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Review

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Review

Design of Multicatalytic Systems Through Self-Assembly

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Abstract: The development of self-assembled multicatalytic systems has emerged as a promising strategy for mimicking enzymatic catalysis in synthetic systems. This approach leverages the use of non-covalent interactions, such as hydrophobic interactions, hydrogen bonding, metal–ligand coordination, and aromatic stacking, to organize multiple catalytic centers within a defined, cooperative framework, allowing for enhanced reactivity, selectivity and efficiency, akin to the behavior of natural enzymes. The versatility of this approach enables the modular design, preparation, screening and optimization of systems capable of concerted catalysis and dynamic adaptation, making them suitable for a wide range of reactions, including asymmetric synthesis. The potential of these systems to emulate the precision and functionality of natural enzymes opens new avenues for the development of artificial multicatalytic systems with tailored and adaptable functions.

Keywords: multicatalysis; self-assembly; non-covalent; cooperative; supramolecular; enzyme mimics

1. Introduction

Enzymes have long fascinated synthetic chemists owing to their remarkable ability to catalyze a wide range of transformations with excellent activity and selectivity under mild conditions, vital to all living organisms. Enzymatic and microbial biocatalysis have found applications to some extent in various industrial processes, spanning sectors such as chemicals, cosmetics and biopharmaceuticals, offering efficient and sustainable alternatives to traditional chemical methods [1]. However, their widespread implementation has often been hindered by challenges such as limited thermal stability and tolerance to solvent, poor substrate versatility, and, to some extent, limited scalability and high production costs. This has driven the development of engineered enzymes through techniques such as recombinant technologies and directed evolution, aiming to adapt the activity of enzymes to abiotic conditions, and even achieve “new-to-nature” reactivities [2–4]. These advancements have been critical for meeting key performance indicators, such as space-time yields, suitable for viable industrialization and commercialization. Simultaneously, artificial enzymes have largely contributed to advance knowledge in biocatalysis, allowing us to draw links between structural and functional aspects of enzyme activity [5,6].

In parallel, the development of “simpler”, “small” synthetic molecules capable of replicating or surpassing the catalytic activity of natural enzymes has been pursued for decades [7–11]. These enzyme mimics have been essentially designed to emulate enzyme functional and/or structural features, covering, for instance, key principles from biological systems such as selective recognition/binding (of substrate and/or transition state), confinement, site isolation, cooperativity as well as activity regulation [10,12–14].



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In particular, multifunctional catalysts involving two or more catalytic groups within an active site—such as the coordinated acid–base–nucleophile catalytic triad (e.g., Ser-His-Asp) commonly found in hydrolases—have recently received significant attention in the design of advanced enzyme mimics. In this family of multifunctional catalysts, different active centers are embedded within a single scaffold and interact synergistically to achieve turnover and selectivity.

Although the taxonomy of multicatalysis is not straightforward and has been the subject of discussions [15], “one-pot” multicatalytic systems (and the multifunctional catalyst versions) can be roughly classified into two main categories inspired by the classification of Martinez et al. [16]:

- cooperative (or synergistic) catalysis, wherein different catalytic groups or moieties (co-catalysts) share their catalytic cycles in a single catalyzed reaction affecting a single bond;
- tandem (or relay catalysis), wherein two or more catalytic systems are involved in non-interfering catalytic cycles to execute a sequence of independent reactions.

Obviously, more complex multicatalytic systems (e.g., >2 catalysts and >2 reactions) have been reported to date that take advantage of synergy between both co-catalysts (synergistic) and catalytic reactions (relay) [16].

While ubiquitous in biological systems, where a number of enzymes can operate simultaneously within complex metabolic pathways, “one-pot” multicatalysis in its broader sense is a relatively recent approach and has been the subject of intense research during the past decades, encompassing both free and immobilized versions. Especially in the latter case, precisely combining different active centers onto ordered scaffolds or assemblies has marked a major advancement in the design of multifunctional catalysts. Recent reviews have explored the preparation of such multicatalysts, highlighting immobilization strategies across various soluble and solid supports, including polymers, mesoporous silica, metal–organic frameworks (MOFs), and folding polymeric chains (foldamers) [15,17–21].

Hence, beyond the “one-pot” mixing of multiple “free” catalysts in solution, anchoring them onto well-defined scaffolds (soluble or not) opens new avenues to create, engineer and regulate synergistic effects. These strategies guide the spatial organization of co-catalysts with the aim to locally optimize their stoichiometry, proximity and/or relative orientation to maximize catalytic efficiency. Furthermore, they may also confine the co-catalysts within defined micro-environments such as nano-pores and cavities to mimic the selective recognition and binding of enzymatic catalytic pockets. Additionally, this approach allows for the coexistence of otherwise incompatible catalysts (e.g., acids and bases) [17] by employing site isolation, thereby preventing their mutual neutralization in solution.

Recent investigations and reviews, including from our group [22–29], have focused on immobilization and engineering strategies to advance the field of multifunctional catalysts [18,20]. The present review seeks to offer a fresh perspective on the field, with a particular focus on leveraging self-assembly approaches in multicatalysis. Driven by non-covalent interactions, self-assembly offers significant advantages over covalent methods, including greater flexibility, ease of access, reversibility, and dynamic nature. These attributes make self-assembly particularly appealing for the design of multicatalysts. Although supramolecular approaches have been largely adopted in bioinspired catalysis [30–36] and for the immobilization of homogeneous catalysts [37–40], there remain many opportunities in the area of multicatalysis. This review, based on selected recent examples, is organized according to the type of dominant non-covalent interactions used for the self-assembly of multicatalysts, as discussed in the following section.

2. Design Considerations for Immobilized Multicatalysis and Self-Assembly

Immobilized multicatalysis has emerged as a promising field for designing highly efficient, enzyme-inspired catalytic systems. Compared to the more largely developed “free” homogeneous multicatalysis (i.e., the simple combination of soluble (co-)catalysts operating in concert, whether it be in a cooperative or tandem fashion), immobilized versions, where active centers are grafted on a scaffold (whether soluble or not), provide a higher degree of control in the design and efficiency of multicatalytic systems. Moreover, as mentioned above, these grafted systems can accommodate otherwise chemically incompatible active centers, overcoming the main limitation of “free” multicatalysis that is essentially restricted to the combination of orthogonal catalysis and catalysts. Furthermore, immobilization may provide handles to control reactivity ordering through compartmentalization and substrate channeling in the case of cascade multicatalysis [41–44].

The design of immobilized multicatalytic systems draws inspiration from enzymes wherein complementary pendant reactive groups arranged in a specific primary sequence are precisely positioned within a flexible and dynamic three-dimensional structure through secondary and tertiary folding of the protein chain. This high degree of organization enables catalytic efficiency and specificity through different levels of cooperativity, as well as possibilities for allosteric regulation. In certain cases, a higher degree of assembly culminates in the formation of quaternary complexes combining different protein sub-units and cofactors for functional properties.

Hence, preparing immobilized multicatalysts involves more than randomly immobilizing active species onto a scaffold, which could serve the not less valuable purpose of catalyst recovery and reuse. Yet, ill-considered immobilization strategies can disrupt and entirely inhibit multicatalysis operation by preventing the necessary proximity and interactions between the catalyst components. Factors such as inadequate local concentration and stoichiometry, heterogeneous spatial distribution (including segregation), insufficient flexibility preventing a proper orientation of the catalytic groups relative to the substrate or transition state, or limitations arising from diffusion and mass transfer can severely hinder the performance of the multicatalytic system. Thus, a rational design approach is essential to maximize catalytic efficiency and leverage the efforts of catalyst immobilization [18–20,45]. This endeavor lies at the level of both the catalytic site and the support scaffold, and overall aims at favoring effective interactions between the synergistic catalytic centers.

