Chemical reactions controlled by remote Zn ... N interactions between substrates and catalysts

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Abstract, for electronic version only: Besides largely implemented hydrogen bonding or ion pairing, reversible Zn···N interactions have appeared as a promising type of kinetically labile interaction to control the reactivity of chemical reactions. Importantly, they have already been exploited in both organocatalysis as well as transition metal catalysis enabling unique selectivities as well as increasing catalyst lifetimes. A summary of these achievements is highlighted in this chapter.

Keywords, for electronic version only: supramolecular chemistry, homogeneous catalysis, transition metals, Zn···N interactions, selectivity

1. Introduction

Homogeneous catalysis is an enabling technology for the sustainable synthesis of daily-relevant chemicals in our society.[1] Typically, small molecules, either organic ones for organocatalysis[2,3] or inorganic ones for metal catalysis,[4] have served to accelerate reactions and control the selectivity for those cases where multiple products can form. Consequently, different reactivities and different selectivities can be reached by fine-tuning of the catalysts, enhancing the stability of the catalytic system as well. In the last decades, the merger of supramolecular catalysis, that is the implementation of strategies based on supramolecular chemistry into chemical catalysis, has shown a tremendous impact in contemporary research.[5] The toolbox offered by supramolecular systems provides new possibilities to address challenges difficult or impossible to tackle with more classic catalysts. These tools are versatile and mainly inspired from the multiple action modes encountered in enzymes, which are Nature's catalysts. Enzymes enabled catalysis to occur under relatively mild reaction conditions with high robustness and activity mainly because the catalytically active site is well protected in hydrophobic pockets.[6] Such feature has inspired scientists to design and study chemical catalysis in confined spaces, generated by covalent chemistry, non-covalent chemistry or coordination chemistry.[7-8]

In addition, enzymes can access key transition states and intermediates by lowering specific energetic pathways which is at the origin of their exquisite selectivity.[9] In fact, multiple reversible interactions mainly based on non-covalent hydrogen bonding fix the substrate around the active site in a given geometrical conformation, thus lowering its degree of freedom and pre-organize it to reach a precise selectivity.[10] Another specificity of enzymes, is the high affinity they have for substrates with respect to the products, which translates into enhanced reaction rates as the products are straightforward released from the active site.[11] As such, kinetically labile interactions have been explored in the design of man-made catalysts for generating new ligands by self-assembly as well as for substrate pre-organization due to ligand-to-catalyst binding.[12-13] The most developed non-covalent interactions so far studied in these directions are hydrogen bonding[14] and ion-pairing,[15] respectively.

In supramolecular chemistry, metalloporphyrins are pivotal building blocks that lead to new dimensions and chemical space owing to their ability to apically bind to nitrogen-containing building blocks (**Figure 1**).[16] Such level of supramolecular engineering has been applied to different fields, being particular relevant for physics (energy or charge transfer, photovoltaics) and materials sciences (molecular tectonics, oligomerization, polymerization, etc.).[17-19] The most studied interaction in this context is likely the one involving the binding of pyridine derivatives to zinc(II)-porphyrins, in which the zinc cation evolves from (almost perfect) square planar geometry to (slight distorted) square pyramidal (**Figure 1**). This type of interaction which is *stricto sensu* a coordination bond, but shares with the previously-described non-covalent interactions the reversible nature of the bonding. Depending on the stereoelectronic properties of the pyridine and the zinc(II)-porphyrin derivative, this Zn···N interaction can be weaker or stronger, which results in a panel of different association constants $K_{1.1}$ =

10^2-10^6 M^{-1} in general,[20-21] which are routinely measured with conventional NMR and/or UV-vis titration techniques.[22] These values are comparable to those observed for instance with those found in hydrogen bonding, which are used in chemical catalysis.

