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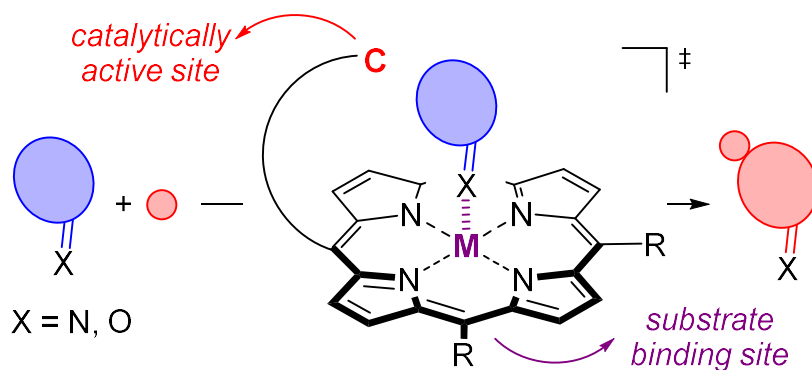
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## Mimicking Enzymes: Taking Advantage of the Substrate-Recognition Properties of Metalloporphyrins in Supramolecular Catalysis

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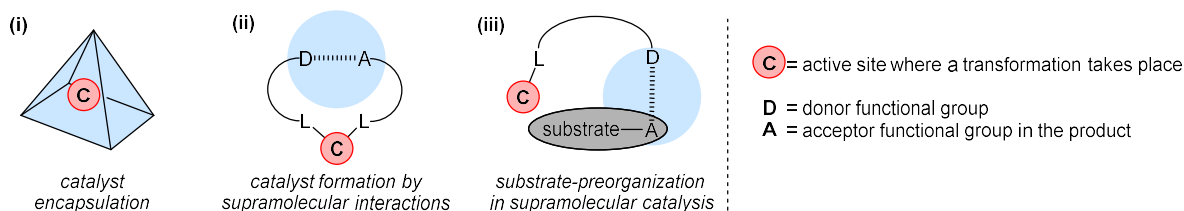


**Abstract:** The present review describes the most relevant advances dealing with supramolecular catalysis in which metalloporphyrins are employed as substrate-recognition sites in the second coordination sphere of the catalyst. The kinetically-labile interaction between metalloporphyrins (typically, those derived from zinc) and nitrogen- or oxygen-containing substrates is energetically comparable to those non-covalent interactions (i.e. hydrogen bonding) found in enzymes enabling substrate-preorganization. Much inspired from this host-guest phenomena, the catalytic systems described in this account display unique activities, selectivities and action modes difficult to reach applying purely covalent strategies.

### 1. Introduction.

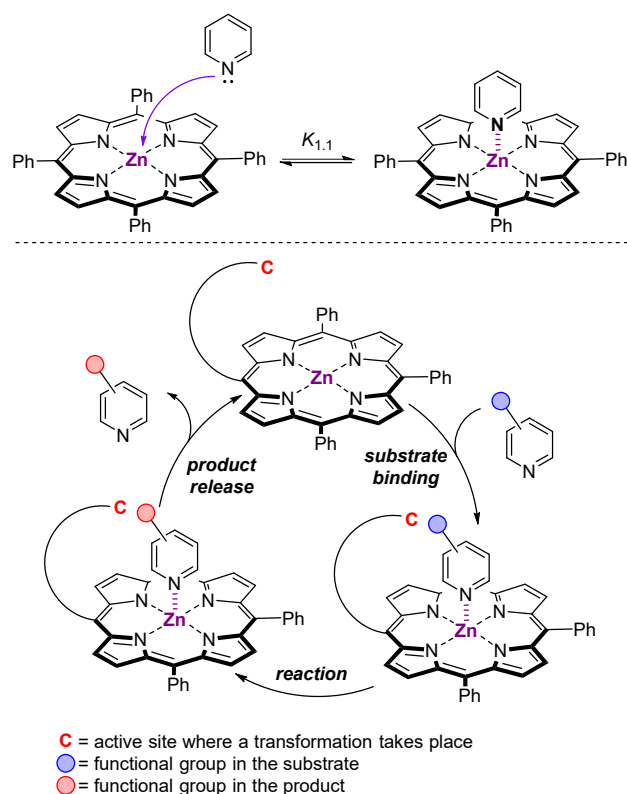
Supramolecular catalysis is nowadays a well-established field in chemical sciences.<sup>[1-2]</sup> It aims at rationally implementing supramolecular strategies in molecular catalysis, mostly taking inspiration from natural catalysts (enzymes) which display unrivaled levels of activity and selectivity.<sup>[3-7]</sup> Three main designs are usually considered for supramolecular catalysts. The first one relies on the encapsulation of the molecular catalyst inside a synthetic, well-defined hollow receptor (i, **Figure 1**).<sup>[8-36]</sup> The encapsulation can be accomplished by the hydrophobic effect between a guest (catalyst) and a host,<sup>[31-32]</sup> template strategies<sup>[33]</sup> or by covalent-linkage of the catalytically active site to cavity-shaped molecules. By these means, different advantages may emerge. For instance, the catalyst can be protected from degradation pathways, the transition states available might be controlled to such an extent that only a certain type of product(s) can form and the reactants can adopt a precise conformation due to the restricted space available, thereby reducing the activation entropy of a reaction. A second supramolecular design is the generation of a catalyst by employing ligand components that self-assemble with each other (ii, **Figure 1**).<sup>[37-41]</sup> In this way, the costs associated to the traditional ligand synthesis based on covalent chemistry are significantly reduced because the catalytic system will spontaneously form by recognition of complementary non-covalent functional groups present in the ligand components, typically *via* hydrogen bonding or ion-pairing. This strategy is particularly powerful to identify optimal catalysts by using mixture of ligands in