Structural flexibility and dynamism are, for instance, key determinants of enzyme activity and specificity. Internal conformational freedom and motions are central to enable substrate binding, product release as well as to handle the different transition states and reaction intermediates, and to a certain extent allow a certain degree of adaptability to widen substrate scope [46–48].

Positioning groups close to each other can be achieved using different techniques, such as, traditionally, through grafting onto scaffolds [17–20,45,49]—whether surfaces or (large) molecules—or, as presented here, through self-assembly via various complementary functions. Both approaches, when thoughtfully designed, enhance the likelihood of proximity between active groups. These methods also offer a certain degree of dynamism. For the first approach, dynamism can be achieved by using flexible scaffolds like chains or by grafting active groups onto rigid surfaces through flexible spacers (typically chains) [27,29]. For the second approach, the dynamic nature of the supramolecular interactions underlying self-assembly is inherently available, which has the advantage of allowing the level of dynamism to be tuned by adjusting the strength and directionality of the interactions involved.

Accordingly, the following discussion, focused on self-assembled multicatalytic systems, is structured by categorizing the different systems based on the “softness” of their individual dominant underlying noncovalent interaction, defined here in terms of bond strength and degree of directionality. The latter is a critical feature that refers to how constrained the relative orientation is between the molecules forming structured assemblies; whereas a strong degree of directionality offers geometrically better-defined catalytic assemblies, it may also decrease the flexibility needed for efficient catalysis. The discussion starts with the weakest interactions—characterized by lower bond energy, poor directionality, and fast exchange dynamics—and progresses to the stronger, often more directional interactions that lead to more “permanent” assemblies. Although this remains a highly qualitative approach, it provides a useful framework to consistently think in terms of the probability of positioning, dynamism flexibility, and permanence. Self-assembled multicatalytic systems will be presented in the following order: (1) weak and non-directional interactions (Van der Waals and hydrophobic interactions), (2) intermediate strength and partly directional interactions (ionic interactions), and (3) strong and highly directional interactions (hydrogen-bonding, π -stacking, donor–acceptor, and metal–ligand coordination). Obviously, although individually weak compared to covalent bonds, these transient interactions can become collectively strong when multiplied and/or combined in any possible way, and multivalency can indeed be considered as a key strategy in the engineering of such multicatalytic systems.

3. Weak and Non-Directional Interactions

3.1. Van der Waals Interactions Between Alkyl Chains in Monolayers

Van der Waals interactions play a pivotal role in the formation and packing of self-assembled monolayers (SAMs). These highly ordered molecular assemblies arise when amphiphilic molecules spontaneously organize on a substrate, aligning their hydrophobic tails to minimize interactions with the surrounding environment. The length of the alkyl chains and the nature of the terminal functional groups can be precisely tuned to tailor surface properties such as hydrophobicity and chemical reactivity. Furthermore, by integrating various functional groups, SAMs can be post-modified to serve as versatile platforms for application in catalysis, molecular recognition, etc. [50]. Concepcion and colleagues [51,52] (Figure 1) utilized van der Waals interactions to construct mixed self-assembled bilayers consisting of water oxidation catalyst and chromophore layers on electrode surfaces. This approach was developed for the preparation of dye-sensitized solar cells and photoelectrosynthetic cells, which require spatially precise integration of chromophores and catalysts. The system was fabricated from a metal oxide electrode by first anchoring the chromophore via its phosphonic acid handles, followed by the addition of the catalyst. The latter was incorporated through noncovalent interactions between the hydrocarbon chains on the anchored chromophore and the catalyst itself. This versatile strategy enabled the rapid exploration of various chromophore/catalyst combinations, offering a flexible platform for optimizing the performance of these hybrid systems. The bilayer functionalized electrodes depicted remarkable activity in continuous operation compared to other dye-sensitized photoelectrosynthesis cell anodes with directly anchored catalysts; greater stability was also noted for bilayers possessing the longer alkyl chains (C6, C7 and C9 alkyl chains).

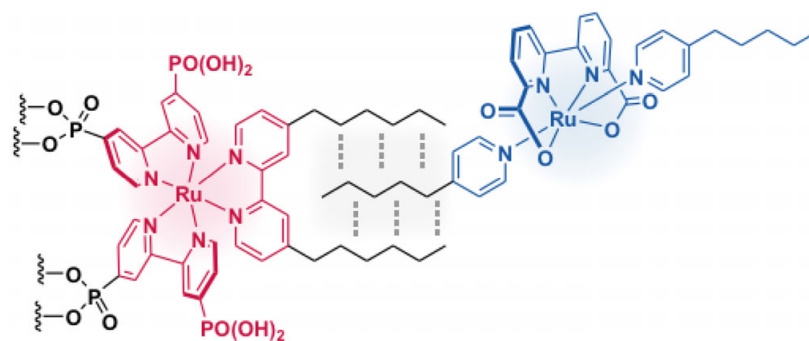


Figure 1. Immobilized multicationic catalysts through self-assembled bilayers.

3.2. Hydrophobic Interactions

Micellar and vesicular systems, formed by the self-assembly of amphiphilic surfactant molecules (either low molecular mass or polymeric) under specific conditions (e.g., temperature and concentration), have been successfully utilized as micro/nanoreactor compartments to facilitate chemical reactions in water [53,54]. With their hydrophobic interior core, these supramolecular assemblies have been widely studied, emulating the hydrophobic binding pockets of enzymes [7,32,33,35]. The reaction acceleration often observed in micellar media, compared to bulk solvents—a phenomenon known as the “micellar effect”—typically results from a combination of factors, of which the solubilization and concentration of reactants within the confined micellar volume primarily dominate. This compartmentalization can also alter or enhance reaction selectivity. Notably, micellar catalysts derived from surfactants with reactive groups (such as metallosurfactants) [55] have attracted significant attention as sustainable alternatives for conducting chemical reactions in water, offering a greener substitute to harmful organic solvents.

Recently, Nothling et al. [56] (Figure 2a) reported the preparation of a multifunctional surfactant incorporating an artificial catalytic triad (ACT-C16)-functionalized head group featuring imidazole, hydroxyl and carboxylate functions, similar to a serine protease active site. This surfactant was co-assembled with a guanidine headgroup surfactant (Guan-C16) acting as an oxyanion hole partner, in the presence of cetyltrimethylammonium bromide (CTAB) to enhance solubility. The resulting three-component co-micelle system displayed remarkable hydrolytic performances on a model hydrophobic ester molecule, achieving a sevenfold higher turnover compared to a native alpha-chymotrypsin protease (although the latter was not placed in its optimal pH and substrate conditions). Interestingly, the parent ACT molecule itself showed only modest activity, underscoring the importance of the confinement and microenvironment.

Ren et al. [57] (Figure 2b) described the development of a two-component self-assembled cooperative catalytic system combining two functionalized surfactants containing 1,4,7-triazacyclononane (TACN)-Cu²⁺ and guanidinium head groups, respectively, designed as a transphosphorylation catalyst. Upon formation of a vesicular structure above the critical assembly concentration and in an optimal DMSO/water solvent mixture (20:80), the system composed of a 1:1 mixture of the two surfactants exhibited a remarkable catalytic activity in a model transphosphorylation reaction. This activity surpassed that of the sum of the individual surfactants (4.5 and 15 times faster than with only the guanidinium surfactant and (TACN)-Cu²⁺, respectively), clearly evidencing a functional synergistic effect. The extent of this synergistic effect was found to strongly depend on the DMSO/water ratio. Notably, the dynamic nature of the self-assembled system was also demonstrated through upregulation of a poorly active binary vesicular system—having a suboptimal ratio of the two cooperative surfactants (e.g., 4:1 (TACN)-Cu²⁺/guanidinium)—to an active

composition (1:3 (TACN)-Cu²⁺)/guanidinium), and back, highlighting the advantage of such a supramolecular system for rapid preparation, modulation and optimization.