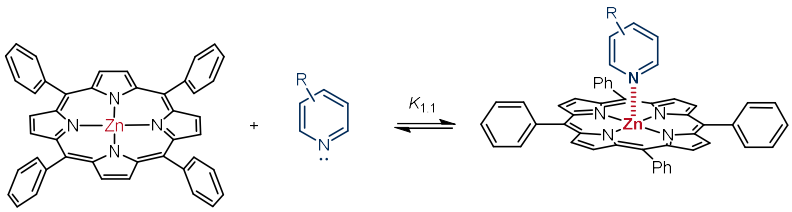

Figure 1. The binding of pyridine derivatives to zinc(II)-porphyrin derivatives is kinetically labile.

2. Organic reactions.

Consequently, the exploitation of Zn···N interactions for controlling the activity and the selectivity of chemical reactions appeared promising as it was shown in the 90's with the pioneering studies from the Sanders group (**Figure 2**).[23,24] They reported a number of trimeric zinc(II)-porphyrin macrocycles that served as Diels-Alderases for pyridinic substrates, with the overarching idea that the intermediates of the reaction will be accessible *via* simultaneous Zn···N interactions inside the macrocyclic structure. Because the systems were designed to fit better the transition state than the substrates and products, enhanced reaction rates and a switch in the stereoisomerism (*exo versus endo*) of the products were observed (**Figure 2A**).[25-28] A catalytic version was developed for acyl transfer reactions between nitrogen-containing reagents (**Figure 2B**).[29] These action modes mimic the tight binding of the transition state encountered in enzymes.[23,24] Later, Nguyen and co-workers reported related catalytic versions for the acyl transfer reactions but using a dimeric zinc(II)-porphyrin macrocycle that allosterically switches on/off between open and closed conformations, the former conformation exhibiting higher reactivity than the latter one (**Figure 3**).[30] Interesting substrate selectivity was observed as the 2-substituted pyridine derivatives reacted poorly with respect to the 3- and 4- isomers. Analogous observations were found when using metal-organic frameworks built up from zinc(II)-porphyrin scaffolds[31] and cyclic tetramers for the methanolysis of phosphate triesters.[32]