deconvolution strategies as well as to combine achiral ligands with chiral ions to tackle asymmetric catalysis.



**Figure 1.** Common strategies applied in supramolecular catalysis. The blue shadows indicate the second coordination sphere of the catalyst.

A third supramolecular strategy is the incorporation of substrate-recognition sites beyond the first coordination sphere of the catalyst (iii, **Figure 1**).<sup>[42-46]</sup> In this way, the substrate will be spatially fixed in a given conformation at a precise distance from the active site through complementary non-covalent interactions. In this scenario, enhancing a preferential catalyst conformation by physical constraints (rigidity) and/or catalyst adaptability are relevant features. Such pre-organization of the substrate around the active site is relevant to study selectivity issues because the distance between the active site and the substrate binding site can be designed in an atom-precise manner for predictive catalysis. In addition, this strategy is useful to avoid catalyst inhibition if the substrate is known to poison the active site, thus resulting in enhanced reaction rates. In this context, the most widely utilized non-covalent interactions for substrate-preorganization catalysis are hydrogen bonding and ion-pairing following enzymes' inspiration. On the other hand, less-conventional non-covalent interactions have also been exploited for substrate-preorganization catalysis such as halogen bonding, pi interactions, amongst others.<sup>[47]</sup> An appealing type of non-covalent interaction is the kinetically-labile coordination between a metalloporphyrin and a polar-coordinating molecule (**Figure 2**, top).<sup>[48]</sup> In this type of interaction, the metal (i.e. zinc) inside the porphyrin might be regarded as a Lewis acid whereas the polar-coordinating substrate, usually pyridine- or oxygen-containing ones, behaves as a Lewis base. This interaction is rather unidirectional with an association constant varying from  $10^3$  to  $10^6$   $M^{-1}$ , and from an energetically point of view surpasses the energy associated to a single hydrogen bond.<sup>[49-54]</sup> Indeed, the coordination of organic molecules to metallo-containing porphyrins have been widely studied in the context of supramolecular chemistry with applications arising from polymerization, photophysics, material sciences, and bio-imaging, just to mention a few.<sup>[55-61]</sup> In the following, we describe the exploitation of this type of interaction for substrate pre-organization catalysis (**Figure 2**, bottom) since the first contributions from Sanders and co-workers on organocatalysis to the most recent examples on metal catalysis.