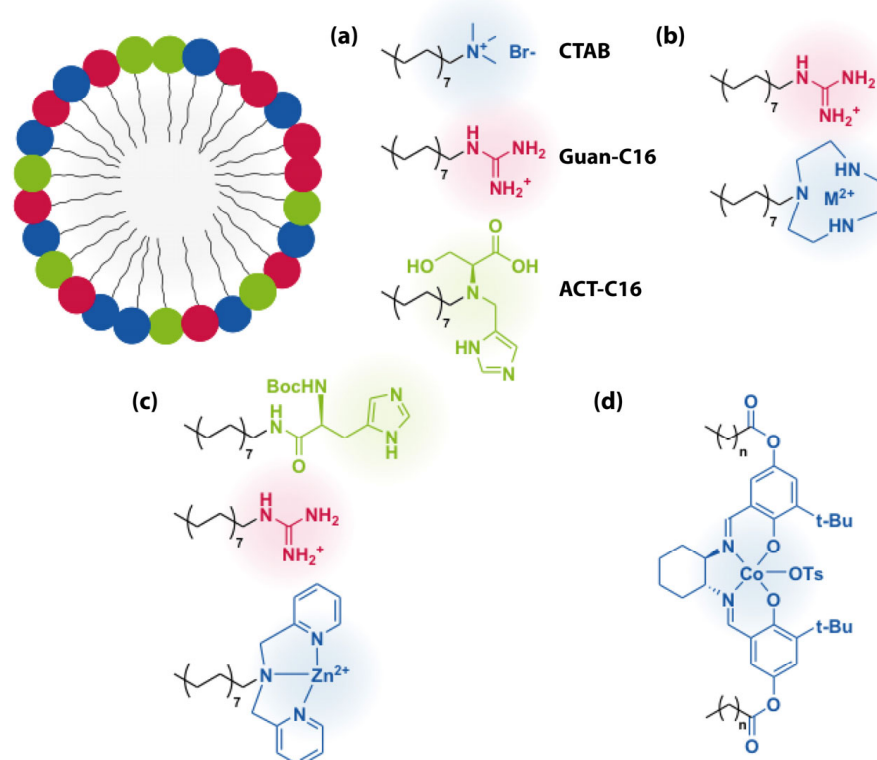


Figure 2. Hydrophobic interactions towards micellar multicatalysts; functional catalytic groups are shown in color. (a) Trifunctional serine protease-mimic [56]; (b) Bifunctional transphosphorylation catalyst [57]; (c) Trifunctional esterase mimic [58]; (d) Co-based catalyst for the hydrolytic kinetic resolution of terminal epoxides [59].

Similarly, Matich et al. [58] (Figure 2c) recently optimized a self-assembled esterase mimic using combinations of functionalized surfactants. Various amphiphiles were designed to introduce key catalytic groups essential to esterase activity onto hydrophobic chains, including histidine (H), carboxylic acid, hydroxyl, and guanidinium (G) head groups—thus mimicking a His-Asp-Ser catalytic triad. Each surfactant was tested individually and in all possible binary combinations, both in the presence and absence of Zn²⁺, which is known to enhance esterase activity. The initial combinatorial screening revealed the superiority of the 1:1 H/G co-assembled system. Detailed analysis evidenced that Zn²⁺ binds to the G motif, in a 1:3 Zn²⁺/G ratio. From this understanding, G was replaced with stronger Zn²⁺ chelators, either 1,4,7-triazacyclononane (TACN) or di-(2-picoly)amine (DPA). Of these, DPA demonstrated superior activity in the co-assembled 1:1 H/DPA system. G was thus reintroduced into the binary H/DPA system to provide oxyanion hole functionality; the resulting 1:1:1 H/G/DPA tertiary structure provided the most efficient catalytic system in the model reaction.

Chen et al. [59] (Figure 2d) presented a homoleptic surfactant-based self-assembled system for the cobalt-catalyzed hydrolytic kinetic resolution (HKR) of terminal epoxides, a process known to mechanistically requires two Co(III) ions to form an active dimeric complex. A Co(salen) complex was flanked with two hydrocarbon chains of varying length ($n = 6, 10, 16$) and tested in HKR reactions under neat biphasic or homogeneous conditions using THF as the solvent in the latter case. It was shown that the longer lipophilic chains provided enhanced activity ($k_{obs} = 2.4, 6.5$ and 8.2 h^{-1} for $n = 6, 10$ and 16 , respectively),

with all cases outperforming a reference Co(salen) lacking pendant hydrocarbon chains ($k_{obs} = 0.86 \text{ h}^{-1}$). Under biphasic conditions, the reaction rate acceleration (nearly tenfold) was attributed to stabilization of the emulsion, increased interfacial area, and a high concentration of the active dimeric Co(salen) complex at the oil–water interface. In homogeneous conditions (THF), the moderate enhancement (five-fold compared to the reference Co(salen) catalyst) was primarily linked to an increased association constant promoting the formation of the active dimeric species.

4. Intermediate Strength and Directional Interactions (Ionic Interactions)

Mandal et al. [60] (Figure 3a) demonstrated that ionic interactions arising from tailored acid–base reaction between two cocatalysts in organic solvents—the latter being critical to ensure relatively permanent self-assembly as opposed to in aqueous solvents—enable the modular formation of self-assembled cooperative catalysts through ionic interactions. In their approach, an ion pair is formed between a proline organocatalyst (L- or D-) and quinidine-thiourea derivatives possessing a tertiary amine side group. Upon mixing, the acid–base reaction between proline and the tertiary amine group of the thiourea resulted in an ammonium salt bringing the two catalysts in close proximity. This system delivered excellent results in a model Michael addition between acetone and trans-beta-nitrostyrene. A strong matching and mismatching effect was observed between the thiourea-derivatized cinchona alkaloid and the D- and L-proline enantiomers, with L-proline failing to provide any reaction product after 72 h with the mismatched quinidine. Optimal yield and enantiomeric excess (*ee*) of 67 and 86% of the (*R*)-enantiomer were obtained, respectively, by combining the D-proline (5 mol%) and the quinidine co-catalysts (5 mol%). The mirror catalytic system (i.e., the L-proline and matched quinidine) afforded the (*S*)-enantiomer in 81% yield and 86%*ee*. Notably, the use of proline derivatives incapable of forming this ion pair with the matched thiourea partner, such as prolinamide or methylprolinate, led to significantly inferior performance, highlighting the essential role of ion pairing in driving cooperative catalysis. Screening of the amino-acid moiety identified L-phenylglycine as the optimal cocatalyst, affording the (*R*)-enantiomer product in 63% yield and 95%*ee*.

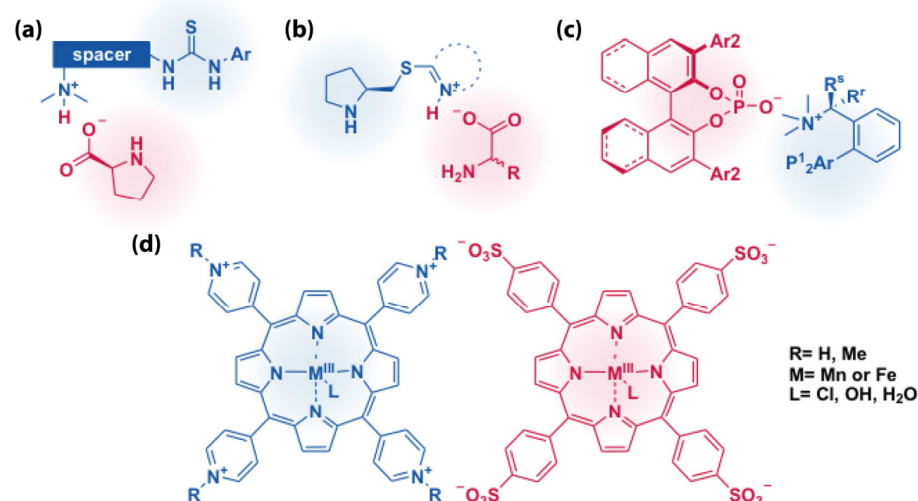


Figure 3. Ion-paired multicatalysts. (a) Ionic pair of co-catalysts used for the Michael addition between acetone and trans-beta-nitrostyrene [60]; (b) Dual organocatalytic ion pair for the Oxa-Michael-Mannich reaction [61]; (c) Ion-paired bifunctional catalyst for Pd-catalyzed allylation [62]; (d) Binuclear Fe(III) and Mn(III) structure for the biomimetic reduction of 4-nitrophenol [63].

