Rissanen and J. R. Nitschke, *Science*, 2009, **324**, 1697-1699.
197.S. Gupta, R. Choudhury, D. Krois, G. Wagner, U. H. Brinker and V. Ramamurthy, *Org. Lett.*, 2011, **13**, 6074-6077.
198.S. Horiuchi, T. Murase and M. Fujita, *J. Am. Chem. Soc.*, 2011, **133**, 12445-12447.
199.C. Y. Gao, L. Zhao and M. X. Wang, *J. Am. Chem. Soc.*, 2012, **134**, 824-827.
200.Z. H. Lin, J. L. Sun, B. Efremovska and R. Warmuth, *Chem. Eur. J.*, 2012, **18**, 12864-12872.
201.J. Chen, S. Körner, S. L. Craig, D. M. Rudkevich and J. Rebek, Jr., *Nature*, 2002, **415**, 385-386.
202.J. Chen, S. L. Craig, S. Lin, D. M. Rudkevich and J. Rebek, Jr., *Proc. Natl. Acad. Sci. U.S.A.*, 2002, **99**, 2593-2596.
203.M. M. J. Smulders and J. R. Nitschke, *Chem. Sci.*, 2012, **3**, 785-788.
204.S. Liu, C. Ruspic, P. Mukhopadhyay, S. Chakrabarti, P. Y. Zavalij and L. Issacs, *J. Am. Chem. Soc.*, 2005, **127**, 15959-15967.
205.A. Shivanyuk and J. Rebek, Jr., *J. Am. Chem. Soc.*, 2002, **124**, 12074-12075.
206.S. D. Choudhury, J. Mohanty, H. Pal and A. C. Bhasikuttan, *J. Am. Chem. Soc.*, 2010, **132**, 1395-1401.
207.I. Ghosh and W. M. Nau, *Adv. Drug Deliv. Rev.*, 2012, **64**, 764-783.
208.W. M. Nau, G. Ghale, A. Hennig, H. Bakirci and D. M. Bailey, *J. Am. Chem. Soc.*, 2009, **131**, 11558-11570.
209.M. K. Sinha, O. Reany, G. Parvari, A. Karmakar and E. Keinan, *Chem. Eur. J.*, 2010, **16**, 9056-9067.
210.G. Ghale, V. Ramalingam, A. R. Urbach and W. M. Nau, *J. Am. Chem. Soc.*, 2011, **133**, 7528-7535.
211.D.-S. Guo, V. D. Uzunova, X. Su, Y. Liu and W. M. Nau, *Chem. Sci.*, 2011, **2**, 1722-1734.
212.R. N. Dsouza, A. Hennig and W. M. Nau, *Chem. Eur. J.*, 2012, **18**, 3444-3459.
213.M. Florea, S. Kudithipudi, A. Rei, M. J. González-Álvarez, A. Jeltsch and W. M. Nau, *Chem. Eur. J.*, 2012, **18**, 3521-3528.
214.J. Báscuas, L. García-Río and J. R. Leis, *Org. Biomol.Chem.*, 2004, **2**, 1186-1193.
215.N. Basilio, L. Garcia-Rio, J. A. Moreira and M. Pessego, *J. Org. Chem.*, 2010, **75**, 848-855.
216.D. T. H. Chou, J. Zhu, X. Huang and A. J. Bennet, *J. Chem. Soc., Perkin Trans. 2*, 2001, 83-89.
217.E. Iglesias, *J. Am. Chem. Soc.*, 1998, **120**, 13057-13069.
218.E. Iglesias and A. Fernández, *J. Chem. Soc., Perkin Trans. 2*, 1998, 1691-1699.
219.C. Klöck, R. N. Dsouza and W. M. Nau, *Org. Lett.*, 2009, **11**, 2595-2598.
220.R. Ravichandran and S. Divakar, *J. Mol. Cat. A: Chem.*, 1999, **137**, 31-39.
221.M. A. Reddy, N. Bhanumathi and K. R. Rao, *Chem. Commun.*, 2001, 1974-1975.
222.K. Surendra, N. S. Krishnaveni, R. Sridhar and K. R. Rao, *J. Org. Chem.*, 2006, **71**, 5819-5821.
223.M. S. Reddy, B. Srinivas, R. Sridhar, M. Narender and K. R. Rao, *J. Mol. Cat. A: Chem.*, 2006, **255**, 180-183.
224.V. P. Kumar, V. P. Reddy, R. Sridhar, B. Srinivas, M. Narender and K. R. Rao, *J. Org. Chem.*, 2008, **73**, 1646-1648.
225.S. N. Murthy, B. Madhav, A. V. Kumar, K. R. Rao and Y. V. D. Nageswar, *Tetrahedron*, 2009, **65**, 5251-5256.
226.S. N. Murthy, B. Madhav, A. V. Kumar, K. R. Rao and Y. V. D. Nageswar, *Helv. Chim. Acta*, 2009, **92**, 2118-2124.
227.B. Madhav, S. N. Murthy, V. P. Reddy, K. R. Rao and Y. V. D. Nageswar, *Tetrahedron Lett.*, 2009, **50**, 6025-6028.
228.K. Ramesh, S. N. Murthy, K. Karnakar and Y. V. D. Nageswar, *Tetrahedron Lett.*, 2011, **52**, 4734-4737.

229.S. N. Murthy and Y. V. D. Nageswar, *Tetrahedron Lett.*, 2011, **52**, 4481-4484.
230.B. Kaboudin and M. Sorbiun, *Tetrahedron Lett.*, 2007, **48**, 9015-9017.
231.P. Suresh and K. Pitchumani, *Tetrahedron: Asymmetry*, 2008, **19**, 2037-2044.
232.K. Kanagaraj and K. Pitchumani, *Tetrahedron Lett.*, 2010, **51**, 3312-3316.
233.K. Kanagaraj, P. Suresh and K. Pitchumani, *Org. Lett.*, 2010, **12**, 4070-4073.
234.D. C. Rideout and R. Breslow, *J. Am. Chem. Soc.*, 1980, **102**, 7816-7817.
235.P. Kim Susanna, G. Leach Andrew and K. N. Houk, *J. Org. Chem.*, 2002, **67**, 4250-4260.
236.W. L. Mock, T. A. Irra, J. P. Wepsiec and M. Adhya, *J. Org. Chem.*, 1989, **54**, 5302-5308.
237.W. L. Mock, T. A. Irra, J. P. Wepsiec and T. L. Manimaran, *J. Org. Chem.*, 1983, **48**, 3619-3620.
238.P. Carlqvist and F. Maseras, *Chem. Commun.*, 2007, 748-750.
239.V. Ramamurthy and A. Parthasarathy, *Isr. J. Chem.*, 2011, **51**, 817-829.
240.V. Ramamurthy and Y. Inoue, eds., *Supramolecular Photochemistry*, Wiley, New York, 2011.
241.V. P. Rao and N. J. Turro, *Tetrahedron Lett.*, 1989, **30**, 4641-4644.
242.J. N. Moorthy, K. Venkatesan and R. G. Weiss, *J. Org. Chem.*, 1992, **57**, 3292-3297.
243.F. Toda, *Acc. Chem. Res.*, 1995, **28**, 480-486.
244.A. N. Sokolov, D.-K. Bučar, J. Baltrusaitis, S. X. Gu and L. R. MacGillivray, *Angew. Chem. Int. Ed.*, 2010, **49**, 4273-4277.
245.K. D. M. Harris, B. A. Palmer and G. R. Edwards-Gau, in *Supramolecular Chemistry: From Molecules to Nanomaterials*, eds. J. W. Steed and P. A. Gale, John Wiley & Sons, Ltd., 2012, DOI: 10.1002/9780470661345.smc9780470661164.
246.J. Stojakovic, B. S. Farris and L. R. MacGillivray, *Chem. Commun.*, 2012, **48**, 7958-7960.
247.Y. Ishida, Y. Kai, S.-y. Kato, A. Misawa, S. Amano, Y. Matsuoka and K. Saigo, *Angew. Chem. Int. Ed.*, 2008, **47**, 8241-8245.
248.T. Bach, H. Bergmann and K. Harms, *Angew. Chem. Int. Ed.*, 2000, **39**, 2302-2304.
249.T. Bach and H. Bergmann, *J. Am. Chem. Soc.*, 2000, **122**, 11525-11526.
250.D. M. Bassani, V. Darcos, S. Mahony and J.-P. Desvergne, *J. Am. Chem. Soc.*, 2000, **122**, 8795-8796.
251.T. Bach, H. Bergmann and K. Harms, *Org. Lett.*, 2001, **3**, 601-603.
252.B. Grosch, C. N. Orlebar, E. Herdtweck, W. Massa and T. Bach, *Angew. Chem. Int. Ed.*, 2003, **42**, 3693-3696.
253.N. McCleanaghan, C. Absalon and D. M. Bassani, *J. Am. Chem. Soc.*, 2003, **125**, 13004-13005.
254.V. Darcos, K. Griffith, X. Sallenave, J.-P. Desvergne, C. Guyard-Duhayon, B. Hasenknopf and D. M. Bassani, *Photochem. Photobiol. Sci.*, 2003, **2**, 1152-1161.
255.B. Grosch, C. N. Orlebar, E. Herdtweck, M. Kaneda, T. Wada, Y. Inoue and T. Bach, *Chem. Eur. J.*, 2004, **10**, 2179-2189.
256.P. Selig and T. Bach, *J. Org. Chem.*, 2006, **71**, 5662-5673.
257.J.-i. Mizoguchi, Y. Kawanami, T. Wada, K. Kodama, K. Anzai, T. Yanagi and Y. Inoue, *Org. Lett.*, 2006, **8**, 6051-6054.
258.Y. Kawanami, T. C. S. Pace, J. Mizoguchi, T. Yanagi, M. Nishijima, T. Mori, T. Wada, C. Bohne and Y. Inoue, *J. Org. Chem.*, 2009, **74**, 7908-7921.
259.K. A. B. Austin, E. Herdtweck and T. Bach, *Angew. Chem. Int. Ed.*, 2011, **50**, 8416-8419.
260.A. Bauer, F. Westkämper, S. Grimme and T. Bach, *Nature*, 2005, **436**, 1139-1140.
261.C. Müller, A. Bauer and T. Bach, *Angew. Chem. Int. Ed.*, 2009, **48**, 6640-6642.
262.C. Müller, A. Bauer, M. M. Maturi, M. C. Cuquerella, M. A. Miranda and T. Bach, *J. Am. Chem. Soc.*, 2011, **133**, 16689-16697.
263.H. Bouas-Laurent, A. Castellan, J.-P. Desvergne and R. Lapouyade, *Chem. Soc. Rev.*, 2000, **29**, 43-55.
264.D. M. Bassani, in *Supramolecular Photochemistry*, eds. V. Ramamurthy and Y. Inoue, John Wiley & Sons, Hoboken, NJ, USA. doi: 10.1002/9781118095300.ch2, New York, 2011.
265.V. Ramamurthy and J. Sivaguru, in *Supramolecular Photochemistry*, eds. V. Ramamurthy and Y. Inoue, John Wiley & Sons, Hoboken, NJ, USA. doi: 10.1002/9781118095300.ch10, 2011.
266.T. Tamaki, T. Kokubu and K. Ichimura, *Tetrahedron*, 1987, **43**, 1485-1494.
267.W. Herrmann, S. Wehrle and G. Wenz, *Chem. Commun.*, 1997, 1709-1710.
268.A. Nakamura and Y. Inoue, *J. Am. Chem. Soc.*, 2003, **125**, 966-972.
269.A. Nakamura and Y. Inoue, *J. Am. Chem. Soc.*, 2005, **127**, 5338-5339.
270.H. Ikeda, T. Nihei and A. Ueno, *J. Org. Chem.*, 2005, **70**, 1237-1242.
271.C. Yang, G. Fukuhara, A. Nakamura, Y. Origane, K. Fujita, D.-Q. Yuan, T. Mori, T. Wada and Y. Inoue, *J. Photochem. Photobiol. A: Chem.*, 2005, **173**, 375-383.
272.C. Yang, A. Nakamura, G. Fukuhara, Y. Origane, T. Mori, T. Wada and Y. Inoue, *J. Org. Chem.*, 2006, **71**, 3126-3136.
273.C. Yang, A. Nakamura, T. Wada and Y. Inoue, *Org. Lett.*, 2006, **8**, 3005-3008.
274.C. Yang, M. Nishijima, A. Nakamura, T. Mori, T. Wada and Y. Inoue, *Tetrahedron Lett.*, 2007, **48**, 4357-4360.
275.C. Yang, T. Mori and Y. Inoue, *J. Org. Chem.*, 2008, **73**, 5786-5794.
276.C. Yang, T. Mori, Y. Origane, Y. H. Ko, N. Selvapalam, K. Kim and Y. Inoue, *J. Am. Chem. Soc.*, 2008, **130**, 8574-8575.
277.L. Luo, G.-H. Liao, X.-L. Wu, L. Lei, C.-H. Tung and L.-Z. Wu, *J. Org. Chem.*, 2009, **74**, 3506-3515.