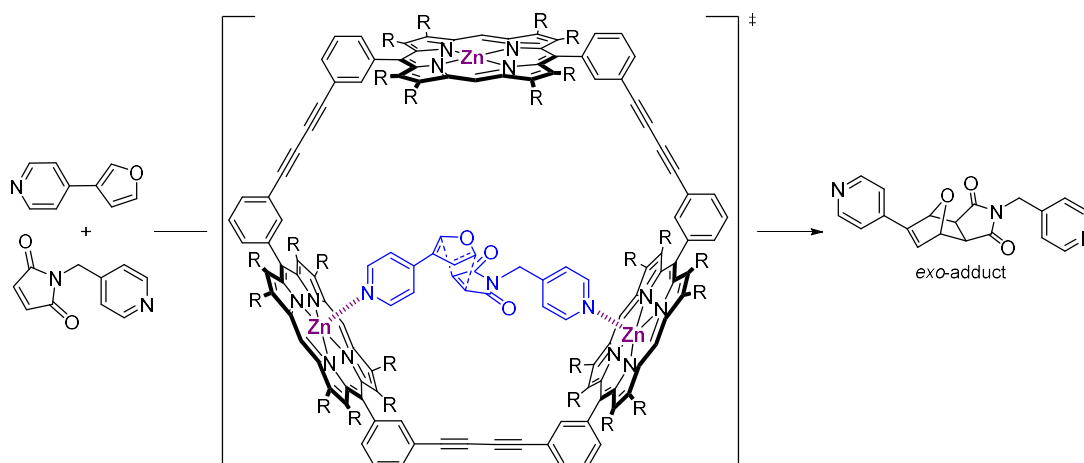


**Figure 2.** The binding of a metalloporphyrin derived from zinc to a pyridine derivative (top) and overarching principle for its integration in substrate-preorganization catalysis for a representative catalyst containing a zinc(II)-porphyrin site enabling molecular recognition of a pyridine-containing substrate (bottom).

## 2. Organo-Catalyzed Reactions.

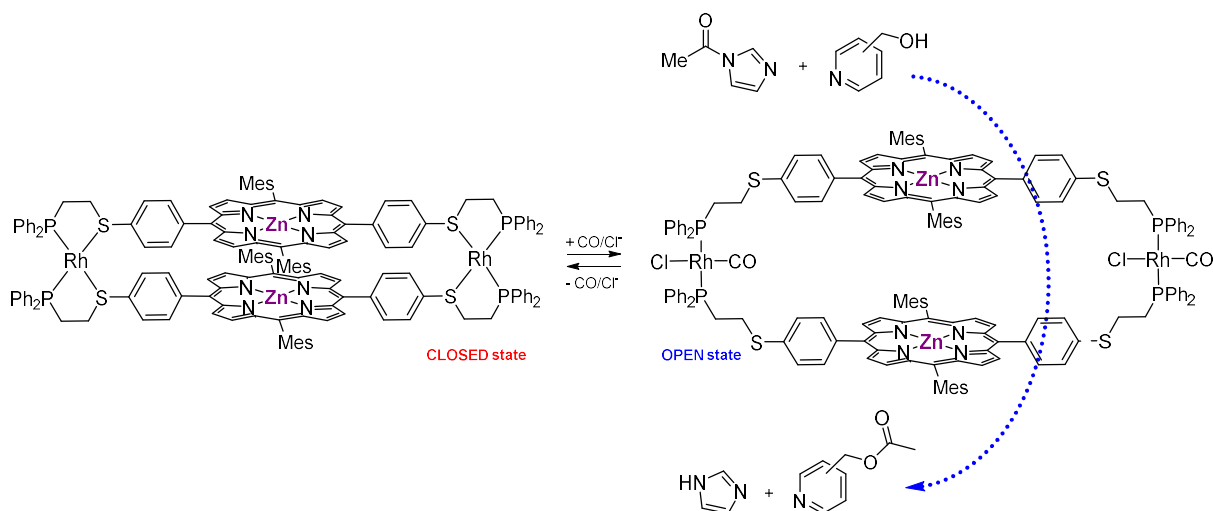
One of the earliest applications of metalloporphyrins as a substrate-recognition sites in catalysis was achieved by the Sanders group at the end of the 20<sup>th</sup> century (**Scheme 1**).<sup>[62-63]</sup> They designed trimeric zinc(II)-porphyrins featuring a cyclic structure in which the metalloporphyrins were connected by alkyne spacers. The resulting cavity contained three zinc centers able to bind to nitrogen-containing substrates and bimolecular organic transformations such as Diels-Alder and acyl transfer reactions were studied within these systems.<sup>[64-69]</sup> The uniqueness of this catalytic approach is that the binding of the two different reagents inside the zinc-containing nanoreactor occurs in such a way that accessing the transition state is highly favored. In other words, the system is designed to resemble the transition state of the reaction upon binding the reagents at a precise distance and a given geometry. As such, the transformations only take place when both reagents are confined and pre-organized within the catalyst in a similar manner as it is found in natural enzymes. The Diels-Alder reactions involving pyridine-containing reagents led to a reversal of the classical selectivity observed for these transformations, being the *exo*-adduct product mainly formed and significantly reducing the formation of the kinetically favored *endo*-adduct. In the case of acyl transfer transformations between alcohol-containing pyridines and acyl-imidazoles, increased reaction rates were achieved when compared to the bulk reaction. The increased reaction rates observed (up to accelerations of more than 1000-fold) were rationalized not only by the substrate pre-organization but also by the high effective substrate concentration inside the cavity. Although simultaneous binding of

two same reagents (i.e. the dienophile) is feasible, the cavity acts as an "entropic trap" in which only the transformation occurs when the two different reagents are present at the same time. This is advantageous because the binding of non-desired intermediates is reversible and leaves the system to undergo catalysis when the desired intermediates form.