Similarly, Xia et al. [61] (Figure 3b) described the preparation of dual organocatalytic ion pair assemblies for the Oxa-Michael-Mannich reaction. In this system, functionalized pyrrolidines bearing a basic site were coupled with primary amino acids. This approach resulted in ion-paired catalysts featuring dual activation centers—one for the electrophile and one for the nucleophile—which demonstrated effective catalytic activity in the model reaction between salicylic aldehyde and cyclohex-2-enone, with quantitative yields and *ee* up to 92%. Notably, substituting the amino acids with their methyl ester derivatives significantly reduced activity (<5% yield and 31%*ee*), underscoring the importance of maintaining the acid–base interactions for catalytic efficiency.

Ohmatsu et al. [62] (Figure 3c) developed a combinatorial approach for the in situ generation of ion-paired bifunctional catalysts and their application in biphasic Pd-catalyzed allylations. Unlike the previous examples, the ion pair in this system was formed by mixing preformed salts of ammonium phosphines and axially chiral phosphoric acids in the presence of K_2CO_3 . The choice of the ammonium salt counterion was critical to ensure rapid exchange with the phosphate anion. For instance, using bromide as the counterion resulted in only moderate reactivity (78% yield and -11% *ee*), comparable to the performance of the reaction with the ammonium ligand alone. Screening various counterions revealed that acetate and hydrogensulfate anions provided optimal results (99% yield 90%*ee*, and 95% yield 93%*ee*, respectively), likely due to their effectiveness in the ion metathesis step. The catalytic performance of these systems was comparable to that of pre-prepared salts of ammonium phosphines and chiral phosphates (99% yield, 92 %*ee*). Building on this, a combinatorial screening of 12 ammonium phosphine hydrogensulfates and 12 chiral phosphoric acids—yielding 144 possible combinations—was conducted. This approach successfully identified a unique pair capable of efficiently catalyzing the allylation of benzothiophene, showcasing the modularity and rapid screening potential of this strategy for catalyst optimization.

In another way, Rebelo and colleagues [63] (Figure 3d) utilized ionic self-assembly to construct binuclear Fe(III) and Mn(III) materials for the biomimetic reduction of 4-nitrophenol. The binuclear structures were formed by co-assembling metalated porphyrins of opposite charge. Specifically, functionalized porphyrins bearing positively charged methylpyridinium groups, ionizable pyridyl groups, or negatively charged sulfonatophenyl groups were combined. This assembly strategy allowed for the formation of various binuclear configurations, including [Fe/Fe], [Mn/Fe], [Fe/Mn], and [Mn/Mn], depending on whether the metal centers (M) were located on the positively or negatively charged porphyrins (denoted as [M(+)/M(−)] porphyrin assemblies). Under simulated sunlight, the heterometallic [Mn/Fe] assembly demonstrated the highest catalytic activity for the reduction of 4-nitrophenol, with an observed rate constant of $539\text{ min}^{-1}\cdot\text{g}^{-1}$. This activity was 13-fold superior to the median performance of the individual precursor porphyrins, indicative of a cooperative catalytic mechanism within the heterometallic assembly.

This ionic self-assembly strategy was also employed by the same authors to create porphyrin-based materials exhibiting biomimetic catalase and peroxidase activities [64]. Among the systems tested, the heterometallic [Mn/Fe] and [Fe/Fe] materials demonstrated superior efficiency in catalase-like activity (ca. 80–100 and ca. 60–80 $\text{U}\cdot\text{mg}^{-1}$, respectively), compared to both homobimetallic and other heterobimetallic systems as well as the corresponding individual porphyrins. In this case, the positively charged porphyrin was derived from protonated pyridine peripheral groups. Notably, the catalase-like activity of the [Mn/Fe] system remained stable across a pH range of 4 to 7, whereas the activity of the [Fe/Fe] system decreased significantly with increasing pH ($<10\text{ U}\cdot\text{mg}^{-1}$ at pH 7). This was attributed to the deprotonation of pyridine groups in the [Fe/Fe] assembly, leading to disassembly of the structure. Subsequently, the [Fe/Fe] and [Mn/Fe] systems, which

demonstrated the highest catalase-like activity, were further tested for the peroxidase-like oxidation of ABTS (2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid)). Again, the [Mn/Fe] material proved the most effective in catalyzing the formation of the ABTS^{•+} radical species, with an activity of ca. $1.0\text{--}1.2 \times 10^{-3} \text{ mol}\cdot\text{dm}^{-3}$ at pH 4 after 5 min of reaction, vs. ca. 0.2 for the [Fe/Fe] metalloporphyrin. Its activity exceeded that of the individual Fe and Mn metalloporphyrins, reinforcing the presence of a cooperative catalytic mechanism within the heterometallic system.

Similarly, the group of Rebello utilized their versatile porphyrin-based ionic self-assembly approach to prepare [Cu/Fe], [Fe/Cu], [Cu/Cu], [Fe/Fe], [Mn/Fe], [Fe/Mn] and [Mn/Mn] materials for application in the hydrogenation of nitroaromatics [65]. The study highlighted a synergistic effect when the less electronegative metal ion was incorporated into the porphyrin cation and the more electronegative metal ion resided in the porphyrin anion, optimizing the catalytic performance of the assemblies.

5. Strong and Highly Directional Interactions

5.1. Hydrogen Bonding

(Multiple) hydrogen bonding is among the most important non-covalent interactions utilized in the self-assembly of supramolecular structures. This is exemplified in biological systems, such as the formation of secondary structures in proteins and the formation of the double helix of DNA, which combines H-bonding between complementary bases and pi-stacking interactions along the helix axis. In these systems, the donor–acceptor framework is commonly used to describe hydrogen-bonding motifs, with “D” and “A” denoting the complementary hydrogen bond donor and acceptor groups, respectively.

In the field of supramolecular catalysis, Breit and colleagues (Figure 4a) pioneered the use of hydrogen bonding as a strategy to rapidly prepare and screen bidentate homo- and heterodimeric ligand libraries through self-assembly, offering a compelling alternative to traditional covalent synthesis of bidentate ligands [66–73]. These self-assembled ligand libraries were applied to a series of transition metal-catalyzed transformations, with heterodimeric combinations demonstrating notable performance in some instances. In this approach, adenine (DA)/thymine (AD) analogous base pair, as well as beta-sheet forming peptides [74] were used.

Inspired by this pioneering work, Clarke et al. [75] (Figure 4b) utilized a complementary DAA-ADD hydrogen-bonding system to self-assemble catalyst libraries combining a chiral pre-catalyst and an achiral additive. Their results demonstrated that the chiral ancillary induced stereoselectivity to the otherwise unselective catalyst, highlighting a synergistic effect between the two entities.