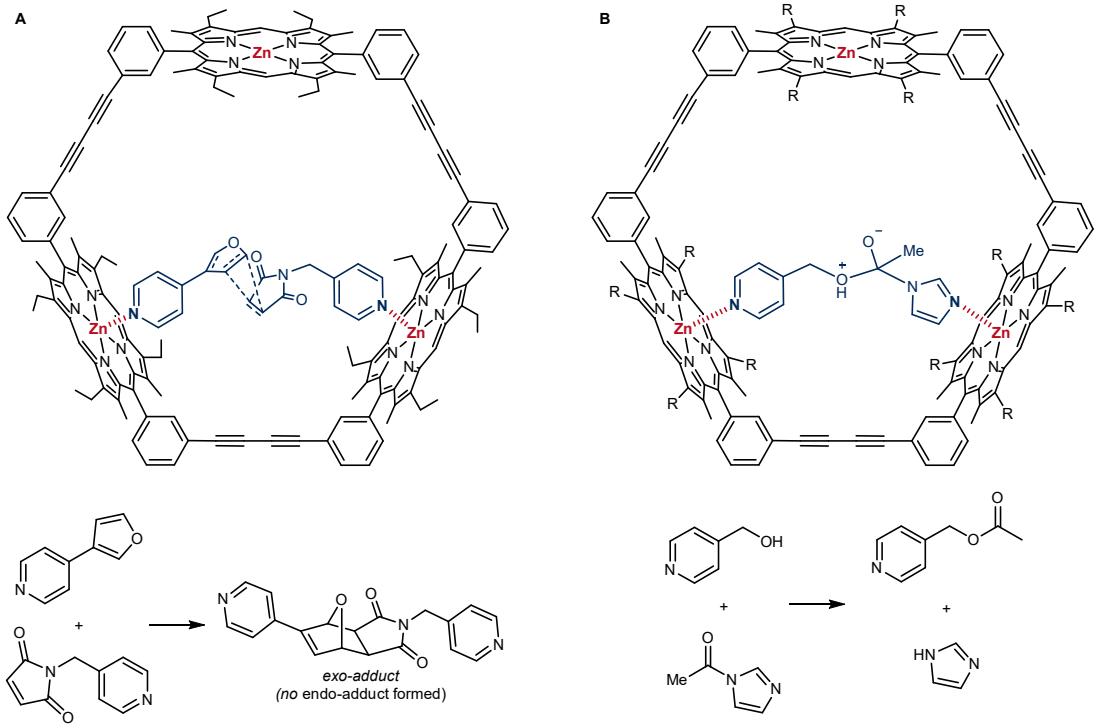

Figure 2. Sanders's pioneering zinc(II)-porphyrin-derived tricyclic Diels-Alderase (**A**) and its application in the acyl transfer reaction in a catalytic fashion (**B**) in which the pyridine-containing substrates react inside the cavity of the trimer.

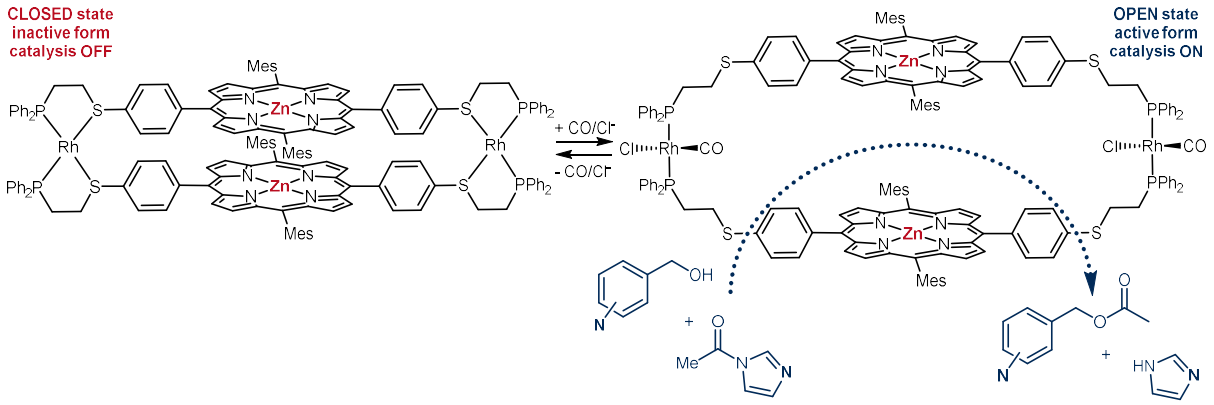

Figure 3. Nguyen's dimeric zinc(II)-porphyrin derivative displaying allosteric control of reactivity and substrate selectivity for acyl transfer reactions. Mes = mesitylene.

3. Transition metal catalysis

Transition metal catalysis has enabled the streaming access to compounds impossible or difficult to obtain by other means.[33-34] Indeed the combination of transition metal ions (which display multiple coordination numbers, geometries and oxidation states) with fine-tuned ligands displaying unique stereoelectronic features, offers a myriad of possibilities to tackle unprecedented challenges in terms of chemical reactivity.[35] In this context, ligands equipped with zinc(II)-porphyrins as the substrate recognition site have been rarely developed for transition metal catalysis. In principle, this type of ligands would enable labile Zn···N interactions with nitrogen-containing substrates, thus inhibiting to some extent the undesired over-coordination of the substrates (or the products) to active metal catalysts, which is a major concern in homogeneous catalysis.

In this respect, Warnmark and co-workers developed a first approach to transition metal catalysts equipped with a substrate recognition site comprising a zinc(II)-porphyrin (**Figure 4**).[36] The overarching idea was to achieve substrate selective catalysis, a concept reminiscent of enzymes, but difficult to implement in abiological catalysis.[37] The design was based on the combination of a substrate-receptor unit and a catalytically active site *via* hydrogen bonding between amide groups. The receptor unit was constituted by a zinc(II)-porphyrin equipped with peripheral 2-pyridone units and the active transition metal catalyst site (i.e. Jacobsen-type manganese epoxidation catalyst) with 2-quinolone units (**Figure 4A**). This strategy gave rise to a dynamic supramolecular catalyst expected to form a heterodimer assembly that was applied in substrate selective epoxidation reactions, in which the nitrogen-containing substrates reacted preferentially over the other ones not containing nitrogen atoms. The nitrogen-containing substrates were claimed to bind inside the generated pocket of the catalyst *via* Zn···N interactions whilst the epoxidation occurred in the olefinic site, that is, in a remote fashion (**Figure 4B**). However, due to the reversible nature in the formation of this supramolecular catalyst, different assemblies could not be discarded, such as dimers, trimers, oligomers or even co-polymers.[38,39] This difficulty prompted the design of more rigid supramolecular catalysts by introducing straps in the recognition as well as in the catalytically active site with the aim to suppress to some extent unselective catalysis occurring outside of the cavity.[40]