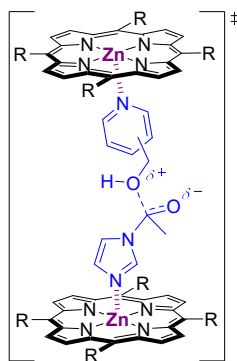


**Scheme 1.** Zinc(II)-porphyrin-derived tricyclic nanoreactor for application in stereoselective Diels-Alder with pyridine-containing substrates.

In 2006, Nguyen, Mirkin and co-workers designed a square-shaped bis-zinc(II)-porphyrin system in which two flexible rhodium-containing fragments were incorporated in two facially-opposed sides (**Scheme 2**).<sup>[70]</sup> The peripheral rhodium sites are responsive to external chemical stimulus because depending on the presence or absence of CO/Cl<sup>-</sup> the coordination geometry switches from a *P,S-cis*-chelate species to a *trans-P,P*-species, thereby leading to a closed or an open molecular box. The change between these two states makes possible to study the reactivity inside the molecular box since the two zinc(II)-porphyrin moieties accommodate nitrogen-containing substrates that are prone to react in acyl transfer transformations. Consequently, the open state system displayed enhanced reactivity compared to the closed system in the formation of the 4- and 3-(acetoxymethyl)-pyridine respectively, whereas no reactivity was observed for the 2-regioisomer. Besides the substrate-selectivity encountered, this system might be regarded as a supramolecular allosterically-regulated catalyst, since the reactivity is controlled by the remote coordination geometry around rhodium which is placed more than ten chemical bonds apart from where the reaction takes place. Later, it was demonstrated that metal-organic frameworks (MOFs) containing zinc(II)-porphyrin as constituents led to analogous observations provided that the distance between both zinc(II)-porphyrin moieties was enough to accommodate the key transition state for these acyl transfer reactions (**Figure 3**).<sup>[71-72]</sup> Indeed, the catalysis within these zinc(II)-porphyrin-containing MOFs led to a >2400-fold rate enhancement compared to the reaction without a catalyst. Just recently, similar observations on acyl transfer catalysis with nitrogen-containing substrates were encountered in discrete, zinc(II)-porphyrin-based metal-organic cages.<sup>[73]</sup>

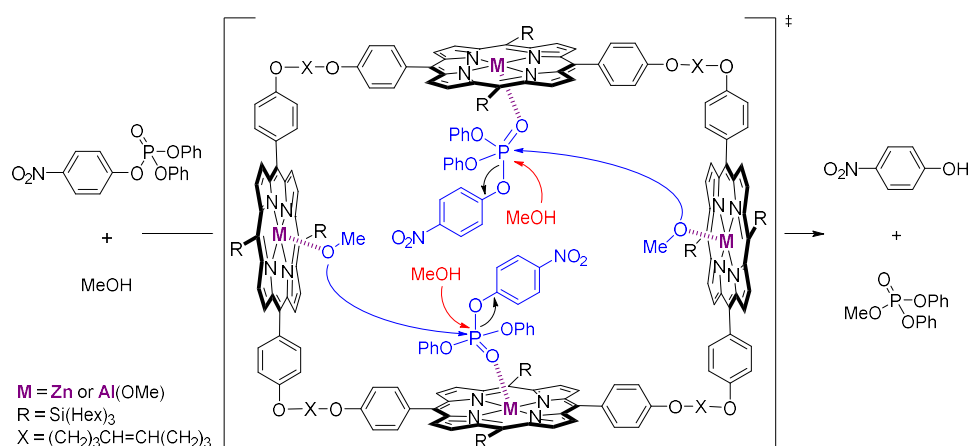


**Scheme 2.** Allosteric control in a dimeric zinc(II)-porphyrin-based supramolecular catalyst for acyl transfer reactions enables substrate-selectivity.