Alternatively, Park et al. [76] utilized multiple complementary hydrogen-bonding motifs to self-assemble homo-dimeric supramolecular macrocycles containing two Co(salen) centers for use in asymmetric Henry reactions. The complex featured terminal hydrogen-bonding pairs (AD, AD) or (AD, DA), with the former allowing self-dimerization in solution. The unsymmetrical Co(salen) catalyst (Figure 4c) exhibited enhanced activity (87% yield, 96%*ee*) compared to its symmetrical (Figure 4d, 18% yield, 87%*ee*) and monomeric counterparts (<11% yield, 55–64%*ee*) in the model Henry reaction between *o*-anisaldehyde and nitromethane. This improvement stemmed from the formation of the self-assembled macrocycle that positioned two Co(salen) centers in close proximity, facilitating the cooperative activation of aldehyde and nitromethane partners via a bimetallic activation pathway. The combined symmetrical ligands most likely formed weaker dimeric species because requiring more geometrical constraints for dimerization. This approach was subsequently applied to other bimetallic catalytic processes [77,78].

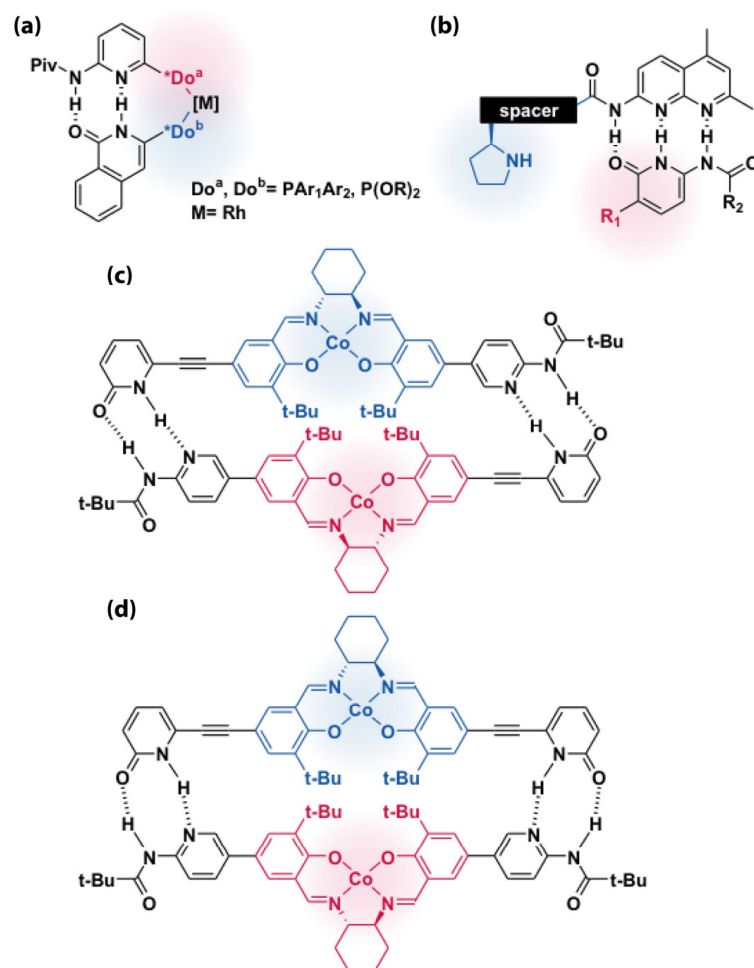


Figure 4. Self-assembled multicatalysts through hydrogen bonding. (a) Homo- and heterodimeric transition metal ligand based on adenine/thymine assembly [66–73] (* indicates chiral moieties); (b) Self-assembled catalyst combining a chiral pre-catalyst and an achiral additive [75]; (c,d) Unsymmetrical (c) and symmetrical (d) self-assembled homo-dimeric supramolecular macrocycles for use in asymmetric Henry reactions [76].

Our group [79] recently prepared sequence-defined oligomers bearing complementary recognition units to drive the self-assembly of supramolecular structures containing all the active sites involved in the (pyta)Cu/TEMPO/NMI-catalyzed aerobic oxidation of alcohols (Figure 5). These active sites were distributed between two oligomers terminated by DNA base analogs (G, T, C, D, Figure 5b,c). While each individual strand exhibited low catalytic activity, a remarkable enhancement of turnover frequency (TOF) of ca. one order of magnitude was observed when combined, surpassing the activity of the complete parent monomeric system at low concentrations. Among the virtually infinite possible self-assembled structures existing in dynamic equilibrium—including free oligomers, linear poly(oligomers), and poly(oligomeric) macrocycles—it was found that the di(oligomeric) macrocycle superstructure predominantly contributed to the catalytic turnover; this specific configuration within the dynamic constitutional library effectively confines all the required active centers in a small catalytic globule. Despite linear configurations also contributing to the complete multicatalytic system, only the dimeric macrocyclic structure increased the effective local concentration of catalytic groups and their probability of encounter, thus driving catalytic performances.

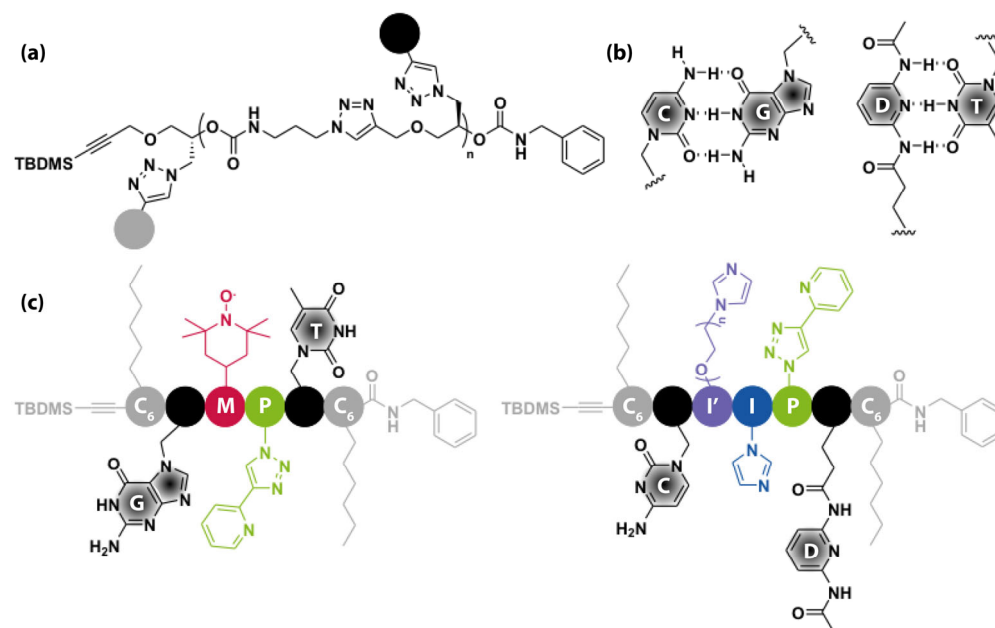


Figure 5. Self-assembled sequence-defined oligomeric multicatalysts for the aerobic oxidation of alcohols [79]. (a) General structure of the catalytic chains; (b) Nucleobase pairing scheme used to assemble the co-catalytic chains; (c) Schematic composition of the co-catalytic chains assembling into cyclic catalytic dimers.

Pimentel et al. [80] (Figure 6a) used DNA self-assembly to create a switchable bifunctional catalyst bearing bipyridine-Cu and TEMPO active sites for the oxidation of alcohols. The two catalytic moieties were separately bioconjugated onto two complementary ssDNAs, which were then annealed to form a duplex architecture. In presence of copper and under dilute conditions, the duplex catalyst (turnover number TON = 22.1 ± 1.6) exhibited a remarkable activity enhancement compared to the unscaffolded versions of the cocatalysts (TON = 0.32 ± 0.06), or a flipped duplex configuration (TON = 0.9 ± 0.1). This result underscored the critical role of effective local concentration, proximity, and intramolecular interactions in such systems. Furthermore, by incorporating a stem-loop motif into the DNA scaffold, the authors demonstrated the ability to regulate the reaction rate through reversible conformational changes. These changes controlled the relative spacing between the two cocatalysts, somehow offering dynamic control over catalytic activity.