278.Q. Wang, C. Yang, C. Ke, G. Fukuhara, T. Mori, Y. Liu and Y. Inoue, *Chem. Commun.*, 2011, **47**, 6849-6851.
279.M. Pattabiraman, A. Natarajan, R. Kaliappan, J. T. Mague and V. Ramamurthy, *Chem. Commun.*, 2005, 4542-4544.
280.S. Y. Jon, Y. H. Ko, S. H. Park, H.-J. Kim and K. Kim, *Chem. Commun.*, 2001, 1938-1939.
281.R. Wang, L. Yuan and D. H. Macartney, *J. Org. Chem.*, 2006, **71**, 1237-1239.
282.M. V. S. N. Maddipatla, L. Kaanumalle, A. Natarajan, M. Pattabiraman and V. Ramamurthy, *Langmuir*, 2007, **23**, 7545-7554.
283.B. C. Pemberton, N. Barooah, D. K. Srivatsava and J. Sivaguru, *Chem. Commun.*, 2010, **46**, 225-227.
284.N. Barooah, B. C. Pemberton and J. Sivaguru, *Org. Lett.*, 2008, **10**, 3339-3342.
285.N. Barooah, B. C. Pemberton, A. C. Johnson and J. Sivaguru, *Photochem. Photobiol. Sci.*, 2008, **7**, 1473-1479.
286.B. C. Pemberton, R. K. Singh, A. C. Johnson, S. Jockusch, J. P. Da Silva, A. Ugrinov, N. J. Turro, D. K. Srivatsava and J. Sivaguru, *Chem. Commun.*, 2011, **47**, 6323-6325.
287.For the initial studies on the Gibb octaacid capsule see the following reference: C. L. D. Gibb and B. C. Gibb, *J. Am. Chem. Soc.*, 2004, **126**, 11408-11409.
288.For photochemical reactions performed inside the Gibb octaacid capsule see the references 288-291: A. Parthasarathy, L. Kaanumalle and V. Ramamurthy, *Org. Lett.*, 2007, **9**, 5059-5062.
289.A. Natarajan, L. Kaanumalle, S. Jockusch, C. L. D. Gibb, B. C. Gibb, N. J. Turro and V. Ramamurthy, *J. Am. Chem. Soc.*, 2007, **129**, 4132-4133.
290.L. Kaanumalle, C. L. D. Gibb, B. C. Gibb and V. Ramamurthy, *Org. Biomol. Chem.*, 2007, **5**, 236-238.
291.L. Kaanumalle and V. Ramamurthy, *Chem. Commun.*, 2007, 1062-1064.
292.M. A. Mateos-Timoneda, M. Crego-Calama and D. N. Reinhoudt, *Chem. Soc. Rev.*, 2004, **33**, 363-372.
293.G. A. Hembury, V. V. Borovkov and Y. Inoue, *Chem. Rev.*, 2008, **108**, 1-73.
294.M. V. Escárcega-Bobadilla and A. W. Kleij, *Chem. Sci.*, 2012, **3**, 2421-2428.
295.T. Aechtner, M. Dressel and T. Bach, *Angew. Chem. Int. Ed.*, 2004, **43**, 5849-5851.
296.R. Kaliappan, L. Kaanumalle and V. Ramamurthy, *Chem. Commun.*, 2005, 4056-4058.

297.L. Kaanumalle, C. L. D. Gibb, B. C. Gibb and V. Ramamurthy, *J. Am. Chem. Soc.*, 2004, **126**, 14366-14367.
298.C. L. D. Gibb, A. K. Sundaresan, V. Ramamurthy and B. C. Gibb, *J. Am. Chem. Soc.*, 2008, **130**, 4069-4080.
299.A. K. Sundaresan and V. Ramamurthy, *Photochem. Photobiol. Sci.*, 2008, **7**, 1555-1564.
300.R. Kulasekharan, R. Choudhury, R. Prabhakar and V. Ramamurthy, *Chem. Commun.*, 2011, **47**, 2841-2843.
301.R. Kaliappan and V. Ramamurthy, *J. Photochem. Photobiol., A*, 2009, **207**, 144-152.
302.K. Ohara, M. Kawano, Y. Inokuma and M. Fujita, *J. Am. Chem. Soc.*, 2010, **132**, 30-31.
303.K. Ohara, Y. Inokuma and M. Fujita, *Angew. Chem. Int. Ed.*, 2010, **49**, 5507-5509.
304.R. M. Yebeutchou and E. Dalcanale, *J. Am. Chem. Soc.*, 2009, **131**, 2452-2453.
305.H. Bricout, F. Hapiot, A. Ponchel, S. Tilloy and E. Monflier, *J. Sustainability Sci. Manage.*, 2009, **1**, 924-945.
306.L. Leclercq and A. R. Schmitzer, *Organometallics*, 2010, **29**, 3442-3449.
307.J. Potier, S. Menuel, D. Fournier, S. Fourmentin, P. Woisel, E. Monflier and F. Hapiot, *ACS Catal.*, 2012, **2**, 1417-1420.
308.R. J. Hooley and J. Rebek, Jr., *J. Am. Chem. Soc.*, 2005, **127**, 11904-11905.
309.R. J. Hooley and J. Rebek, Jr., *Org. Biomol. Chem.*, 2007, **5**, 3631-3636.
310.B. W. Purse, A. Gissot and J. Rebek, Jr., *J. Am. Chem. Soc.*, 2005, **127**, 11222-11223.
311.S. M. Butterfield and J. Rebek, Jr., *Chem. Commun.*, 2007, 1605-1607.
312.O. B. Berryman, A. C. Sather, A. Lledó and J. Rebek, Jr., *Angew. Chem. Int. Ed.*, 2011, **50**, 9400-9403.
313.M. A. Sarmentero, H. Fernandez-Perez, E. Zuidema, C. Bo, A. Vidal-Ferran and P. Ballester, *Angew. Chem. Int. Ed.*, 2010, **49**, 7489-7492.
314.H. Amouri, C. Desmarets and J. Moussa, *Chem Rev*, 2012, **112**, 2015-2041.
315.M. Raynal, P. Ballester, A. Vidal-Ferran and P. W. N. M. van Leeuwen, *Chem. Soc. Rev.*, 2013, DOI: .
316.For recent comments on the Pauling paradigm and notably the involvement of covalent bonds in enzymatic catalysis see the following review: X. Zhang and K. N. Houk, *Acc. Chem. Res.*, 2005, **38**, 379-385.
317.L. G. Mackay, R. S. Wylie and J. K. M. Sanders, *J. Am. Chem. Soc.*, 1994, **116**, 3141-3142.
318.C. J. Walter, H. L. Anderson and J. K. M. Sanders, *J. Chem. Soc., Chem. Commun.*,, 1993, 458-460.
319.Z. Clyde-Watson, A. Vidal-Ferran, L. J. Twyman, C. J. Walter, D. W. J. McCallien, S. Fanni, N. Bampos, R. Stephen Wylie and J. K. M. Sanders, *New J. Chem.*, 1998, **22**, 493-502.
320.M. Nakash, Z. Clyde-Watson, N. Feeder, J. E. Davies, S. J. Teat and J. K. M. Sanders, *J. Am. Chem. Soc.*, 2000, **122**, 5286-5293.
321.M. Marty, Z. Clyde-Watson, L. J. Twyman, M. Nakash and J. K. M. Sanders, *Chem. Commun.*, 1998, 2265-2266.
322.M. Nakash and J. K. M. Sanders, *J. Org. Chem.*, 2000, **65**, 7266-7271.
323.R. K. Totten, P. Ryan, B. Kang, S. J. Lee, L. J. Broadbelt, R. Q. Snurr, J. T. Hupp and S. T. Nguyen, *Chem. Commun.*, 2012, **48**, 4178-4180.
324.B. Kang, J. W. Kurutz, K.-T. Youm, R. K. Totten, J. T. Hupp and S. T. Nguyen, *Chem. Sci.*, 2012, **3**, 1938-1944.
325.F. Ishikawa, T. Tsumuraya and I. Fujii, *J. Am. Chem. Soc.*, 2009, **131**, 456-457.
326.G. Wulff, T. Gross and R. Schönfeld, *Angew. Chem. Int. Ed. Engl.*, 1997, **36**, 1961-1964.
327.A. Biffis and G. Wulff, *New J. Chem.*, 2001, **25**, 1537-1542.
328.J.-q. Liu and G. Wulff, *J. Am. Chem. Soc.*, 2004, **126**, 7452-7453.
329.J.-q. Liu and G. Wulff, *J. Am. Chem. Soc.*, 2008, **130**, 8044-8054.
330.A. Cutivet, C. Schembri, J. Kovensky and K. Haupt, *J. Am. Chem. Soc.*, 2009, **131**, 14699-14702.
331.B. Sellergren, *Nature Chem.*, 2010, **2**, 7-8.
332.J.-M. Lehn, *Chem. Eur. J.*, 1999, **5**, 2455-2463.
333.S. J. Rowan, S. J. Cantrill, G. R. L. Cousins, J. K. M. Sanders and J. F. Stoddart, *Angew. Chem. Int. Ed.*, 2002, **41**, 898-952.
334.P. T. Corbett, J. Leclaire, L. Vial, K. R. West, J.-L. Wietor, J. K. M. Sanders and S. Otto, *Chem. Rev.*, 2006, **106**, 3652-3711.
335.J.-M. Lehn, *Chem. Soc. Rev.*, 2007, **36**, 151-160.
336.G. Gasparini, M. Dal Molin and L. J. Prins, *Eur. J. Org. Chem.*, 2010, 2429-2440.
337.G. Gasparini, M. Dal Molin, A. Lovato and L. J. Prins, in *Supramolecular Chemistry: From Molecules to Nanomaterials*, eds. J. W. Steed and P. A. Gale, John Wiley & Sons, Ltd. DOI: 10.1002/9780470661345.smc161, 2012.
338.F. B. L. Cougnon and J. K. M. Sanders, *Acc. Chem. Res.*, 2012, **45**, 2211-2221.
339.B. Brisig, J. K. M. Sanders and S. Otto, *Angew. Chem. Int. Ed.*, 2003, **42**, 1270-1273.
340.G. Gasparini, L. J. Prins and P. Scrimin, *Angew. Chem. Int. Ed.*, 2008, **47**, 2475-2479.
341.G. E. Oosterom, J. N. H. Reek, P. C. J. Kamer and P. W. N. M. van Leeuwen, *Angew. Chem. Int. Ed.*, 2001, **40**, 1828-1849.
342.D. Astruc and F. Chardac, *Chem. Rev.*, 2001, **101**, 2991-3023.
343.L. J. Twyman, A. S. H. King and I. K. Martin, *Chem. Soc. Rev.*, 2002, **31**, 69-82.
344.J. N. H. Reek, D. de Groot, G. E. Oosterom, P. C. J. Kamer and P. W. N. M. van Leeuwen, *C. R. Chimie*, 2003, **6**, 1061-1077.
345.D. Astruc, K. Heuzé, S. Gatard, D. Méry, S. Nlate and L. Plault, *Adv. Synth. Catal.*, 2005, **347**, 329-338.
346.C. Liang and J. M. J. Fréchet, *Prog. Polym. Sci.*, 2005, **30**, 385-402.
347.B. Helms and J. M. J. Fréchet, *Adv. Synth. Catal.*, 2006, **348**, 1125-1148.
348.D. Astruc, *Tetrahedron: Asymmetry*, 2010, **21**, 1041-1054.
349.D. Astruc, C. Ornelas, A. K. Diallo and J. Ruiz, *Molecules*, 2010, **15**, 4947-4960.
350.A.-M. Caminade, A. Ouali, M. Keller and J.-P. Majoral, *Chem. Soc. Rev.*, 2012, **41**, 4113-4125.
351.B. Ramussen and J. B. Christensen, *Org. Biomol.Chem.*, 2012, **10**, 4821-4835.
352.J. M. Fraile, J. I. García and J. A. Mayoral, *Chem. Rev.*, 2009, **109**, 360-417.
353.M. E. Davis, *Acc. Chem. Res.*, 1993, **26**, 111-115.
354.N. J. Turro, *Acc. Chem. Res.*, 2000, **33**, 637-646.
355.J. M. Thomas and R. Raja, *Chem. Commun.*, 2001, 675-687.
356.N. J. Turro, *Chem. Commun.*, 2002, 2279-2292.
357.C.-H. Tung, L.-Z. Wu, L.-P. Zhang and B. Chen, *Acc. Chem. Res.*, 2003, **36**, 39-47.
358.J. C. Vartuli and T. F. Degnan, Jr, in *Stud. Surf. Sci. Catal.*, eds. J. Čejka, H. van Bekkum, A. Corma and F. Schüth, 2007, vol. 168, pp. 837-854.
359.X. S. Zhao, X. Y. Bao, W. Guo and F. Y. Lee, *Mater. Today*, 2009, **9**, 32-39.
360.A. P. Côté, A. I. Benin, N. W. Ockwig, M. O´Keeffe, A. J. Matzger and O. M. Yaghi, *Science*, 2005, **310**, 1166-1170.