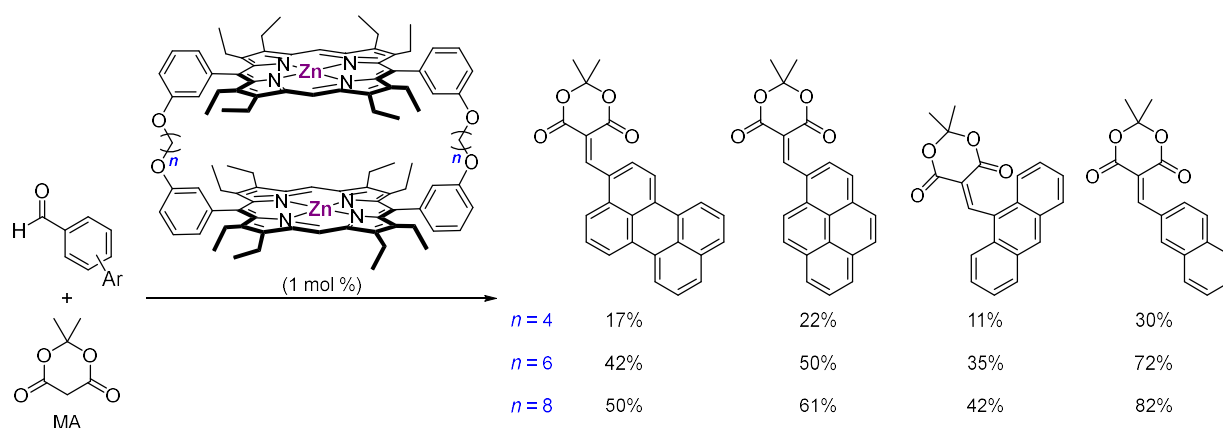
**Figure 3.** Accommodation of the transition state between two zinc(II)-porphyrins for the catalyzed acyl transfer reaction between pyridylcarbinol and *N*-acylimidazole.

Hupp, Nguyen and co-workers reported in 2012 a cyclic, tetrameric metallo-porphyrin system that displayed a high catalytic activity in the methanolysis of phosphate triesters.<sup>[74]</sup> It was found that a distinct mechanism was likely taking place depending on the nature of the cation inside the porphyrin (**Scheme 3**). Whereas in the case of zinc, the methanol reagent is not activated, in the case of aluminum, the methanol becomes more nucleophilic, being the catalytic reaction >400 times faster than the uncatalyzed reaction. As such, not only the pre-organization of substrates within the cavity but also an increased nucleophilicity are at play in this case.



**Scheme 3.** Cyclic tetrameric metalloporphyrins as supramolecular catalysts for the methanolysis of phosphate triesters. Blue arrows indicate the postulated mechanism operating for the most active aluminum-based catalyst while red arrows concern the less reactive zinc-based catalyst.

In 2017, Rath and co-workers studied the influence of the size of cyclic zinc(II)-based bis-porphyrins in the catalytic Knoevenagel condensation between polycyclic aromatic aldehydes and active methylene compounds (**Scheme 4**).<sup>[75]</sup> In depth UV-vis, NMR spectroscopy and X-ray studies indicated that the length of the linkers between the two zinc(II)-porphyrin moieties controls the different type of substrate encapsulation inside the cavities. For instance, the compound in which the porphyrins are linked by a C4 chain leads to species in which a single polycyclic aromatic aldehyde is trapped by  $\pi$ - $\pi$  stacking. A larger system comprising a C8 chain favored the encapsulation of two polycyclic aromatic aldehydes by coordination of the carbonyl group of each molecule to a different zinc(II) centre *via*  $\text{C}=\text{O} \cdots \text{Zn}$  binding. On the other hand, the C6-containing derivative led to encapsulation of two substrates but without  $\text{C}=\text{O} \cdots \text{Zn}$  binding. Such difference of substrate encapsulation inside these zinc(II)-porphyrins was highlighted in the different catalytic trends observed for the transformation of 3-perylenecarboxaldehyde, 1-pyrenealdehyde, 9-anthraldehyde, and 2-naphthaldehyde respectively, under Knoevenagel conditions with Meldrum's acid (MA). By using 1 mol% of cyclic zinc(II)-based bis-porphyrin the catalytic transformations followed an increase of reactivity upon increasing the chain length between the two zinc(II)-porphyrin sites, being the highest reactivity observed for the one bearing a C8 chain (**Scheme 4**). Similar observations were observed using 1,3-dimethylbarbituric acid in place of MA as well as with other polycyclic aromatic aldehydes such as 9-phenanthrenecarboxaldehyde, 1-naphthaldehyde, 6-methoxy-2-naphthaldehyde or indole-3-carboxaldehyde. On the other hand, there was no such a supramolecular control of reactivity observed when employing benzaldehyde or aliphatic aldehydes (i.e. cyclohexanecarboxaldehyde, isobutyraldehyde), thereby suggesting the uniqueness of polycyclic aromatic aldehydes for these type of supramolecular catalysis.