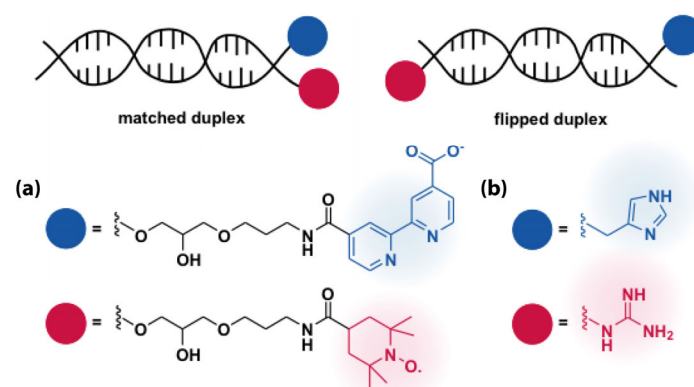


Figure 6. DNA-scaffolded cooperative catalysts. (a) Active groups used in a DNA-assembled switchable bifunctional catalyst for the oxidation of alcohols [80]. (b) Active groups in a DNA-scaffold mimicking the catalytic core of hydrolases [81].

Zheng et al. [81] (Figure 6b) later employed this DNA-scaffolded approach to mimic the catalytic core of hydrolases using histidine and arginine terminal catalytic sites. This method allowed for the precise positioning, co-localization and spacing of the cooperative catalytic amino acids, resulting in a notable improvement in activity compared to the corresponding flipped duplex or free amino acids in a model hydrolysis reaction. Additionally, hierarchical immobilization of the duplex on one-dimensional and two-dimensional DNA nanostructures further enhanced the catalytic performance by a factor of 1.3 and 4.2, respectively, demonstrating the versatility and efficiency of this approach.

5.2. Aromatic Donor–Acceptor and π -Stacking Interactions

In an early example, Chuzel et al. [82] (Figure 7a) developed self-assembled homo- and heterodimeric bidentate oxazoline ligands utilizing charge transfer interactions between functionalized electron-rich anthracene donors and electron-deficient 2,4,7-trinitrofluorene-9-one acceptors, both decorated with various chiral monodentate oxazoline motifs. The resulting combinatorial libraries of self-assembled ligands were tested in a Diels–Alder reaction in the presence of $\text{Cu}(\text{OTf})_2$. However, when combining different mono-oxazoline partners, an equilibrium between π -stacking and charge transfer interactions resulted in a mixture of homo- and heterodimeric bidentate ligands. This dynamic mixture led to reduced enantioselectivities in the reaction.

Blechschmidt et al. (Figure 7b) [83], in a way similar to the work of Park et al. using hydrogen-bonding [78], utilized charge transfer interactions to self-assemble $\text{Co}(\text{salen})$ complex for the HKR of epichlorhydrin, a reaction proceeding through a cooperative bimetallic mechanism, as already mentioned. The $\text{Co}(\text{salen})$ was decorated with two electron-deficient (acceptor) moieties (1,4,5,8-naphthalenediimide (NDI) or pyromellitic diimide (PDI)) positioned on either side of the organometallic core, employing various acceptor molecules and spacers. These bis-acceptor $\text{Co}(\text{salen})$ derivatives, having different spacers, were evaluated in the model HKR reaction of epichlorohydrin, with and without aromatic donor molecules (pyrene, 1,5-dimethoxynaphthalene (DMN), perylene, coronene) and using CHCl_3 as the solvent. Notably, no effect of the donor molecules was observed with the catalyst bearing the NDI acceptors and phenyl spacers (NDI-phenyl) compared to the reference Jacobsen catalyst. Introducing a more flexible, non-conjugated alkyl spacer (NDI-alkyl) led to enhanced catalytic activity, in terms of both reaction rate and enantioselectivity. In this case, the nature of the donor molecules influenced the enantioselectivity, with %ee decreasing as the donor conjugation size increases. The PDI-alkyl system further surpassed the catalytic activity of the NDI-alkyl system. These results highlight the role of structural flexibility in promoting catalytic efficiency through the assembly of multi-metallic superstructures.

The same group (Figure 7c) later reported a variation of their design, this time preparing an unsymmetrical $\text{Co}(\text{salen})$ complex functionalized with pyrene-naphthalenediimide donor–acceptor motifs and its evaluation in the HKR of various epoxides [84]. This catalyst, equipped with an alkyl spacer between the $\text{Co}(\text{salen})$ and donor/acceptor sites, outperformed its combination of symmetrical versions (i.e., bearing either two pyrene or two naphthalenediimide groups) in terms of reaction rate ($k_{\text{obs}} = 1.54$ vs. 0.58 h^{-1}). Interestingly, the unsymmetrical system provided results comparable to those obtained when combining mono-functionalized $\text{Co}(\text{salen})$ containing a single donor and acceptor group. Building on this understanding, the same group (Figure 7d) prepared monofunctional prolinamide and thiourea organocatalysts bearing pyrene and NDI motifs, respectively, for application in the asymmetric aldol reaction [85]. The donor–acceptor-driven self-assembly of the dual catalyst achieved > 99% conversion ($k_{\text{obs}} = 0.523 \text{ h}^{-1}$) and 92%ee in the model reaction between cyclohexanone and *p*-nitrobenzaldehyde. This performance surpassed control experiments

using the pyrene-prolinamide derivative alone (>99% conversion, 77%*ee*, $k_{obs} = 0.297 \text{ h}^{-1}$) and in combination with a model thiourea (>99% conversion, 85%*ee*, $k_{obs} = 0.168 \text{ h}^{-1}$).

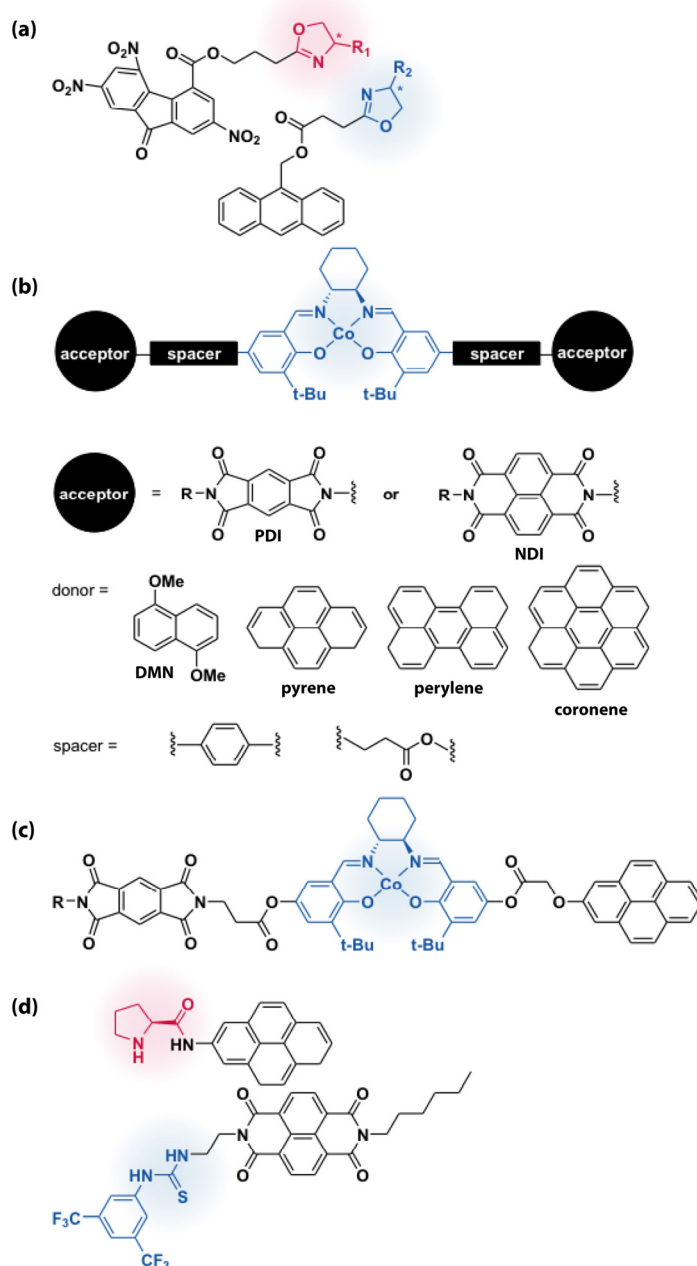


Figure 7. Self-assembled multicatalysts through donor–acceptor interactions. (a) Self-assembled homo- and heterodimeric bidentate oxazoline metal utilized in a Diels–Alder reaction [82] (* indicates chiral centers); (b) Co(salen) complex for the hydrolytic kinetic resolution of epichlorhydrin [83]; (c) Unsymmetrical Co(salen) complex for the hydrolytic kinetic resolution of various epoxides [84]; (d) Self-assembled prolinamide-thiourea organocatalyst utilized in an asymmetric aldol reaction [85].