361.S.-Y. Ding, J. Gao, Q. Wang, Y. Zhang, W.-G. Song, C.-Y. Su and W. Wang, *J. Am. Chem. Soc.*, 2011, **133**, 19816-19822.
362.A. W. Bosman, R. Vestberg, A. Heumann, J. M. J. Fréchet and C. J. Hawker, *J. Am. Chem. Soc.*, 2003, **125**, 715-728.
363.T. Terashima, M. Kamigaito, K.-Y. Baek, T. Ando and M. Sawamoto, *J. Am. Chem. Soc.*, 2003, **125**, 5288-5289.
364.B. Helms, S. J. Guillaudeu, Y. Xie, M. McMurdo, C. J. Hawker and J. M. J. Fréchet, *Angew. Chem. Int. Ed.*, 2005, **44**, 6384-6387.
365.Y. Chi, S. T. Scroggins and J. M. J. Fréchet, *J. Am. Chem. Soc.*, 2008, **130**, 6322-6323.
366.A. Shultz, O. K. Farha, J. T. Hupp and S. T. Nguyen, *Chem. Sci.*, 2011, **2**, 686-689.
367.P. Kaur, J. T. Hupp and S. T. Nguyen, *ACS Catal.*, 2011, **1**, 819-835.
368.G. Lu, S. Li, Z. Guo, O. K. Farha, B. G. Hauser, X. Qi, Y. Wang, X. Wang, S. Han, X. Liu, J. S. DuChene, H. Zhang, Q. Zhang, X. Chen, J. Ma, S. C. J. Loo, W. D. Wei, Y. Yang, J. T. Hupp and F. Huo, *Nature Chem.*, 2012, **4**, 310-316.
369.A. Dhakshinamoorthy and H. Garcia, *Chem. Soc. Rev.*, 2012, **41**, 5262-5284.

370. Y. Inokuma, M. Kawano and M. Fujita, *Nature Chem.*, 2011, **3**, 349-358.
371. Y. Inokuma, N. Kojima, T. Arai and M. Fujita, *J. Am. Chem. Soc.*, 2011, **133**, 19691-19693.
372. K. Ikemoto, Y. Inokuma and M. Fujita, *J. Am. Chem. Soc.*, 2011, **133**, 16806-16808.
373. Y. Inokuma, T. Arai and M. Fujita, *Nature Chem.*, 2010, **2**, 780-783.
374. M. Fujita, K. Umemoto, M. Yoshizawa, N. Fujita, T. Kusukawa and K. Biradha, *Chem. Commun.*, 2001, 509-518.
375. D. L. Caulder and K. N. Raymond, *J. Chem. Soc., Dalton Trans.*, 1999, 1185-1200.
376. M. J. Wiester, P. A. Ulmann and C. A. Mirkin, *Angew. Chem. Int. Ed.*, 2011, **50**, 114-137.
377. J. Kang, J. Santamaria, G. Hilmersson and J. Rebek, Jr., *J. Am. Chem. Soc.*, 1998, **120**, 7389-7390.
378. M. D. Pluth, R. G. Bergman and K. N. Raymond, *Angew. Chem. Int. Ed.*, 2007, **46**, 8587-8589.
379. M. D. Pluth, R. G. Bergman and K. N. Raymond, *J. Org. Chem.*, 2009, **74**, 58-63.
380. T. Murase, Y. Nishijima and M. Fujita, *J. Am. Chem. Soc.*, 2012, **134**, 162-164.
381. D. Hilvert, K. W. Hill, K. D. Nared and M.-T. M. Auditor, *J. Am. Chem. Soc.*, 1989, **111**, 9262-9263.
382. D. Fiedler, R. G. Bergman and K. N. Raymond, *Angew. Chem. Int. Ed.*, 2004, **43**, 6748-6751.
383. C. J. Hastings, D. Fiedler, R. G. Bergman and K. N. Raymond, *J. Am. Chem. Soc.*, 2008, **130**, 10977-10983.
384. D. Fiedler, H. van Halbeek, R. G. Bergman and K. N. Raymond, *J. Am. Chem. Soc.*, 2006, **128**, 10240-10252.
385. C. J. Brown, R. G. Bergman and K. N. Raymond, *J. Am. Chem. Soc.*, 2009, **131**, 17530-17531.
386. C. J. Hastings, M. D. Pluth, R. G. Bergman and K. N. Raymond, *J. Am. Chem. Soc.*, 2010, **132**, 6938-6940.
387. M. Fujita, D. Oguro, M. Miyazawa, H. Oka, K. Yamaguchi and K. Ogura, *Nature*, 1995, **378**, 469-471.
388. M. Fujita, S.-Y. Yu, T. Kusukawa, H. Funaki, K. Ogura and K. Yamaguchi, *Angew. Chem. Int. Ed.*, 1998, **37**, 2082-2085.
389. M. Yoshizawa, J. Nakagawa, K. Kumazawa, M. Nagao, M. Kawano, T. Ozeki and M. Fujita, *Angew. Chem. Int. Ed.*, 2005, **44**, 1810-1813.
390. W.-Y. Sun, M. Yoshizawa, T. Kusukawa and M. Fujita, *Curr. Opin. Chem. Biol.*, 2002, **6**, 757-764.
391. M. Fujita, M. Tominaga, A. Hori and B. Therrien, *Acc. Chem. Res.*, 2005, **38**, 371-380.
392. V. Maurizot, M. Yoshizawa, M. Kawano and M. Fujita, *Dalton Trans.*, 2006, 2750-2756.
393. M. Yoshizawa, Y. Takeyama, T. Kusukawa and M. Fujita, *Angew. Chem. Int. Ed.*, 2002, **41**, 1347-1349.
394. M. Yoshizawa, Y. Takeyama, T. Okano and M. Fujita, *J. Am. Chem. Soc.*, 2003, **125**, 3243-3247.
395. M. Yoshizawa, M. Tamura and M. Fujita, *Science*, 2006, **312**, 251-254.
396. Y. Nishioka, T. Yamaguchi, M. Yoshizawa and M. Fujita, *J. Am. Chem. Soc.*, 2007, **129**, 7000-7001.
397. Y. Nishioka, T. Yamaguchi, M. Kawano and M. Fujita, *J. Am. Chem. Soc.*, 2008, **130**, 8160-8161.
398. T. Murase, S. Horiuchi and M. Fujita, *J. Am. Chem. Soc.*, 2010, **132**, 2866-2867.
399. T. Murase, S. Peschard, S. Horiuchi, Y. Nishioka and M. Fujita, *Supramol. Chem.*, 2011, **23**, 199-208.
400. T. Murase, H. Takezawa and M. Fujita, *Chem. Commun.*, 2011, **47**, 10960-10962.
401. Y. Yamauchi and M. Fujita, *Chem. Commun.*, 2010, **46**, 5897-5899.
402. D. Fiedler, D. H. Leung, R. G. Bergman and K. N. Raymond, *Acc. Chem. Res.*, 2005, **38**, 351-360.
403. C. J. Hastings, M. P. Backlund, R. G. Bergman and K. N. Raymond, *Angew. Chem. Int. Ed.*, 2011, **50**, 10570-10573.
404. W. M. Hart-Cooper, K. N. Clary, F. D. Toste, R. G. Bergman and K. N. Raymond, *J. Am. Chem. Soc.*, 2012, **134**, 17873-17876.
405. M. D. Pluth, R. G. Bergman and K. N. Raymond, *Science*, 2007, **316**, 85-88.
406. M. D. Pluth, R. G. Bergman and K. N. Raymond, *J. Am. Chem. Soc.*, 2008, **130**, 11423-11429.
407. A. V. Davis, D. Fiedler, M. Ziegler, A. Terpin and K. N. Raymond, *J. Am. Chem. Soc.*, 2007, **129**, 15354-15363.
408. M. P. Frushicheva, S. Mukherjee and A. Warshel, *J. Phys. Chem. B*, 2012, **116**, 13353-13360.
409. A. Warshel, P. K. Sharma, M. Kato, Y. Xiang, H. B. Liu and M. H. M. Olsson, *Chem. Rev.*, 2006, **106**, 3210-3235.
410. M. D. Pluth, R. G. Bergman and K. N. Raymond, *J. Am. Chem. Soc.*, 2007, **129**, 11459-11467.
411. D. Fiedler, D. Pagliero, J. L. Brumaghim, R. G. Bergman and K. N. Raymond, *Inorg. Chem.*, 2004, **43**, 846-848.
412. D. H. Leung, D. Fiedler, R. G. Bergman and K. N. Raymond, *Angew. Chem. Int. Ed.*, 2004, **43**, 963-966.
413. D. Fiedler, R. G. Bergman and K. N. Raymond, *Angew. Chem. Int. Ed.*, 2006, **45**, 745-748.
414. S. For the unusual reactivity of a ruthenium complex within cage **50** see the following reference: Horiuchi, T. Murase and M. Fujita, *Angew. Chem. Int. Ed.*, 2012, **51**, 12029-12031.
415. D. H. Leung, R. G. Bergman and K. N. Raymond, *J. Am. Chem. Soc.*, 2007, **129**, 2746-2747.
416. Z. J. Wang, C. J. Brown, R. G. Bergman, K. N. Raymond and F. D. Toste, *J. Am. Chem. Soc.*, 2011, **133**, 7358-7360.
417. Z. J. Wang, K. N. Clary, R. G. Bergman, K. N. Raymond and F. D. Toste, *Nature Chem.*, 2013, **5**, 100-103.
418. M. L. Merlau, M. del Pilar Mejia, S. T. Nguyen and J. T. Hupp, *Angew. Chem. Int. Ed.*, 2001, **40**, 4239-4242.
419. G. A. E. Oxford, M. C. Curet-Arana, D. Majumder, R. W. Gurney, M. L. Merlau, S. T. Nguyen, R. Q. Snurr and L. J. Broadbelt, *J. Catal.*, 2009, **266**, 145-155.
420. S. J. Lee, K. L. Mulfort, X. Zuo, A. J. Goshe, P. J. Wesson, S. T. Nguyen, J. T. Hupp and D. M. Tiede, *J. Am. Chem. Soc.*, 2008, **130**, 836-838.
421. S. J. Lee, S.-H. Cho, K. L. Mulfort, D. M. Tiede, J. T. Hupp and S. T. Nguyen, *J. Am. Chem. Soc.*, 2008, **130**, 16828-16829.
422. J. Kang and J. Rebek, Jr., *Nature*, 1997, **385**, 50-52.
423. J. Kang, G. Hilmersson, J. Santamaria and J. Rebek, Jr., *J. Am. Chem. Soc.*, 1998, **120**, 3650-3656.
424. J. Chen and J. Rebek, Jr., *Org. Lett.*, 2002, **4**, 327-329.
425. A. Shivanyuk and J. Rebek, Jr., *Proc. Natl. Acad. Sci. U.S.A.*, 2001, **98**, 7662-7665.
426. L. Avram and Y. Cohen, *Org. Lett.*, 2002, **4**, 4365-4368.
427. E. S. Barrett, T. J. Dale and J. Rebek, Jr., *J. Am. Chem. Soc.*, 2008, **130**, 2344-2350.
428. A. Cavarzan, A. Scarso, P. Sgarbossa, G. Strukul and J. N. H. Reek, *J. Am. Chem. Soc.*, 2011, **133**, 2848-2851.
429. For a study on the nature of the encapsulated Au complex species within the resorcinarene capsule see the following reference: L. Adriaenssens, A. Escribano-Cuesta, A. Homs, A. M. Echavarren and P. Ballester, *Eur. J. Org.Chem.*, 2013, 1494-1500.
430. S. F. M. van Dongen, H.-P. M. de Hoog, R. J. R. W. Peters, M. Nallani, R. J. M. Nolte and J. C. M. van Hest, *Chem. Rev.*, 2009, **109**, 6212-6274.
431. K. T. Kim, S. A. Meeuwissen, R. J. M. Nolte and J. C. M. van Hest, *Nanoscale*, 2010, **2**, 844-858.
432. T. Dwars, E. Paetzold and G. Oehme, *Angew. Chem. Int. Ed.*, 2005, **44**, 7174-7199.
433. E. Moulin and N. Giuseppone, in *Supramolecular Chemistry: From Molecules to Nanomaterials*, eds. J. W. Steed and P. A. Gale, John Wiley & Sons, Ltd., 2012, DOI: 10.1002/9780470661345.smc9780470661166.
434. F. Mancin, P. Scrimin, P. Tecilla and U. Tonellato, *Coord. Chem. Rev.*, 2009, **253**, 2150-2165.
435. S. Bhattacharya and N. Kumari, *Coord. Chem. Rev.*, 2009, **253**, 2133-2149.
436. J. Zhang, X.-G. Meng, X.-C. Zeng and X.-Q. Yu, *Coord. Chem. Rev.*, 2009, **253**, 2166-2177.
437. M. Shiri and M. A. Zolfigol, *Tetrahedron*, 2009, **65**, 587-598.
438. K. T. Kim, J. J. L. M. Cornelissen, R. J. M. Nolte and J. C. M. van Hest, *Adv. Mater.*, 2009, **21**, 2787-2791.

439.H.-P. M. de Hoog, I. W. C. E. Arends, A. E. Rowan, J. J. L. M. Cornelissen and R. J. M. Nolte, *Nanoscale*, 2010, **2**, 709-716.