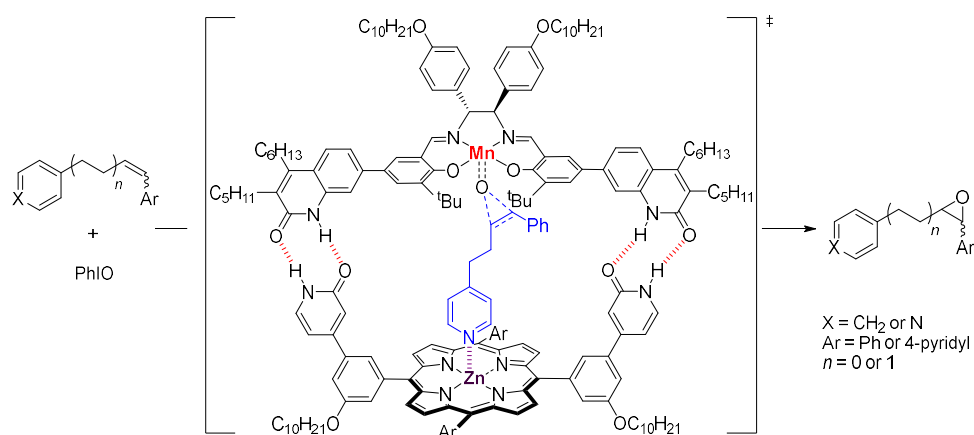


**Scheme 4.** Cyclic dimeric zinc(II)-porphyrins acting as supramolecular catalysts for the Knoevenagel reaction of polycyclic aromatic aldehydes with Meldrum's acid (MA).

### 3. Metal-Catalyzed Reactions.

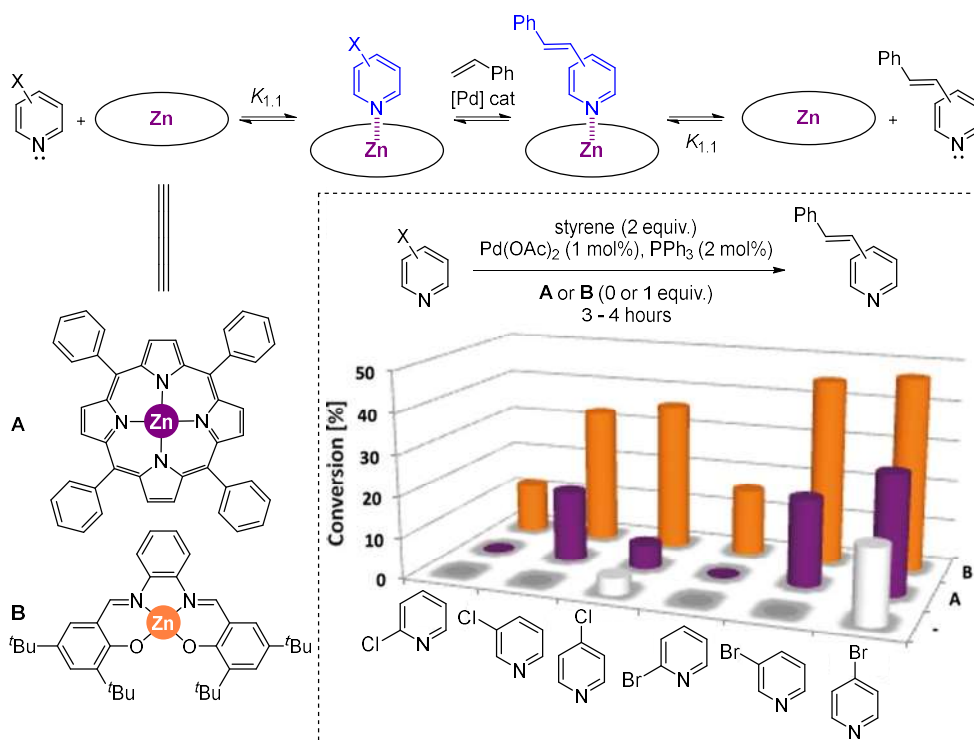
Metal-catalyzed processes have also been studied while exploiting the substrate-recognition properties of metalloporphyrins. In this context, it is relevant to emphasize that a major issue on metal-based catalysis is that polar, strongly-coordinating functional groups in the substrates might behave as inhibitors because they can over-coordinate the metal catalyst leading to inactive systems.<sup>[76-79]</sup> On the other hand, this strongly-coordinating functional groups can be utilized as molecular handles to reversibly bind to a substrate-recognition site in an appropriately-designed supramolecular catalyst.<sup>[42-46]</sup> In this vein, Wärnmark and co-workers developed a supramolecular version of the Jacobsen–Katsuki catalyst.<sup>[80-83]</sup> A manganese(III)-based salen catalyst was substituted with 2-quinolone motifs in the second coordination sphere that underwent hydrogen bonding with 2-pyridone moieties grafted in a zinc(II)-porphyrin backbone (**Scheme 5**). In this way, the zinc(II)-porphyrin unit behave as a potential substrate-recognition site for binding pyridine derivatives *via* kinetically labile Zn<sup>II</sup>–N interactions whereas the active manganese site remains available to perform oxidation reactions. This approach was successfully applied in the epoxidation of olefins comprising a 4-pyridyl substituent. These substrates reacted faster than those comprising no nitrogen atoms with an estimated selectivity of 1.66. This modest substrate selectivity was explained by the fact that only 70% of the manganese unit was involved in the formation of the hydrogen-bonded system. Additional control experiments as well as competition ones revealed that the catalysis was occurring at the inside of the self-assembled catalyst. On the other hand, the formation of homodimers resulting from self-assembly of the manganese-based site and the zinc-based site, respectively, compete with the formation of the expected heterodimer species (the supramolecular catalyst) owing to the dynamic nature of the hydrogen bonding system. In addition, formation to some extent of undesired oligomeric aggregates could not be ruled out. These self-assembly issues were in part circumvented by designing a supramolecular catalyst in which both the catalytically active site and the substrate-recognition site comprised a covalently-linked strap around them that sterically hamper external binding of the substrate, thus limiting unselective catalysis outside of the cavity.<sup>[84]</sup> A chromium-based version at the place of manganese has been reported although no catalytic activity is known at this stage.<sup>[85]</sup>