In another way, the group of Xu (Figure 8a) further advanced these approaches by employing polymer supports bearing aromatic side chains to effectively immobilize properly decorated cooperative catalytic partners via aromatic stacking interactions. In a first example [86], pyrene- and anthracene-functionalized polystyrene (PP and PA, respectively) were used to immobilize the three cooperative components—(pyta)Cu (L), TEMPO (T) and DMAP (D)—involved in the aerobic oxidation of benzyl alcohol. The CuAAC reaction was employed for derivatizing both the polystyrene copolymer containing azidomethyl

functions, and the catalytic groups with either anthracene or pyrene moieties. Catalytic systems prepared from either pyrene or anthracene (on both polymer and catalysts) were tested in the model aerobic oxidation. It became apparent that the pyrene-based system afforded enhanced activity compared to the anthracene system for all the tested compositions (i.e., L/T/D/PP/PA constituent ratio), most likely due to stronger stacking interactions between the pyrene motifs. When no polymer support was used, the functionalized catalysts showed only moderate activity. The effect of the pyrene content in the PP copolymer support was also evaluated at the optimal L/T/D mol ratio (5/5/10), revealing a minimal pyrene-to-styrene ratio of 0.28 ($\text{TOF} = 0.45 \text{ h}^{-1}$) required to minimize dilution effects. Finally, the addition of an NDI aromatic donor to the L/T/D/PP-pyrene catalytic system enhanced interactions between the components and the polymer, achieving a TOF of 0.67 h^{-1} . This self-assembly approach likely provided sufficient flexibility to facilitate self-adaptation of the catalytic site, enabling the optimal alignment and matching of the three catalytic groups.

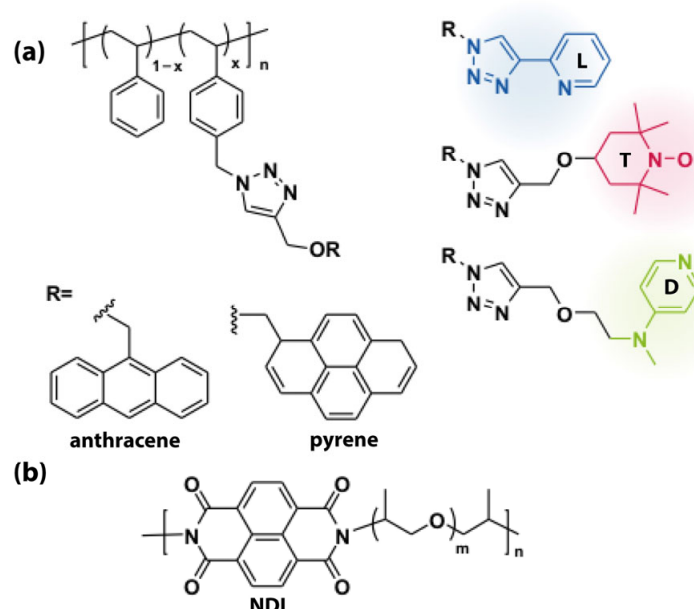


Figure 8. Polymer-supported supramolecular multicatalysts based on donor–acceptor interactions. (a) Pyrene- and anthracene-functionalized polystyrene assemblies with pyrene- or anthracene-derivatized catalytic components involved in the aerobic oxidation of benzyl alcohol; (b) A similar approach in which the pyrene- or anthracene-modified polymer is replaced by naphthalene diimide (NDI)-based polyimides [87].

Building on this work, Xu and colleagues (Figure 8b) similarly employed naphthalene diimide (NDI)-based polyimides as polymeric supports for the non-covalent immobilization of the pyta/TEMPO/DMAP catalytic centers, the latter being derivatized by pyrene moieties [87].

5.3. Metal–Ligand Coordination

Metal–ligand coordination has been extensively employed in supramolecular chemistry to construct a wide range of topological structures from cages to polymers, such as MOF, particularly for application in catalysis. The strength, directionality, and rigidity of these interactions make them ideal for such purposes. However, the specific use of metal–ligand interactions for the non-covalent assembly of cooperative multicatalytic systems remains less explored, probably because the rigidity of such interactions limits the flexibility required for effective interactions between the catalytic components.

Meggers and co-workers have arguably pioneered this approach using coordinative bonds to self-assemble multicatalytic systems. In their approach, an octahedral iridium metal center serves as an inert structural template to organize cooperative catalytic sites in the three-dimensional space, offering the added advantage of imparting at-metal chirality to the self-assembled structure. In this approach, catalyst-functionalized ligands are assembled around the inert metal center, forming a well-defined, rigid metal complex. In a first example (Figure 9) [88], bis-cyclometalated iridium(III) complexes were synthesized, containing a thiourea-like double-hydrogen-bond donor and two hydroxymethyl hydrogen bond acceptor sites, located on different bidentate ligands. These sites activate nucleophile and electrophile partners in the asymmetric transfer hydrogenation of substituted nitroalkenes. Excellent yield and asymmetric induction were achieved at low catalyst loading, especially through increasing the steric hindrance of the ligands. Further modifying the nature and number of the hydrogen bond donor and acceptor sites led to even more efficient catalysts with loadings as low as 40 ppm [89].

This modular design was further adapted for the Michael addition of carbon nucleophiles to disubstituted nitroalkenes by introducing a stronger carboxamide hydrogen bond acceptor [90]. Similarly, other modified versions of these active octahedral complexes were developed by combining various cooperative organocatalysts for use in a variety of reactions, including sulfa-Michael, aza-Henry reactions and Friedel–Crafts alkylation [91–97]. In these systems, the inert metal center serves as the exclusive source of chirality.

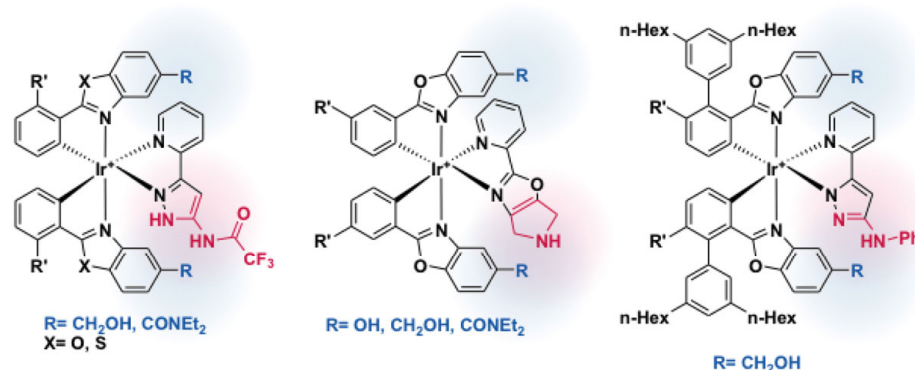


Figure 9. Examples of chiral-at-metal multicatalysts. For a review, see ref. [98].