440.D. A. Wilson, R. J. M. Nolte and J. C. M. van Hest, *Nature Chem.*, 2012, **4**, 268-274.
441.M. O. Guler and S. I. Stupp, *J. Am. Chem. Soc.*, 2007, **129**, 12082-12083.
442.F. Rodriguez-Llansola, J. F. Miravet and B. Escuder, *Chem. Commun.*, 2009, 7303-7305.
443.A. Dawn, N. Fujita, S. Haraguchi, K. Sada and S. Shinkai, *Chem. Commun.*, 2009, 2100-2102.
444.A. Dawn, N. Fujita, S. Haraguchi, K. Sada, S. Tamaru and S. Shinkai, *Org. Biomol. Chem.*, 2009, **7**, 4378-4385.
445.B. Escuder, F. Rodriguez-Llansola and J. F. Miravet, *New J. Chem.*, 2010, **34**, 1044-1054.
446.A. Dawn, T. Shiraki, S. Haraguchi, H. Sato, K. Sada and S. Shinkai, *Chem. Eur. J.*, 2010, **16**, 3676-3689.
447.F. Rodríguez-Llansola, J. F. Miravet and B. Escuder, *Chem. Eur. J.*, 2010, **16**, 8480-8486.
448.Q. X. Jin, L. Zhang, H. Cao, T. Y. Wang, X. F. Zhu, J. Jiang and M. H. Liu, *Langmuir*, 2011, **27**, 13847-13853.
449.D. Díaz Díaz, D. Kühbeck and R. J. Koopmans, *Chem. Soc. Rev.*, 2011, **40**, 427-448.
450.A. N. Khlobystov, *ACS Nano*, 2011, **5**, 9306-9312.
451.I. J. Minten, L. J. A. Hendriks, R. J. M. Nolte and J. J. L. M. Cornelissen, *J. Am. Chem. Soc.*, 2009, **131**, 17771-17773.
452.I. J. Minten, V. I. Claessen, K. Blank, A. E. Rowan, R. J. M. Nolte and J. J. L. M. Cornelissen, *Chem. Sci.*, 2011, **2**, 358-362.
453.S. A. Bode, I. J. Minten, R. J. M. Nolte and J. J. L. M. Cornelissen, *Nanoscale*, 2011, **3**, 2376-2389.
454.For "on water" organic reactions and the possible involvment of hydrogen bond interactions see the following review and references 455-456: A. Chanda and V. V. Fokin, *Chem. Rev.*, 2009, **109**, 725-748.
455.Y. S. Jung and R. A. Marcus, *J. Am. Chem. Soc.*, 2007, **129**, 5492-5502.
456.J. K. Beattie, C. S. P. McErlean and C. B. W. Phippen, *Chem. Eur. J.*, 2010, **16**, 8972-8974.
457.Besides hydrogen bond interactions and hydrophobic interactions, other effects can play a role for Diels-Alder reactions perfomed in water. For a discussion on the orgin of the observed enhanced rates in water see reviews 457-459: R. Breslow, *Acc. Chem. Res.*, 1991, **24**, 159-164.
458.S. Otto and J. B. F. N. Engberts, *Pure Appl. Chem.*, 2000, **72**, 1365-1372.
459.S. Otto and J. B. F. N. Engberts, *Org. Biomol. Chem.*, 2003, **1**, 2809-2820.
460.R. Breslow and Z. Zhu, *J. Am. Chem. Soc.*, 1995, **117**, 9923-9924.
461.E. T. Kool and R. Breslow, *J. Am. Chem. Soc.*, 1988, **110**, 1596-1597.
462.R. Breslow, *Acc. Chem. Res.*, 2004, **37**, 471-478.
463.R. Breslow and R. V. Connors, *J. Am. Chem. Soc.*, 1995, **117**, 6601-6602.
464.M. R. Biscoe and R. Breslow, *J. Am. Chem. Soc.*, 2003, **125**, 12718-12719.
465.M. R. Biscoe, C. Uyeda and R. Breslow, *Org. Lett.*, 2004, **6**, 4331-4334.
466.C. Uyeda, M. Biscoe, P. LePlae and R. Breslow, *Tetrahedron Lett.*, 2006, **47**, 127-130.
467.M. Biscoe and R. Breslow, *J. Am. Chem. Soc.*, 2005, **127**, 10812-10813.
468.R. Breslow and R. Connors, *J. Am. Chem. Soc.*, 1996, **118**, 6323-6324.
469.R. Breslow, K. Groves and M. U. Mayer, *J. Am. Chem. Soc.*, 2002, **124**, 3622-3635.
470.R. Breslow, *J. Phys. Org. Chem.*, 2006, **19**, 813-822.
471.B. Fell, C. Schobben and G. Papadogianakis, *J. Mol. Cat. A: Chem.*, 1995, **101**, 179-186.
472.G. Oehme, I. Grassert, S. Ziegler, R. Meisel and H. Fuhrmann, *Catal. Today*, 1998, **42**, 459-470.
473.H. Chen, Y. Li, J. Chen, P. Cheng, Y.-e. He and X. Li, *J. Mol. Cat. A: Chem.*, 1999, **149**, 1-6.
474.L. Wang, H. Chen, Y.-e. He, Y. Li, M. Li and X. Li, *Appl. Catal., A*, 2003, **242**, 85-88.
475.H. Fu, M. Li, H. Chen and X. Li, *J. Mol. Cat. A: Chem.*, 2006, **259**, 156-160.
476.S. L. Desset, D. J. Cole-Hamilton and D. F. Foster, *Chem. Commun.*, 2007, 1933-1935.
477.S. L. Desset, S. W. Reader and D. J. Cole-Hamilton, *Green Chem.*, 2009, **11**, 630-637.
478.H. Ding, B. E. Hanson, T. Bartik and B. Bartik, *Organometallics*, 1994, **13**, 3761-3763.
479.H. Ding, B. E. Hanson and J. Bakos, *Angew. Chem. Int. Ed. Engl.*, 1995, **34**, 1645-1647.
480.T. Bartik, H. Ding, B. Bartik and B. E. Hanson, *J. Mol. Cat. A: Chem.*, 1995, **98**, 117-122.
481.B. E. Hanson, H. Ding and C. W. Kohlpaintner, *Catal. Today*, 1998, **42**, 421-429.
482.M. S. Goedheijt, B. E. Hanson, J. N. H. Reek, P. C. J. Kamer and P. W. N. M. van Leeuwen, *J. Am. Chem. Soc.*, 2000, **122**, 1650-1657.
483.H. Hattori, K.-I. Fujita, T. Muraki and A. Sakaba, *Tetrahedron Lett.*, 2007, **48**, 6817-6820.
484.M. Ferreira, H. Bricout, N. Azaroual, D. Landy, S. Tilloy, F. Hapiot and E. Monflier, *Adv. Synth. Catal.*, 2012, **354**, 1337-1346.
485.H. Bricout, E. Leonard, C. Len, D. Landy, F. Hapiot and E. Monflier, *Beilstein J. Org. Chem.*, 2012, **8**, 1479-1484.
486.S. Elias and A. Vigalok, *Adv. Synth. Catal.*, 2009, **351**, 1499-1504.
487.L. Pasquato, F. Rancan, P. Scrimin, F. Mancin and C. Frigeri, *Chem. Commun.*, 2000, 2253-2254.
488.F. Manea, F. B. Houillon, L. Pasquato and P. Scrimin, *Angew. Chem. Int. Ed.*, 2004, **43**, 6165-6169.
489.P. Pengo, S. Polizzi, L. Pasquato and P. Scrimin, *J. Am. Chem. Soc.*, 2005, **127**, 1616-1617.
490.P. Pengo, L. Baltzer, L. Pasquato and P. Scrimin, *Angew. Chem. Int. Ed.*, 2007, **46**, 400-404.
491.R. Bonomi, F. Selvestrel, V. Lombardo, C. Sissi, S. Polizzi, F. Mancin, U. Tonellato and P. Scrimin, *J. Am. Chem. Soc.*, 2008, **130**, 15744-15745.
492.For the supramolecular anchoring of organocatalytic peptides at the surface of gold nanoparticles see references 492-493: D. Zaramella, P. Scrimin and L. J. Prins, *J. Am. Chem. Soc.*, 2012, **134**, 8396-8399.
493.D. Zaramella, P. Scrimin and L. J. Prins, *Int. J. Mol. Sci.*, 2013, **14**, 2011-2021.
494.J. T. Groves and R. Neumann, *J. Am. Chem. Soc.*, 1989, **111**, 2900-2909.
495.J. van Esch, M. F. M. Roks and R. J. M. Nolte, *J. Am. Chem. Soc.*, 1986, **108**, 6093-6094.
496.A. P. H. J. Schenning, D. H. W. Hubert, J. van Esch, M. C. Feiters and R. J. M. Nolte, *Angew. Chem. Int. Ed. Engl.*, 1994, **33**, 2468-2470.
497.A. P. H. J. Schenning, J. H. L. Spelberg, M. C. P. F. Driessen, M. J. B. Hauser, M. C. Feiters and R. J. M. Nolte, *J. Am. Chem. Soc.*, 1995, **117**, 12655-12656.
498.A. P. H. J. Schenning, J. H. L. Spelberg, D. H. W. Hubert, M. C. Feiters and R. J. M. Nolte, *Chem. Eur. J.*, 1998, **4**, 871-880.
499.S. Luo, X. Mi, S. Liu, H. Xu and J.-P. Cheng, *Chem. Commun.*, 2006, 3687-3689.
500.Y. Hayashi, S. Aratake, T. Okano, J. Takahashi, T. Sumiya and M. Shoji, *Angew. Chem. Int. Ed.*, 2006, **45**, 5527-5529.
501.N. Mase, Y. Nakai, N. Ohara, H. Yoda, K. Takabe, F. Tanaka and C. F. Barbas III, *J. Am. Chem. Soc.*, 2006, **128**, 734-735.
502.M. Gruttadauria, F. Giacalone and R. Noto, *Adv. Synth. Catal.*, 2009, **351**, 33-57.
503.N. Mase and C. F. Barbas III, *Org. Biomol.Chem.*, 2010, **8**, 4043-4050.
504.M. Raj and V. K. Singh, *Chem. Commun.*, 2009, 6687-6703.
505.Y. Tang, L. P. Zhou, J. X. Li, Q. A. Luo, X. Huang, P. Wu, Y. G. Wang, J. Y. Xu, J. C. Shen and J. Q. Liu, *Angew. Chem. Int. Ed.*, 2010, **49**, 3920-3924.
506.D. S. Guo, K. Wang, Y. X. Wang and Y. Liu, *J. Am. Chem. Soc.*, 2012, **134**, 10244-10250.
507.D. K. Smith and F. Diederich, *Chem. Eur. J.*, 1998, **4**, 1353-1361.

508. S. Bandyopadhyay, W. Zhou and R. Breslow, *Org. Lett.*, 2007, **9**, 1009-1012.
509. T. Terashima, M. Ouchi, T. Ando and M. Sawamoto, *J. Polym. Sci., Part A: Polym. Chem.*, 2009, **48**, 373-379.
510. V. Rodionov, H. Gao, S. Scroggins, D. A. Unruh, A.-J. Avestro and J. M. J. Fréchet, *J. Am. Chem. Soc.*, 2010, **132**, 2570-2572.
511. T. Terashima, T. Mes, T. F. A. De Greef, M. A. Gillissen, P. Besenius, A. R. A. Palmans and E. W. Meijer, *J. Am. Chem. Soc.*, 2011, **133**, 4742-4745.
512. J. M. Heemstra and J. S. Moore, *J. Am. Chem. Soc.*, 2004, **126**, 1648-1649.
513. J. Kofoed and J.-L. Reymond, *Curr. Opin. Chem. Biol.*, 2005, **9**, 656-664.
514. R. Breslow, S. Bandyopadhyay, M. Levine and W. Zhou, *ChemBioChem*, 2006, **7**, 1491-1496.
515. J.-L. Reymond and T. Darbre, *Org. Biomol. Chem.*, 2012, **10**, 1483-1492.
516. E. Delort, T. Darbre and J.-L. Reymond, *J. Am. Chem. Soc.*, 2004, **126**, 15642-15643.
517. E. Delort, N.-Q. Nguyen-Trung, T. Darbre and J.-L. Reymond, *J. Org. Chem.*, 2006, **71**, 4468-4480.
518. G. Zaupa, P. Scrimin and L. J. Prins, *J. Am. Chem. Soc.*, 2008, **130**, 5699-5709.
519. G. Zaupa, L. J. Prins and P. Scrimin, *Biiorg. Med. Chem. Lett.*, 2009, **19**, 3816-3820.
520. H. Zhao, F. W. Foss and R. Breslow, *J. Am. Chem. Soc.*, 2008, **130**, 12590-12591.
521. I. M. Klotz, G. P. Royer and I. S. Scarpa, *Proc. Natl. Acad. Sci. U.S.A.*, 1971, **68**, 263-264.
522. J. Suh, *Synlett*, 2001, **9**, 1343-1363.
523. I. M. Klotz and J. Suh, in *Artificial Enzymes*, ed. R. Breslow, Wiley-VCH, Weinheim, 2005, pp. 63-88.
524. M. Martin, F. Manea, R. Fiammengo, L. J. Prins, L. Pasquato and P. Scrimin, *J. Am. Chem. Soc.*, 2007, **129**, 6982-6983.