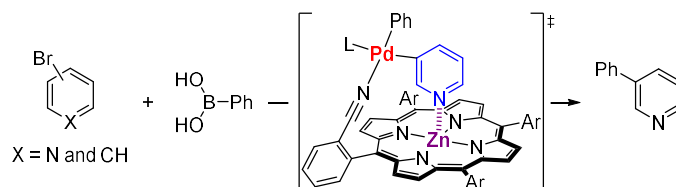
**Scheme 5.** A zinc(II)-porphyrin-based supramolecular manganese catalyst applied in substrate-selective epoxidation exploiting remote  $\text{Zn}^{\text{II}}\cdots\text{N}$  interactions. Intermolecular hydrogen bonds are indicated by red dashed lines.

In 2017, our group reported carbon-carbon bond-forming reactions in which halopyridine substrates were selectively bound to zinc(II)-containing scaffolds *via*  $\text{Zn}^{\text{II}}\cdots\text{N}$  interactions whilst a trivial palladium/triphenylphosphine catalytic system was operating (**Figure 4**).<sup>[86]</sup> Zinc(II)-porphyrin **A** and zinc(II)-salphen **B** were employed in this study as they led to different type of binding with the halopyridine substrates. For instance, no binding occurred between **A** and *ortho*-halosubstituted pyridines due to steric shields. On the other hand, the binding of **B** towards halopyridines was typically 2-3 orders of magnitude higher than using **A** (*ca.*  $10^6 \text{ M}^{-1}$  with **B** vs *ca.*  $10^3 \text{ M}^{-1}$  with **A**). These remarkable difference of substrate binding was roughly correlated with the reactivity of these substrates encountered in palladium-catalyzed Mizoroki-Heck reactions with styrene. The stronger the substrate was bound to the zinc-scaffold, the higher reactivity was observed. This was explained by the unfavorable formation of pyridine-over-coordinated palladium species, which are catalytically unproductive in this case. A less pronounced effect was observed in Suzuki-Miyaura reactions between halopyridines and phenylboronic acid. Overall, the active phosphine-ligated palladium species remained catalytically active provided that the halopyridine substrates are bound to the zinc scaffold.



**Figure 4.** Remote Zn<sup>II</sup>...N interactions at work to control the reactivity of halopyridines in palladium-catalyzed cross-coupling reactions.

Later, a supramolecular ligand derived from a zinc(II)-porphyrin equipped with nitrile groups in the *ortho* position of the *meso* phenyl rings was synthesized and studied in palladium-catalyzed Suzuki-Miyaura reactions between bromopyridines and phenylboronic acids (**Scheme 6**).<sup>[87]</sup> The nitrile groups were engaged in the coordination of the catalytically active palladium ions whereas the zinc(II) centre was available to bind pyridine substrates. Interestingly, in depth characterization studies indicated that the remote binding of nitriles to palladium increased the association strength between the zinc and the pyridyl nitrogen, thereby featuring an allosteric effect reminiscent from enzymes. The application of this supramolecular catalyst in substrate-selective catalysis was evidenced by an increase in the kinetics associated to the *meta*-bromopyridine substrate without altering the kinetic trends observed for the other regioisomers (i.e. *ortho*- and *para*-bromopyridine). *In situ* competition experiments between bromobenzene and *meta*-bromopyridine as the substrates revealed a two-fold increase of reactivity for the pyridine substrate compared to the same experiment carried out in the absence of the ligand. Replacing the Zn(II) center by other metals such as Cu(II) or Ru(II)CO led to poor substrate-selective catalysts due to the absence of substrate binding in the first case and due to the high kinetic stability of the substrate-to-ruthenium assembly in the second case.