Serra-Pont et al. [99] (Figure 10a) employed this metal template approach in a rather different conceptual framework to create dynamic self-assembled prolinamide-thiourea bifunctional catalysts for use in the asymmetric aldol reaction. In this case, ZnCl₂ was used as the neutral metal center, with monodentate pyridine ligands containing the separate catalytic centers, resulting in the formation of tetrahedral complexes. Unlike Meggers' approach, which utilizes an isolated rigid metal complex, this strategy involved directly performing the catalytic experiments with the mixture of all three components—ZnCl₂ and the two functionalized ligands—allowing for expedited catalyst preparation and screening. As expected, a dynamic equilibrium necessarily arises from this mixture, and was evidenced by NMR and mass spectrometry. Noticeably, it was shown that the pyridine isomeric substitution pattern (i.e., pyridine functionalized at position 2, 3 or 4) significantly influenced catalytic performances, the best results (81% conversion, 95/5 anti/syn d.r., 92%*ee* in the model aldol reaction between cyclohexanone and *p*-nitrobenzaldehyde) being achieved when the pyridine was functionalized at position 3. The same group later reported the use of CuSO₄·5H₂O metal template as a more efficient substitute for ZnCl₂ in the model reaction (98% conversion, 93/7 anti/syn d.r., 95%*ee* after 24 h reaction) [100].

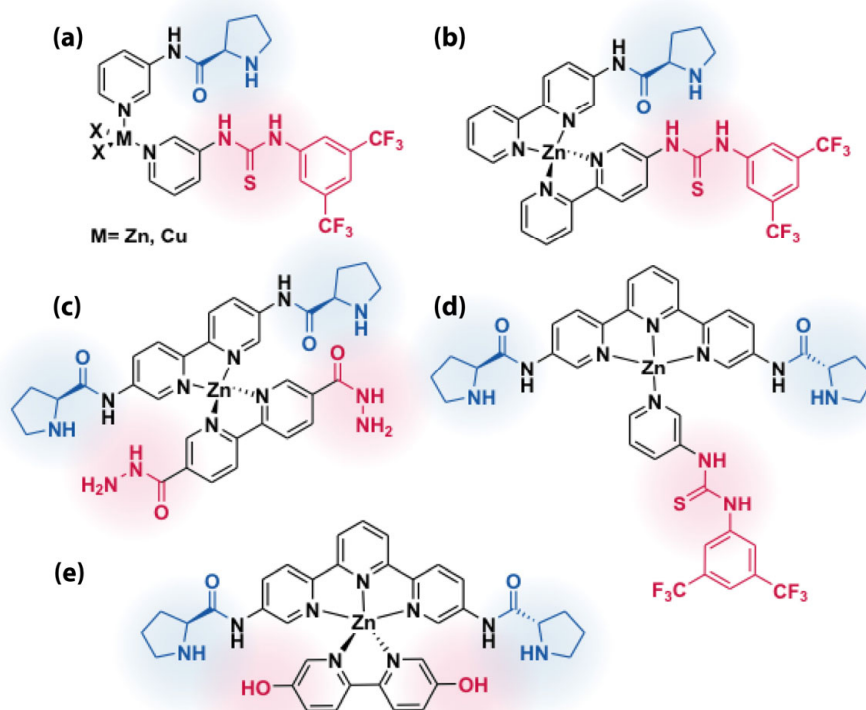


Figure 10. Metal-templated multicatalysts. (a) Dynamic self-assembled prolinamide-thiourea bifunctional catalysts for use in the asymmetric aldol reaction [99]; (b) A similar approach, using bidentate bipyridine ligands [101]; (c) Improved version of the previous catalyst, using two bis-functionalized bipyridine ligands, each bearing either two prolinamide units or two dihydrazide units [102]; (d,e) Tetra- (d) and penta- (e) coordinated dual catalytic complexes for application in the asymmetric aldol reaction [103].

Following these results, bidentate bipyridine ligands separately functionalized with prolinamide and thiourea groups were combined with $\text{Zn}(\text{O}_2\text{CCF}_3)_2$ (Figure 10b) and investigated in the same model reaction (96% conversion, 92/8 anti/syn d.r., 99%*ee* after 8 h reaction) [101]. This system was further optimized by using two bis-functionalized bipyridine ligands, each bearing either two prolinamide units or two dihydrazide units (Figure 10c) (97% conversion, 14/1 anti/syn d.r., 98%*ee* after 20 h reaction) [102]. This redundancy enhanced the initial TOF by a factor of 5, allowing them to lower the catalyst loadings down to 2 mol%. It was demonstrated that the reaction followed first-order kinetics with respect to the catalyst, implying that only half of the catalytic sites were utilized at any given time, rendering the other sites redundant.

Recently, the same group reported the improvement of their Zn-templated catalytic complexes by using a functionalized tridentate terpyridine ligand to maximize the formation of heterodimeric bifunctional catalysts [103]. The terpyridine was flanked by two pendant prolinamide groups and combined with pyridine (Figure 10d) or bipyridine (Figure 10e) bearing hydrogen bond donor groups for application in the asymmetric aldol reaction. In particular, the combination of the readily accessible functionalized terpyridine and bipyridine provided the best results (99% conversion, 14/1 anti/syn d.r., 97%*ee* after 22–23 h reaction). The evaluation of equilibrium constants between $\text{Zn}(\text{TFA})_2$, terpyridine and bipyridine allowed them to determine conditions for which the formation of the pentacoordinated dual catalytic complex is favored.

6. Conclusions

Self-assembly offers a highly modular and adaptable design approach towards multicatalytic systems. By harnessing non-covalent interactions, such as metal–ligand coordination, hydrogen bonding, hydrophobic, ionic, aromatic, and charge transfer interactions—and a combination of these—various complementary catalytic sites can be structured and positioned in close proximity. This provides a valuable tool to orchestrate synergistic effects tailored for specific multicatalytic reactions, whether cooperative or tandem (the latter being less explored due to often requiring changes in reaction conditions). The resulting increased effective local concentrations and optimal stoichiometries of the active species enable faster reaction rates, higher turnovers and the ability to use lower catalyst loadings. This offers a real advantage over free “one-pot” multicatalytic systems, compensating therefore for the need to derivatize each catalytic center to enable their self-assembly. Obviously, this family of catalysts shares several design principles with enzymes, particularly in terms of self-assembly, multiple active site synergy, flexibility and dynamic behavior—capitalizing on the directed self-organization of complex active sites to achieve high efficiency and selectivity.

Moreover, as presented here, the versatility of self-assembly allows for rapid preparation, screening and optimization of multicatalyst combinations. The dynamic nature of some of these self-assembled multicatalytic systems may allow for catalytic site adaptation in the course of the reaction and for adaptability to different substrates. However, and like enzymes, the stability of such self-assembled structure depends on factors such as equilibrium constants and dynamics, which are influenced by temperature, solvent, pH, etc. Therefore, selecting the appropriate non-covalent interactions leading to more or less permanent assemblies for a given catalytic system is crucial. Notably, retaining a certain degree of flexibility in the self-assembled structure, either through the supramolecular link or through the incorporation of flexible handles between the non-covalent node and the catalytic centers, can be advantageous in increasing the probability of close presence and effective interactions.

Additionally, these non-covalent interactions may offer opportunities for catalyst recovery and reuse, such as through affinity capture and release [38].

In summary, the self-assembly approach for constructing multicatalysts provides a powerful and versatile strategy for developing efficient and selective catalytic systems, often surpassing their parent free form or covalent multicatalyst version. With remarkable advantages in terms of modularity, efficiency, and adaptability, this approach has the potential to open new opportunities in the design of advanced, bioinspired catalytic systems across a wide range of chemical processes.

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