525. F. Avenier, J. B. Domingos, L. D. Van Vliet and F. Hollfelder, *J. Am. Chem. Soc.*, 2007, **129**, 7611-7619.
526. I. K. Martin and L. J. Twyman, *Tetrahedron Lett.*, 2001, **42**, 1123-1126.
527. J. L. Burnett, A. S. H. King, I. K. Martin and L. J. Twyman, *Tetrahedron Lett.*, 2002, **43**, 2431-2433.
528. J. J. Chruma, L. Liu, W. Zhou and R. Breslow, *Biiorg. Med. Chem.*, 2005, **13**, 5873-5883.
529. L. Liu and R. Breslow, *J. Am. Chem. Soc.*, 2002, **124**, 4978-4979.
530. L. Liu and R. Breslow, *J. Am. Chem. Soc.*, 2003, **125**, 12110-12111.
531. W. Zhou, L. Liu and R. Breslow, *Helv. Chim. Acta*, 2003, **86**, 3560-3567.
532. L. Liu, W. Zhou, J. Chruma and R. Breslow, *J. Am. Chem. Soc.*, 2004, **126**, 8136-8137.
533. R. Breslow, S. Wei and C. Kenesky, *Tetrahedron*, 2007, **63**, 6317-6321.
534. S. Wei, J. Wang, S. Venhuizen, R. Skouta and R. Breslow, *Biiorg. Med. Chem. Lett.*, 2009, **19**, 5543-5546.
535. Y. Chi, S. T. Scroggins, E. Boz and J. M. J. Fréchet, *J. Am. Chem. Soc.*, 2008, **130**, 17287-17289.
536. J. C. Garcia-Martinez, R. Lezutekong and R. M. Crooks, *J. Am. Chem. Soc.*, 2005, **127**, 5097-5103.
537. K. Akagawa, S. Sakamoto and K. Kudo, *Tetrahedron Lett.*, 2005, **46**, 8185-8187.
538. D. Font, C. Jimeno and M. A. Pericàs, *Org. Lett.*, 2006, **8**, 4653-4655.
539. F. Giacalone, M. Gruttadauria, A. M. Marculescu and R. Noto, *Tetrahedron Lett.*, 2007, **48**, 255-259.
540. E. Alza, X. C. Cambeiro, C. Jimeno and M. A. Pericàs, *Org. Lett.*, 2007, **9**, 3717-3720.
541. K. Akagawa, H. Akabane, S. Sakamoto and K. Kudo, *Org. Lett.*, 2008, **10**, 2035-2037.
542. K. Akagawa, T. Fujiwara, S. Sakamoto and K. Kudo, *Chem. Commun.*, 2010, **46**, 8040-8042.
543. K. Akagawa and K. Kudo, *Adv. Synth. Catal.*, 2011, **353**, 843-847.
544. Y. Wu, Y. Zhang, M. Yu, G. Zhao and S. Wang, *Org. Lett.*, 2006, **8**, 4417-4420.
545. E. Huerta, P. J. M. Stals, E. W. Meijer and A. R. A. Palmans, *Angew. Chem. Int. Ed.*, 2013, **52**, 2906-2910.
546. F. Biedermann, V. D. Uzunova, O. A. Scherman, W. M. Nau and A. De Simone, *J. Am. Chem. Soc.*, 2012, **134**, 15318-15323.
547. G. von Kiedrowski, *Angew. Chem. Int. Ed. Engl.*, 1986, **25**, 932-935.
548. W. S. Zielinski and L. E. Orgel, *Nature*, 1987, **327**, 346-347.
549. G. von Kiedrowski, B. Wlotzka and J. Helbing, *Angew. Chem. Int. Ed. Engl.*, 1989, **28**, 1235-1237.
550. G. von Kiedrowski, B. Wlotzka, J. Helbing, M. Matzen and S. Jordan, *Angew. Chem. Int. Ed. Engl.*, 1991, **30**, 423-426.
551. T. Achilles and G. von Kiedrowski, *Angew. Chem. Int. Ed. Engl.*, 1993, **32**, 1198-1201.
552. D. Sievers and G. von Kiedrowski, *Nature*, 1994, **369**, 221-224.
553. D. Sievers and G. von Kiedrowski, *Chem. Eur. J.*, 1998, **4**, 629-641.
554. D. H. Lee, J. R. Granja, J. A. Martinez, K. Severin and M. R. Ghadiri, *Nature*, 1996, **382**, 525-528.
555. K. Severin, D. H. Lee, J. A. Martinez and M. R. Ghadiri, *Chem. Eur. J.*, 1997, **3**, 1017-1024.
556. S. Yao, I. Ghosh, R. Zutshi and J. Chmielewski, *J. Am. Chem. Soc.*, 1997, **119**, 10559-10560.
557. S. Yao, I. Ghosh, R. Zutshi and J. Chmielewski, *Angew. Chem. Int. Ed.*, 1998, **37**, 478-481.
558. P. A. Bachmann, P. L. Luisi and J. Lang, *Nature*, 1992, **357**, 57-59.
559. P. Walde, R. Wick, M. Fresta, A. Mangone and P. L. Luisi, *J. Am. Chem. Soc.*, 1994, **116**, 11649-11654.
560. A. Terfort and G. von Kiedrowski, *Angew. Chem. Int. Ed. Engl.*, 1992, **31**, 654-656.
561. For the seminal work of Rebek and co-workers see the following reference and references 32 and 562-563. For mechanistic studies on this system see references 564, 565, 567, 571 and 572. J. S. Nowick, Q. Feng, T. Tjivikua, P. Ballester and J. Rebek, Jr., *J. Am. Chem. Soc.*, 1991, **113**, 8831-8839.
562. V. Rotello, J.-I. Hong and J. Rebek, Jr., *J. Am. Chem. Soc.*, 1991, **113**, 9422-9423.
563. Q. Feng, T. K. Park and J. Rebek, Jr., *Science*, 1992, **256**, 1179-1180.
564. E. A. Wintner, M. M. Conn and J. Rebek, Jr., *J. Am. Chem. Soc.*, 1994, **116**, 8877-8884.
565. M. M. Conn, E. A. Wintner and J. Rebek, Jr., *Angew. Chem. Int. Ed. Engl.*, 1994, **33**, 1577-1579.
566. For kinetic studies of minimal self-replicating systems see references 566-568: G. von Kiedrowski, in *Bioorganic Chemistry Frontiers 3*, ed. H. Dugas, Verlag: Springer, Berlin, 1993.
567. D. N. Reinhoudt, D. M. Rudkevich and F. de Jong, *J. Am. Chem. Soc.*, 1996, **118**, 6880-6889.
568. I. Stahl and G. von Kiedrowski, *J. Am. Chem. Soc.*, 2006, **128**, 14014-14015.
569. N. Paul and G. F. Joyce, *Curr. Opin. Chem. Biol.*, 2004, **8**, 634-639.
570. M. Kindermann, I. Stahl, M. Reimold, W. M. Pankau and G. von Kiedrowski, *Angew. Chem. Int. Ed.*, 2005, **44**, 6750-6755.
571. F. M. Menger, A. V. Eliseev and N. A. Khanjin, *J. Am. Chem. Soc.*, 1994, **116**, 3613-3614.
572. F. M. Menger, A. V. Eliseev, N. A. Khanjin and M. J. Sherrod, *J. Org. Chem.*, 1995, **60**, 2870-2878.
573. S. Kamioka, D. Ajami and J. Rebek, Jr., *Proc. Natl. Acad. Sci. U.S.A.*, 2010, **107**, 541-544.
574. V. del Amo, A. M. Z. Slawin and D. Philp, *Org. Lett.*, 2008, **10**, 4589-4592.
575. S. Xu and N. Giuseppone, *J. Am. Chem. Soc.*, 2008, **130**, 1826-1827.
576. R. Nguyen, L. Allouche, E. Buhler and N. Giuseppone, *Angew. Chem. Int. Ed.*, 2009, **48**, 1093-1096.
577. B. Wang and I. O. Sutherland, *Chem. Commun.*, 1997, 1495-1496.
578. R. J. Pearson, E. Kassianidis, A. M. Z. Slawin and D. Philp, *Org. Biomol. Chem.*, 2004, **2**, 3434-3441.
579. E. Kassianidis, R. J. Pearson and D. Philp, *Org. Lett.*, 2005, **7**, 3833-3836.
580. R. J. Pearson, E. Kassianidis, A. M. Z. Slawin and D. Philp, *Chem. Eur. J.*, 2006, **12**, 6829-6840.
581. E. Kassianidis, R. J. Pearson and D. Philp, *Chem. Eur. J.*, 2006, **12**, 8798-8812.
582. A. Dieckmann, S. Beniken, C. Lorenz, N. L. Doltsinis and G. von Kiedrowski, *J. Syst. Chem.*, 2010, **1**, 10.

583.A. Dieckmann, S. Beniken, C. D. Lorenz, N. L. Doltsinis and G. von Kiedrowski, *Chem. Eur. J.*, 2011, **17**, 468-480.
584.V. C. Allen, D. Philp and N. Spencer, *Org. Lett.*, 2001, **3**, 777-780.
585.E. Kassianidis and D. Philp, *Angew. Chem. Int. Ed.*, 2006, **45**, 6344-6348.
586.E. Kassianidis and D. Philp, *Chem. Commun.*, 2006, 4072-4074.
587.A. Vidonne and D. Philp, *Tetrahedron*, 2008, **64**, 8464-8475.
588.J. W. Sadownik and D. Philp, *Angew. Chem. Int. Ed.*, 2008, **47**, 9965-9970.
589.E. Kassianidis, R. J. Pearson, E. A. Wood and D. Philp, *Faraday Discuss.*, 2010, **145**, 235-254.
590.N. Wagner and G. Ashkenasy, *Chem. Eur. J.*, 2009, **15**, 1765-1775.
591.J. M. A. Carnall, C. A. Waudby, A. M. Belenguer, M. C. A. Stuart, J. J.-P. Peyralans and S. Otto, *Science*, 2010, **327**, 1502-1506.
592.J. Li, J. M. A. Carnall, M. C. A. Stuart and S. Otto, *Angew. Chem. Int. Ed.*, 2011, **50**, 8384-8386.
593.E. A. Wintner, M. M. Conn and J. Rebek, Jr., *Acc. Chem. Res.*, 1994, **27**, 198-203.
594.E. A. Wintner and J. Rebek, Jr., *Acta Chem. Scand.*, 1996, **50**, 469-485.
595.B. G. Bag and G. von Kiedrowski, *Pure Appl. Chem.*, 1996, **68**, 2145-2152.
596.D. H. Lee, K. Severin and M. R. Ghadiri, *Curr. Opin. Chem. Biol.*, 1997, **1**, 491-496.
597.A. Robertson, A. J. Sinclair and D. Philp, *Chem. Soc. Rev.*, 2000, **29**, 141-152.
598.R. Issac, Y.-W. Ham and J. Chmielewski, *Curr. Opin. Struct. Biol.*, 2001, **11**, 458-463.
599.N. Paul and G. F. Joyce, *Curr. Biol.*, 2003, **13**, R46.
600.X. Li and J. Chmielewski, *Org. Biomol. Chem.*, 2003, **1**, 901-904.
601.I. Ghosh and J. Chmielewski, *Curr. Opin. Chem. Biol.*, 2004, **8**, 640-644.
602.V. Patzke and G. von Kiedrowski, *Arkivoc*, 2007, **v**, 293-310.
603.Z. Dadon, N. Wagner and G. Ashkenasy, *Angew. Chem. Int. Ed.*, 2008, **47**, 6128-6136.
604.A. Vidonne and D. Philp, *Eur. J. Org. Chem.*, 2009, 593-610.
605.V. del Amo and D. Philp, *Chem. Eur. J.*, 2010, **16**, 13304-13318.
606.J. Huck and D. Philp, in *Supramolecular Chemistry: From Molecules to Nanomaterials*, eds. J. W. Steed and P. A. Gale, John Wiley & Sons, Ltd., 2012, DOI: 10.1002/9780470661345.smc9780470661158.
607.Z. Dadon, N. Wagner, R. Cohen-Luria and G. Ashkenasy, in *Supramolecular Chemistry: From Molecules to Nanomaterials*, eds. J. W. Steed and P. A. Gale, John Wiley & Sons, Ltd., 2012, DOI: 10.1002/9780470661345.smc9780470661162.
608.S. Otto, *Acc. Chem. Res.*, 2012, **45**, 2200-2210.
609.N. Giuseppone, *Acc. Chem. Res.*, 2012, **45**, 2178-2188.