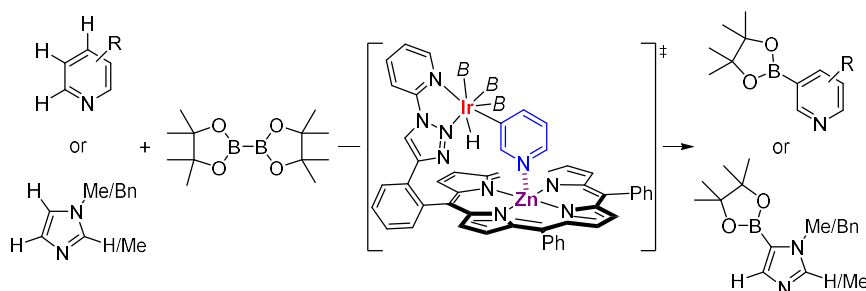


**Scheme 6.** A supramolecular palladium catalyst enabling substrate-recognition *via* remote Zn<sup>II</sup>...N interactions. Ar = 2-CN-C<sub>6</sub>H<sub>4</sub>, L = acetate or other ligand.

In 2021, a similar approach was implemented for the challenging iridium-catalyzed C-H bond borylation of pyridines (**Scheme 7**).<sup>[88]</sup> The supramolecular catalyst featured a zinc(II)-porphyrin site enabling the binding of pyridine derivatives *via* Zn<sup>II</sup>–N interactions and a peripheral iridium-based *N,N*-chelating site. Although the substrate recognition site and the catalytically active site are wide apart by nine chemical bonds, the ideal geometry and distance makes possible to reach exclusive C-H bond activation in the *meta* position of pyridines and  $\beta$  position of imidazoles. The high selectivity of the system was apparent by the lack of formation of *ortho* and *para* regioisomers. Kinetic and in situ NMR studies established the following peculiarities:

- (1) the resting state of the catalysis did not involve pyridine coordination to iridium, but rather a simultaneous pyridine coordination to zinc and formation of iridium-chelated tris-boryl species;
- (2) the reaction was first order in pyridine substrate, that contrasts to the zero order encountered using a non-supramolecular catalyst;
- (3) there was no product inhibition, thus suggesting that the supramolecular iridium catalyst has a binding preference for the substrate rather than the product;
- (4) the catalysis followed the Michaelis-Menten rate law equation, and
- (5) *ortho*- and *para*-substituted pyridines were unreactive, a feature that was exploited in substrate-selective catalysis.

In addition, it was possible to exploit this supramolecular system in dormant reactivity as pyridinium salts were reactive only upon addition of a base (external chemical stimuli) at a given time.



**Scheme 7.** A supramolecular iridium catalyst with a molecular recognition site for aza-containing substrates enables selective C-H bond borylations. B = (pinacolato)boron.

#### 4. Conclusion and Perspectives.

In summary, the substrate-recognition properties of metalloporphyrins in catalysis have been studied rarely compared to other motifs featuring hydrogen bonding or ion pairing. Nevertheless, a strong pre-organization of nitrogen- or oxygen-containing substrates has already led to interesting reactivities occurring in the peripheral side of the porphyrin. As such, the introduction of catalytically active sites at an atom-precise distance from the porphyrin substrate recognition site might be relevant to tackle reactivity and selectivity issues currently existing in chemical synthesis.<sup>[89-92]</sup> Moreover, this supramolecular approach appears intriguing to implement enzymatic features in abiological catalysis. Since synthetic methodologies enabling the access of highly elaborated metalloporphyrins in a straightforward manner are available nowadays, new progress exploiting the substrate-recognition properties of metalloporphyrins could be anticipated.<sup>[93]</sup> Overall, this review showcases that there is much knowledge to be explored beyond the *more classical* reactivity associated to the metal embedded in the porphyrin core.<sup>[94-100]</sup>

## 5. Acknowledgements.

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- [33] The template strategy relies on building blocks that contain multiple orthogonal binding sites: the central building block contains the active site for catalysis, while other binding sites facilitate the

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## **7. Biography.**

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Rafael Gramage-Doria received his PhD from the University of Strasbourg (France) under the supervision of Dominique Matt and Dominique Armpach. After postdoctoral research with Joost N. H. Reek at the University of Amsterdam (Netherlands) and later with Takashi Ooi at Nagoya University (Japan), he was appointed CNRS senior researcher at the Institute of Chemical Sciences of the University of Rennes 1 (France), where he obtained his Habilitation diploma (2019). His research activities include transition metal catalysis for fine chemicals and green chemistry applications, C-H bond functionalization, supramolecular and coordination chemistry, and supramolecular and bio-inspired catalysis.