610.R. J. Pieters, I. Huc and J. Rebek, Jr., *Angew. Chem. Int. Ed. Engl.*, 1994, **33**, 1579-1581.
611.R. J. Pieters, I. Huc and J. Rebek, Jr., *Tetrahedron*, 1995, **51**, 485-498.
612.D. H. Lee, K. Severin, Y. Yokobayashi and M. R. Ghadiri, *Nature*, 1997, **390**, 591-594.
613.H. Schöneborn, J. Bülle and G. von Kiedrowski, *ChemBioChem*, 2001, **12**, 922-927.
614.M. Levy and A. D. Ellington, *Proc. Natl. Acad. Sci. U.S.A.*, 2003, **100**, 6416-6421.
615.D.-E. Kim and G. F. Joyce, *Chem. Biol.*, 2004, **11**, 1505-1512.
616.E. J. Hayden, G. von Kiedrowski and N. Lehman, *Angew. Chem. Int. Ed.*, 2008, **47**, 8424-8428.
617.T. A. Lincoln and G. F. Joyce, *Science*, 2009, **323**, 1229-1232.
618.A. Saghatelian, Y. Yokobayashi, K. Soltani and M. R. Ghadiri, *Nature*, 2001, **409**.
619.G. Ashkenasy and M. R. Ghadiri, *J. Am. Chem. Soc.*, 2004, **126**, 11140-11141.
620.G. Ashkenasy, R. Jagasia, M. Yadav and M. R. Ghadiri, *Proc. Natl. Acad. Sci. U.S.A.*, 2004, **101**, 10872-10877.
621.B. Rubinov, N. Wagner, H. Rapaport and G. Ashkenasy, *Angew. Chem. Int. Ed.*, 2009, **48**, 6683-6686.
622.P. Stano and P. L. Luisi, *Chem. Commun.*, 2010, **46**, 3639-3653.
623.P. Walde, *BioEssays*, 2010, **32**, 296-303.
624.I. Hamachi, R. Eboshi, J.-I. Watanabe and S. Shinkai, *J. Am. Chem. Soc.*, 2000, **122**, 4530-4531.
625.A. Saghatelian, K. M. Guckian, D. A. Thayer and M. R. Ghadiri, *J. Am. Chem. Soc.*, 2003, **125**, 344-345.
626.L. Kovbasyuk and R. Krämer, *Chem. Rev.*, 2004, **104**, 3161-3187.
627.L. Zhu and E. V. Anslyn, *Angew. Chem. Int. Ed.*, 2006, **45**, 1190-1196.
628.N. Kumagai and M. Shibasaki, *Catal. Sci. Technol.*, 2013, **3**, 41-57.
629.J. Rebek, Jr. and J. E. Trend, *J. Am. Chem. Soc.*, 1978, **100**, 4315-4316.
630.J. Rebek, Jr., T. Costello and R. Wattley, *J. Am. Chem. Soc.*, 1985, **107**, 7487-7493.
631.T. J. van Bergen and R. M. Kellog, *J. Am. Chem. Soc.*, 1977, **99**, 3882-3884.
632.J. G. de Vries and R. M. Kellog, *J. Am. Chem. Soc.*, 1979, **101**, 2759-2761.
633.J. Rebek, Jr., J. E. Trend, R. V. Wattley and S. Chakravorti, *J. Am. Chem. Soc.*, 1979, **101**, 4333-4337.
634.R. Wakabayashi, Y. Kubo, O. Hirata, M. Takeuchi and S. Shinkai, *Chem. Commun.*, 2005, 5742-5744.
635.S. Shinkai, Y. Ishikawa, H. Shinkai, T. Tsuno and O. Manabe, *Tetrahedron Lett.*, 1983, **24**, 1539-1542.
636.S. Shinkai, Y. Ishikawa, H. Shinkai, T. Tsuno, H. Makishima, K. Ueda and O. Manabe, *J. Am. Chem. Soc.*, 1984, **106**, 1801-1808.
637.S. Shinkai, K. Kameoka, K. Ueda and O. Manabe, *J. Am. Chem. Soc.*, 1987, **109**, 923-924.
638.J. H. Griffin and P. B. Dervan, *J. Am. Chem. Soc.*, 1987, **109**, 6840-6842.
639.I. O. Fritsky, R. Ott and R. Krämer, *Angew. Chem. Int. Ed.*, 2000, **39**, 3255-3258.
640.I. O. Fritsky, R. Ott, H. Pritzkow and R. Krämer, *Chem. Eur. J.*, 2001, **7**, 1221-1231.
641.T. Tozawa, S. Tokita and Y. Kubo, *Tetrahedron Lett.*, 2002, **43**, 3455-3457.
642.A. Scarso, U. Scheffer, M. Göbel, Q. B. Broxterman, B. Kaptein, F. Formaggio, C. Toniolo and P. Scrimin, *Proc. Natl. Acad. Sci. U.S.A.*, 2002, **99**, 5144-5149.
643.I. O. Fritsky, R. Ott, H. Pritzkow and R. Krämer, *Inorg. Chim. Acta*, 2003, **346**, 111-118.
644.S. Takebayashi, M. Ikeda, M. Takeuchi and S. Shinkai, *Chem. Commun.*, 2004, 420-421.
645.L. Kovbasyuk, H. Pritzkow, R. Krämer and I. O. Fritsky, *Chem. Commun.*, 2004, 880-881.
646.A. Scarso, G. Zaupa, F. B. Houillon, L. J. Prins and P. Scrimin, *J. Org. Chem.*, 2007, **72**, 376-385.
647.S. Takebayashi, S. Shinkai, M. Ikeda and M. Takeuchi, *Org. Biomol. Chem.*, 2008, **6**, 493-499.
648.P. Dydio, C. Rubay, T. Gadzikwa, M. Lutz and J. N. H. Reek, *J. Am. Chem. Soc.*, 2011, **133**, 17176-17179.
649.K. Ohmatsu, M. Ito, T. Kunieda and T. Ooi, *Nature Chem.*, 2012, **4**, 473-477.
650.V. W.-W. Yam, X.-X. Lu and C.-C. Ko, *Angew. Chem. Int. Ed.*, 2003, **42**, 3385-3388.
651.X.-X. Lu, H.-S. Tang, C.-C. Ko, J. K.-Y. Wong, N. Zhu and V. W.-W. Yam, *Chem. Commun.*, 2005, 1572-1574.
652.I. Mon, D. A. Jose and A. Vidal-Ferran, *Chem. Eur. J.*, 2013, **19**, 2720-2725.
653.F. Mancin, P. Scrimin and P. Tecilla, *Chem. Commun.*, 2012, **48**, 5545-5559.
654.P. Braunstein and F. Naud, *Angew. Chem. Int. Ed.*, 2001, **40**, 680-699.
655.N. C. Gianneschi, M. S. Masar III and C. A. Mirkin, *Acc. Chem. Res.*, 2005, **38**, 825-837.
656.C. G. Oliveri, P. A. Ulmann, M. J. Wiester and C. A. Mirkin, *Acc. Chem. Res.*, 2008, **41**, 1618-1629.
657.N. C. Gianneschi, P. A. Bertin, S. T. Nguyen, C. A. Mirkin, L. N. Zakharov and A. L. Rheingold, *J. Am. Chem. Soc.*, 2003, **125**, 10508-10509.
658.N. C. Gianneschi, S.-H. Cho, A. N. Nguyen and C. A. Mirkin, *Angew. Chem. Int. Ed.*, 2004, **43**, 5503-5507.

659.N. C. Gianneschi, S. T. Nguyen and C. A. Mirkin, *J. Am. Chem. Soc.*, 2005, **127**, 1644-1645.
660.C. G. Oliveri, N. C. Gianneschi, S. T. Nguyen, C. A. Mirkin, C. L. Stern, Z. Wawrzak and M. Pink, *J. Am. Chem. Soc.*, 2006, **128**, 16286-16296.
661.M. S. Masar III, N. C. Gianneschi, C. G. Oliveri, C. L. Stern, S. T. Nguyen and C. A. Mirkin, *J. Am. Chem. Soc.*, 2007, **129**, 10149-10158.
662.H. J. Yoon and C. A. Mirkin, *J. Am. Chem. Soc.*, 2008, **130**, 11590-11591.
663.H. J. Yoon, J. Heo and C. A. Mirkin, *J. Am. Chem. Soc.*, 2007, **129**, 14182-14183.
664.H. J. Yoon, J. Kuwabara, J.-H. Kim and C. A. Mirkin, *Science*, 2010, **330**, 66-69.
665.M. Schmittel, S. De and S. Pramanik, *Angew. Chem. Int. Ed.*, 2012, **51**, 3832-3836.
666.T. Fenske, H.-G. Korth, A. Mohr and C. Schmuck, *Chem. Eur. J.*, 2012, **18**, 738-755.
667.M. Benaglia, J. Chiefari, Y. K. Chong, G. Moad, E. Rizzardo and S. H. Thang, *J. Am. Chem. Soc.*, 2009, **131**, 6914-6915.
668.S. Oishi, J. Yoshimoto and S. Saito, *J. Am. Chem. Soc.*, 2009, **131**, 8748-8749.
669.V. Blanco, A. Carlone, K. D. Hänni, D. A. Leigh and B. Lewandowski, *Angew. Chem. Int. Ed.*, 2012, **51**, 5166-5169.
670.D. E. Bergbreiter, P. L. Osburn, A. Wilson and E. M. Sink, *J. Am. Chem. Soc.*, 2000, **122**, 9058-9064.
671.Y. Lu, Y. Mei, M. Drechsler and M. Ballauf, *Angew. Chem. Int. Ed.*, 2006, **45**, 813-816.
672.F. Rodríguez-Llansola, B. Escuder and J. F. Miravet, *J. Am. Chem. Soc.*, 2009, **131**, 11478-11484.
673.S. Li, Y. Ge, A. Tiwari, S. Wang, A. P. F. Turner and S. A. Piletsky, *J. Catal.*, 2011, **278**, 173-180.
674.R. Hirsch, E. Katz and I. Willner, *J. Am. Chem. Soc.*, 2000, **122**, 12053-12054.
675.R. Peng, W. Zhang, Q. Ran, C. Liang, L. Jing, S. Ye and Y. Xian, *Langmuir*, 2011, **27**, 2910-2916.
676.R. S. Stoll and S. Hecht, *Angew. Chem. Int. Ed.*, 2010, **49**, 5054-5075.
677.F. Würthner and J. Rebek, Jr., *Angew. Chem. Int. Ed. Engl.*, 1995, **34**, 446.
678.A. Ueno, K. Takahashi and T. Osa, *J. Chem. Soc., Chem. Commun.*,, 1981, 94-96.
679.M. Kawamura, R. Kiyotake and K. Kudo, *Chirality*, 2002, **14**, 724-726.
680.S.-i. Naya, M. Teranishi, T. Isobe and H. Tada, *Chem. Commun.*, 2010, **46**, 815-817.
681.P. Wu, R. Xiao, C. Zhang, L. Zhou, Q. Luo, J. Xu and J. Liu, *Catal. Lett.*, 2010, **138**, 62-67.
682.J. Wang, B. Mao, J. L. Gole and C. Burda, *Nanoscale*, 2010, **2**, 2257-2261.
683.Y. Yang, L. Yue, H. L. Li, E. Maher, Y. G. Li, Y. Z. Wang, L. X. Wu and V. W. W. Yam, *Small*, 2012, **8**, 3105-3110.
684.M. Süßner and H. Plenio, *Angew. Chem. Int. Ed.*, 2005, **44**, 6885-6888.
685.M. R. Ringenberg, S. L. Kokatam, Z. M. Heiden and T. B. Rauchfuss, *J. Am. Chem. Soc.*, 2008, **130**, 788-789.
686.A. G. Tennyson, V. M. Lynch and C. W. Bielawski, *J. Am. Chem. Soc.*, 2010, **132**, 9420-9429.
687.A. J. D. Magenau, N. C. Strandwitz, A. Gennaro and K. Matyjaszewsji, *Science*, 2011, **332**, 81-84.
688.S. Mortezaei, N. R. Catarineu and J. W. Canary, *J. Am. Chem. Soc.*, 2012, **134**, 8054-8057.
689.U. Lüning, *Angew. Chem. Int. Ed.*, 2012, **51**, 8163-8165.
690.J. Wang and B. L. Feringa, *Science*, 2011, **331**, 1429-1432.
691.P. F. Mugford, U. G. Wagner, Y. Jiang, K. Faber and R. J. Kazlauskas, *Angew. Chem. Int. Ed.*, 2008, **47**, 8782-8793.
692.I. Hara, T. Ueno, S. Ozaki, S. Itoh, K. Lee, N. Ueyama and Y. Watanabe, *J. Biol. Chem.*, 2001, **276**, 36067-36070.
693.J. Podtetenieff, A. Taglieber, E. Bill, E. J. Reijerse and M. T. Reetz, *Angew. Chem. Int. Ed.*, 2010, **49**, 5151-5155.
694.O. Shoji and Y. Watanabe, *Metallomics*, 2011, **3**, 379-388.
695.D. Qi, C.-M. Tann, D. Haring and M. D. Distefano, *Chem. Rev.*, 2001, **101**, 3081-3111.
696.C. M. Thomas and T. R. Ward, *Chem. Soc. Rev.*, 2005, **34**, 337-346.
697.T. R. Ward, *Chem. Eur. J.*, 2005, **11**, 3798-3804.
698.R. Krämer, *Angew. Chem. Int. Ed.*, 2006, **45**, 858-860.
699.C. Letondor and T. R. Ward, *ChemBioChem*, 2006, **7**, 1845-1852.
700.J. Steinreiber and T. R. Ward, *Coord. Chem. Rev.*, 2008, **252**, 751-766.
701.T. R. Ward, ed., *Bio-inspired Catalysts*, Springer, 2009.
702.V. Köhler, Y. M. Wilson, C. Lo, A. Sardo and T. R. Ward, *Curr. Opin. Biotechnol.*, 2010, **21**, 744-752.
703.T. Heinisch and T. R. Ward, *Curr. Opin. Chem. Biol.*, 2010, **14**, 184-199.
704.T. R. Ward, *Acc. Chem. Res.*, 2011, **44**, 47-57.
705.M. R. Ringenberg and T. R. Ward, *Chem. Commun.*, 2011, **47**, 8470-8476.
706.P. J. Deuss, R. den Heeten, W. Laan and P. C. J. Kamer, *Chem. Eur. J.*, 2011, **17**, 4680-4698.
707.S. Park and H. Sugiyama, *Molecules*, 2012, **17**, 12792-12803.
708.L. Panella, J. Broos, J. Jin, M. W. Fraaije, D. B. Janssen, M. Jeronimus-Stratingh, B. L. Feringa, A. J. Minnaard and J. G. de Vries, *Chem. Commun.*, 2005, 5656-5658.
709.W. Laan, B. K. Muñoz, R. den Heeten and P. C. J. Kamer, *ChemBioChem*, 2010, **11**, 1236-1239.
710.R. den Heeten, B. K. Muñoz, G. Popa, W. Laan and P. C. J. Kamer, *Dalton Trans.*, 2010, **39**, 8477-8483.
711.P. J. Deuss, G. Popa, C. H. Botting, W. Laan and P. C. J. Kamer, *Angew. Chem. Int. Ed.*, 2010, **49**, 5315-5317.
712.C. Mayer, D. G. Gillingham, T. R. Ward and D. Hilvert, *Chem. Commun.*, 2011, **47**, 12068-12070.
713.E. T. Kaiser and D. S. Lawrence, *Science*, 1984, **226**, 505-511.
714.R. R. Davies and M. D. Distefano, *J. Am. Chem. Soc.*, 1997, **119**, 11643-11652.
715.D. Häring and M. D. Distefano, *Bioconjugate Chem.*, 2001, **12**, 385-390.
716.J. R. Carey, S. K. Ma, T. D. Pfister, D. K. Garner, H. K. Kim, J. A. Abramite, Z. Wang, Z. Guo and Y. Lu, *J. Am. Chem. Soc.*, 2004, **126**, 10812-10813.
717.M. T. Reetz, M. Rentzsch, A. Pletsch, A. Taglieber, F. Hollmann, R. J. G. Mondière, N. Dickman, B. Höcker, S. Cerrone, M. Haeger and R. Sterner, *ChemBioChem*, 2008, **9**, 552-564.
718.N. Yokoi, Y. Miura, C.-Y. Huang, N. Takatani, H. Inaba, T. Koshiyama, S. Kanamaru, F. Arisaka, Y. Watanabe, S. Kitagawa and T. Ueno, *Chem. Commun.*, 2011, **47**, 2074-2076.
719.G. Roelfes, *ChemCatChem*, 2011, **3**, 647-648.
720.J. Bos, F. Fusetti, A. J. M. Driessen and G. Roelfes, *Angew. Chem. Int. Ed.*, 2012, **51**, 7472-7475.
721.S. R. Gilbertson, G. Chen and M. McLoughlin, *J. Am. Chem. Soc.*, 1994, **116**, 4481-4482.
722.A. M. Porte, W. A. van der Donk and K. Burgess, *J. Org. Chem.*, 1998, **63**, 5262-5264.
723.S. R. Gilbertson and D. Xie, *Angew. Chem. Int. Ed.*, 1999, **38**, 2750-2752.
724.S. R. Gilbertson, S. E. Collibee and A. Agarkov, *J. Am. Chem. Soc.*, 2000, **122**, 6522-6523.
725.S. J. Greenfield, A. Agarkov and S. R. Gilbertson, *Org. Lett.*, 2003, **5**, 3069-3072.
726.A. Agarkov, S. J. Greenfield, T. Ohishi, S. E. Collibee and S. R. Gilbertson, *J. Org. Chem.*, 2004, **69**, 8077-8085.
727.C. A. Christensen and M. Meldal, *Chem. Eur. J.*, 2005, **11**, 4121-4131.
728.A. Agarkov, S. Greenfield, D. Kie, R. Pawlick, G. Starkey and S. R. Gilbertson, *Biopolymers (Peptides Sci.)*, 2006, **84**, 48-73.
729.J. F. Jensen, K. Worm-Leonhard and M. Meldal, *Eur. J. Org. Chem.*, 2008, 3785-3797.
730.K. Worm-Leonhard and M. Meldal, *Eur. J. Org. Chem.*, 2008, 5244-5253.
731.D. Coquière, J. Bos, J. Beld and G. Roelfes, *Angew. Chem. Int. Ed.*, 2009, **48**, 5159-5162.
732.S. Burck, S. G. A. van Assema, B. Lastdrager, J. C. Slootweg, A. Ehlers, J. M. Otero, B. Dacunha-Marinho, A. L. Llamas-Saiz, M.

Overhand, M. J. van Raaij and K. Lammertsma, *Chem. Eur. J.*, 2009, **15**, 8134-8145.
733. R. Sambasivan and Z. T. Ball, *J. Am. Chem. Soc.*, 2010, **132**, 9289-9291.
734. R. Sambasivan and Z. T. Ball, *Angew. Chem. Int. Ed.*, 2012, **51**, 8568-8572.
735. B. V. Popp and Z. T. Ball, *J. Am. Chem. Soc.*, 2010, **132**, 6660-6662.
736. B. V. Popp and Z. T. Ball, *Chem. Sci*., 2011, **2**, 690-695.
737. Z. Chen, B. V. Popp, C. L. Bovet and Z. T. Ball, *ACS Chem. Biol.*, 2011, **6**, 920-925.
738. Z. Chen, F. Vohidov, J. M. Coughlin, L. J. Stagg, S. T. Arold, J. E. Ladbury and Z. T. Ball, *J. Am. Chem. Soc.*, 2012, **134**, 10138-10145.
739. I. Hamachi and S. Shinkai, *Eur. J. Org. Chem.*, 1999, 539-549.
740. F. van de Velde, L. Könemann, F. van Rantwijk and R. A. Sheldon, *Chem. Commun.*, 1998, 1891-1892.
741. F. Van de Velde, L. Könemann, F. van Rantwijk and R. A. Sheldon, *Biotechnol. Bioeng.*, 2000, **67**, 87-96.
742. K. Okrasa and R. J. Kazlauzkas, *Chem. Eur. J.*, 2006, **12**, 1587-1596.
743. Fernández-Gacio, A. Codina, J. Fastrez, O. Riant and P. Soumillon, *ChemBioChem*, 2006, **7**, 1013-1016.
744. Q. Jing, K. Okrasa and R. J. Kazlauzkas, *Chem. Eur. J.*, 2009, **15**, 1370-1376.
745. Q. Jing and R. J. Kazlauzkas, *ChemCatChem*, 2010, **2**, 953-957.
746. T. Ueno, T. Koshiyama, M. Ohashi, K. Kondo, M. Kono, A. Suzuki, T. Yamane and Y. Watanabe, *J. Am. Chem. Soc.*, 2005, **127**, 6556-6562.
747. T. Hayashi, Y. Hitomi, T. Ando, T. Mizutani, Y. Hisaeda, S. Kitagawa and H. Ogoshi, *J. Am. Chem. Soc.*, 1999, **121**, 7747-7750.
748. M. Ohashi, T. Koshiyama, T. Ueno, M. Yanase, H. Fujii and Y. Watanabe, *Angew. Chem. Int. Ed.*, 2003, **42**, 1005-1008.
749. T. Hayashi, D. Murata, M. Makino, H. Sugimoto, T. Matsuo, H. Sato, Y. Shiro and Y. Hisaeda, *Inorg. Chem.*, 2006, **45**, 10530-10536.
750. T. Ueno, T. Koshiyama, S. Abe, N. Yokoi, M. Ohashi, H. Nakajima and Y. Watanabe, *J. Organomet. Chem.*, 2007, **692**, 142-147.
751. A. Pordea, M. Creus, J. Panek, C. Duboc, D. Mathis, M. Novic and T. R. Ward, *J. Am. Chem. Soc.*, 2008, **130**, 8085-8088.
752. V. Köhler, J. Mao, T. Heinisch, A. Pordea, A. Sardo, Y. M. Wilson, L. Knörr, M. Creus, J.-C. Prost, T. Schirmer and T. R. Ward, *Angew. Chem. Int. Ed.*, 2011, **50**, 10863-10866.
753. R. Ricoux, R. Dubuc, C. Dupont, J.-D. Marechal, A. Martin, M. Sellier and J.-P. Mahy, *Bioconjugate Chem.*, 2008, **19**, 899-910.
754. R. Ricoux, M. Allard, R. Dubuc, C. Dupont, J.-D. Maréchal and J.-P. Mahy, *Org. Biomol. Chem.*, 2009, **7**, 3208-3211.
755. M. Allard, C. Dupont, V. M. Robles, N. Doucet, A. Lledós, J.-D. Maréchal, A. Urvoas, J.-P. Mahy and R. Ricoux, *ChemBioChem*, 2012, **13**, 240-251.
756. T. Ueno, M. Suzuki, T. Goto, T. Matsumoto, K. Nagayama and Y. Watanabe, *Angew. Chem. Int. Ed.*, 2004, **43**, 2527-2530.
757. M. Suzuki, M. Abe, T. Ueno, S. Abe, T. Goto, Y. Toda, T. Akita, Y. Yamada and Y. Watanabe, *Chem. Commun*., 2009, 4871-4873.
758. S. Abe, T. Hikage, Y. Watanabe, S. Kitagawa and T. Ueno, *Inorg. Chem.*, 2010, **49**, 6967-6973.
759. Y. Takezawa, P. Böckmann, N. Sugi, Z. Wang, S. Abe, T. Murakami, T. Hikage, G. Erker, Y. Watanabe, S. Kitagawa and T. Ueno, *Dalton Trans.*, 2011, **40**, 2190-2195.
760. Z. Wang, Y. Takezawa, H. Aoyagi, S. Abe, T. Hikage, Y. Watanabe, S. Kitagawa and T. Ueno, *Chem. Commun.*, 2011, **47**, 170-172.
761. T. Sugimoto, Y. Matsumura, S. Tanimoto and M. Okano, *J. Chem. Soc., Chem. Commun.*,, 1978, 926-927.
762. T. Sugimoto, T. Kokubo, J. Miyazaki, S. Tanimoto and M. Okano, *J. Chem. Soc., Chem. Commun.*,, 1979, 402-404.
763. T. Kokubo, T. Sugimoto, S. Tanimoto and M. Okano, *J. Chem. Soc., Chem. Commun.*,, 1983, 769-770.
764. S. Colonna, S. Banfi, F. Fontana and M. Sommaruga, *J. Org. Chem.*, 1985, **50**, 769-771.
765. S. Colonna, A. Manfredi and R. Annunziata, *Tetrahedron Lett.*, 1988, **29**, 3347-3350.
766. L. Trynda and F. Pruchnik, *J. Inorg. Biochem.*, 1995, **58**, 69-77.
767. L. Trynda-Lemiesz and F. Pruchnik, *J. Inorg. Biochem.*, 1997, **66**, 187-192.
768. M. Marchetti, G. Mangano, S. Paganelli and C. Botteghi, *Tetrahedron Lett.*, 2000, **41**, 3717-3720.
769. C. Bertucci, C. Botteghi, D. Giunta, M. Marchetti and S. Paganelli, *Adv. Synth. Catal.*, 2002, **344**, 556-562.
770. A. Mahammed, H. B. Gray, J. J. Weaver, K. Sorasaenee and Z. Gross, *Bioconjugate Chem.*, 2004, **15**, 738-746.
771. A. Mahammed and Z. Gross, *J. Am. Chem. Soc.*, 2005, **127**, 2883-2887.
772. M. T. Reetz and N. Jiao, *Angew. Chem. Int. Ed.*, 2006, **45**, 2416-2419.
773. S. Crobu, M. Marchetti and G. Sanna, *J. Inorg. Biochem.*, 2006, **100**, 1514-1520.
774. M. Nishijima, T. C. S. Pace, A. Nakamura, T. Mori, T. Wada, C. Bohne and Y. Inoue, *J. Org. Chem.*, 2007, **72**, 2707-2715.
775. M. Nishijima, T. Wada, T. Mori, T. C. S. Pace, C. Bohne and Y. Inoue, *J. Am. Chem. Soc.*, 2007, **129**, 3478-3479.
776. T. C. S. Pace, M. Nishijima, T. Wada, Y. Inoue and C. Bohne, *J. Phys. Chem. B*, 2009, **113**, 10445-10453.
777. P. Rousselot-Pailley, C. Bochot, Marchi-Delapierre, A. Jorge-Robin, L. Martin, J. C. Fontecilla-Camps, C. Cavazza and S. Ménage, *ChemBioChem*, 2009, **10**, 545-552.
778. M. J. Borerakker, J. M. Hannink, P. H. H. Bomans, P. M. Frederik, R. J. M. Nolte, E. M. Meijer and N. A. J. M. Sommerdijk, *Angew. Chem. Int. Ed.*, 2002, **41**, 4239-4241.
779. I. C. Reynhout, J. J. L. M. Cornelissen and R. J. M. Nolte, *J. Am. Chem. Soc.*, 2007, **129**, 2327-2332.
780. I. C. Reynhout, J. J. L. M. Cornelissen and R. J. M. Nolte, *Acc. Chem. Res.*, 2009, **47**, 681-692.
781. G. Delaittre, I. C. Reynhout, J. J. L. M. Cornelissen and R. J. M. Nolte, *Chem. Eur. J.*, 2009, **15**, 12600-12603.
782. R. Ricoux, Q. Raffy and J.-P. Mahy, *C. R. Chimie*, 2007, **10**, 684-702.
783. H. Yamaguchi, T. Hirano, H. Kiminami, D. Taura and A. Harada, *Org. Biomol. Chem.*, 2006, **4**, 3571-3573.
784. Q. Raffy, R. Ricoux and J.-P. Mahy, *Tetrahedron Lett.*, 2008, **49**, 1865-1869.
785. Q. Raffy, R. Ricoux, E. Sansiaume, S. Pethe and J.-P. Mahy, *J. Mol. Cat. A: Chem.*, 2010, **317**, 19-26.
786. E. Sansiaume, R. Ricoux, D. Gori and J.-P. Mahy, *Tetrahedron: Asymmetry*, 2010, **21**, 1593-1600.
787. For catalysis with ribozymes see references 787-790: T. M. Tarasow, S. L. Tarasow and B. E. Eaton, *Nature*, 1997, **389**, 54-57.
788. B. Seelig, S. Keiper, F. Stuhlmann and A. Jäschke, *Angew. Chem. Int. Ed.*, 2000, **39**, 4576-4579.
789. F. Stuhlmann and A. Jäschke, *J. Am. Chem. Soc.*, 2002, **124**, 3238-3244.
790. A. Serganov, S. Keiper, L. Malinina, V. Tereshko, E. Skripkin, C. Höbartner, A. Polonskaia, A. T. Phan, R. Wombacher, R. Micura, Z. Dauter, A. Jäschke and D. J. Patel, *Nat. Struct. Biol.*, 2005, **12**, 218-224.
791. For catalysis with deoxyribozymes see references 791-794: D. A. Baum and S. K. Silverman, *Cell. Mol. Life Sci.*, 2008, **65**, 2156-2174.
792. K. Schlosser and Y. Li, *Chem. Biol.*, 2009, **16**, 311-322.
793. S. K. Silverman, *Chem. Commun.*, 2010, 3467-3485.
794. S. K. Silverman, *Angew. Chem. Int. Ed.*, 2010, **49**, 7180-7201.
795. F. Rosati and G. Roelfes, *ChemCatChem*, 2010, **2**, 916-927.
796. A. J. Boersma, R. P. Megens, B. L. Feringa and G. Roelfes, *Chem. Soc. Rev.*, 2010, **39**, 2083-2092.
797. G. Roelfes and B. L. Feringa, *Angew. Chem., Int. Ed.*, 2005, **44**, 3230-3232.
798. G. Roelfes, A. J. Boersma and B. L. Feringa, *Chem. Commun.*, 2006, 635-637.
799. A. J. Boersma, B. L. Feringa and G. Roelfes, *Org. Lett.*, 2007, **9**, 3647-3650.
800. A. J. Boersma, J. E. Klijn, B. L. Feringa and G. Roelfes, *J. Am. Chem. Soc.*, 2008, **130**, 11783-11790.
801. F. Rosati, A. J. Boersma, J. E. Klijn, A. Meetsma, B. L. Feringa and G. Roelfes, *Chem. Eur. J.*, 2009, **15**, 9596-9605.
802. R. P. Megens and G. Roelfes, *Org. Biomol. Chem.*, 2010, **8**, 1387-1393.
803. F. Rosati and G. Roelfes, *ChemCatChem*, 2011, **3**, 973-977.

804.A. J. Boersma, B. de Bruin, B. L. Feringa and G. Roelfes, *Chem. Commun.*, 2012, **48**, 2394-2396.
805.D. Coquiere, B. L. Feringa and G. Roelfes, *Angew. Chem., Int. Ed.*, 2007, **46**, 9308-9311.
806.E. W. Dijk, A. J. Boersma, B. L. Feringa and G. Roelfes, *Org. Biomol. Chem.*, 2010, **8**, 3868-3873.
807.R. P. Megens and G. Roelfes, *Chem. Commun.*, 2012, **48**, 6366-6368.
808.A. J. Boersma, D. Coquière, D. Geerdink, F. Rosati, B. L. Feringa and G. Roelfes, *Nature Chem.*, 2010, **2**, 991-995.
809.E. W. Dijk, B. L. Feringa and G. Roelfes, *Tetrahedron: Asymmetry*, 2008, **19**, 2374-2377.
810.N. Shibata, H. Yasui, S. Nakamura and T. Toru, *Synlett*, 2007, **7**, 1153-1157.
811.Z. Tang, D. P. N. Gonçalves, M. Wieland, A. Marx and J. S. Hartig, *ChemBioChem*, 2008, **9**, 1061-1064.
812.C. Yu, H.-Y. Chan, K. M.-C. Wong and V. W.-W. Yam, *Chem. Commun.*, 2009, 3756-3758.
813.T. Li, L. Shi, E. Wang and S. Dong, *Chem. Eur. J.*, 2009, **15**, 3347-3350.
814.S. Roe, D. J. Ritson, T. Garner, M. Searle and J. E. Moses, *Chem. Commun.*, 2010, **46**, 4309-4311.
815.M. E. Wilson and G. M. Whitesides, *J. Am. Chem. Soc.*, 1978, **100**, 306-307.
816.C.-C. Lin, C.-W. Lin and A. S. C. Chan, *Tetrahedron: Asymmetry*, 1999, **10**, 1887-1893.
817.J. Collot, J. Gradinaru, N. Humbert, M. Skander, A. Zocchi and T. R. Ward, *J. Am. Chem. Soc.*, 2003, **125**, 9030-9031.
818.M. Skander, N. Humbert, J. Collot, J. Gradinaru, G. Klein, A. Loosli, J. Sauser, A. Zocchi, F. Gilardoni and T. R. Ward, *J. Am. Chem. Soc.*, 2004, **126**, 14411-14418.
819.G. Klein, N. Humbert, J. Gradinaru, A. Ivanova, F. Gilardoni, U. E. Rusbandi and T. R. Ward, *Angew. Chem. Int. Ed.*, 2005, **44**, 7764-7767.
820.M. Skander, C. Malan, A. Ivanova and T. R. Ward, *Chem. Commun.*, 2005, 4815-4817.
821.U. E. Rusbandi, C. Lo, M. Skander, A. Ivanova, M. Creus, N. Humbert and T. R. Ward, *Adv. Synth. Catal.*, 2007, **349**, 1923-1930.
822.U. E. Rusbandi, M. Skander, A. Ivanova, C. Malan and T. R. Ward, *C. R. Chimie*, 2007, **10**, 678-683.
823.C. Letondor, N. Humbert and T. R. Ward, *Proc. Natl. Acad. Sci. U.S.A.*, 2005, **102**, 4683-4687.
824.C. Letondor, A. Pordea, N. Humbert, A. Ivanova, S. Mazurek, M. Novic and T. R. Ward, *J. Am. Chem. Soc.*, 2006, **128**, 8320-8328.
825.M. Creus, A. Pordea, T. Rossel, A. Sardo, C. Letondor, A. Ivanova, I. LeTrong, R. E. Stenkamp and T. R. Ward, *Angew. Chem. Int. Ed.*, 2008, **47**, 1400-1404.
826.A. Pordea, M. Creus, C. Letondor, A. Ivanova and T. R. Ward, *Inorg. Chim. Acta*, 2010, **363**, 601-604.
827.M. Dürrenberger, T. Heinisch, Y. M. Wilson, T. Rossel, E. Nogueira, L. Knörr, A. Mutschler, K. Kersten, M. J. Zimbron, J. Pierron, T. Schirmer and T. R. Ward, *Angew. Chem. Int. Ed.*, 2011, **50**, 3026-3029.
828.J. Pierron, C. Malan, M. Creus, J. Gradinaru, I. Hafner, A. Ivanova, A. Sardo and T. R. Ward, *Angew. Chem. Int. Ed.*, 2008, **47**, 701-705.
829.C. M. Thomas, C. Letondor, N. Humbert and T. R. Ward, *J. Organomet. Chem.*, 2005, **690**, 4488-4491.
830.A. Pordea, D. Mathis and T. R. Ward, *J. Organomet. Chem.*, 2009, **694**, 930-936.
831.C. Lo, M. R. Ringenberg, D. Gnandt, Y. Wilson and T. R. Ward, *Chem. Commun.*, 2011, **47**, 12065-12067.
832.T. K. Hyster, L. Knörr, T. R. Ward and T. Rovis, *Science*, 2012, **338**, 500-503.
833.M. Creus and T. R. Ward, *Org. Biomol.Chem.*, 2007, **5**, 1835-1844.
834.A. Pordea and T. R. Ward, *Chem. Commun.*, 2008, 4239-4249.
835.M. T. Reetz, *Tetrahedron*, 2002, **58**, 6595-6602.
836.M. T. Reetz, J. J.-P. Peyralans, A. Maichele, Y. Fu and M. Maywald, *Chem. Commun.*, 2006, 4318-4320.
837.R. B. Hill, D. P. Raleigh, A. Lombardi and W. F. Degrado, *Acc. Chem. Res.*, 2000, **33**, 745-754.
838.D. A. Moffet and M. H. Hecht, *Chem. Rev.*, 2001, **101**, 3191-3203.
839.L. Baltzer and J. Nilsson, *Curr. Opin. Biotechnol.*, 2001, **12**, 355-360.
840.D. N. Bolon, C. A. Voigt and S. L. Mayo, *Curr. Opin. Biotechnol.*, 2002, **6**, 125-129.
841.A. Zanghellini, L. Jiang, A. M. Wollacott, G. Cheng, J. Meiler, E. A. Althoff, D. Röthlisberger and D. Baker, *Protein Sci.*, 2006, **15**, 2785-2794.
842.V. Nanda and R. L. Koder, *Nature Chem.*, 2010, **2**, 15-24.
843.L. Jiang, E. A. Althoff, F. R. Clemente, L. Doyle, D. Röthlisberger, A. Zanghellini, J. L. Gallaher, J. L. Betker, F. Tanaka, C. F. Barbas III, D. Hilvert, K. N. Houk, B. L. Stoddard and D. Baker, *Science*, 2008, **319**, 1387-1391.
844.D. Röthlisberger, O. Khersonsky, A. M. Wollacott, L. Jiang, J. DeChancie, J. Betker, J. L. Gallaher, E. A. Althoff, A. Zanghellini, O. Dym, S. Albeck, K. N. Houk, D. S. Tawfik and D. Baker, *Nature*, 2008, **453**, 190-197.
845.J. B. Siegel, A. Zanghellini, H. M. Lovick, G. Kiss, A. R. Lambert, J. L. St.Clair, J. L. Gallaher, D. Hilvert, M. H. Gelb, B. L. Stoddard, K. N. Houk, F. E. Michael and D. Baker, *Science*, 2010, **329**, 309-313.
846.M. A. Case and G. L. McLendon, *Acc. Chem. Res.*, 2004, **37**, 754-762.
847.Y. Lu, N. Yeung, N. Sieracki and N. M. Marshall, *Nature*, 2009, **460**, 855-862.
848.J. Kaplan and W. F. DeGrado, *Proc. Natl. Acad. Sci. U.S.A.*, 2004, **101**, 11566-11570.
849.N. Yeung, Y.-W. Lin, Y.-G. Gao, X. Zhao, B. S. Russel, L. Lei, K. D. Miner, H. Robinson and Y. Lu, *Nature*, 2009, **462**, 1079-1084.
850.M. L. Zastrow, A. F. A. Peacock, J. A. Stuckey and V. L. Pecoraro, *Nature Chem.*, 2012, **4**, 118-123.
851.S. J. Miller, *Acc. Chem. Res.*, 2004, **37**, 601-610.
852.E. A. C. Davie, S. M. Mennen, Y. Xu and S. J. Miller, *Chem. Rev.*, 2007, **107**, 5759-5812.

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