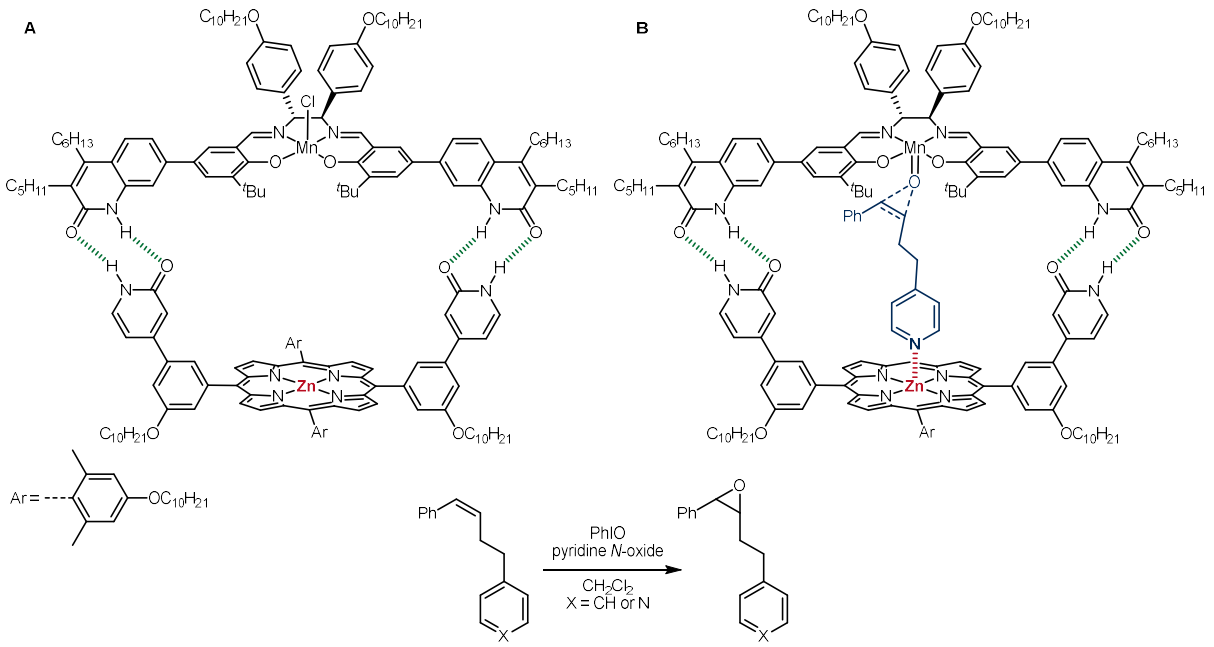

Figure 4. Warnmark's zinc(II)-porphyrin-based dynamic supramolecular manganese catalysts featuring substrate selectivity in epoxidation reactions *via* remote Zn···N interactions between the catalyst and the substrate (**A**) and the corresponding postulated transition state (**B**). Green dashed lines indicate intermolecular hydrogen bonding.

In our laboratories, we have recently established a research line devoted to exploiting the substrate-recognition properties of porphyrins in transition metal catalysis with the aim to tackle issues difficult to address with traditional stereoelectronic ligand modification. In 2017, we showed that palladium-catalyzed cross-coupling reactions with halopyridine derivatives are controlled by the presence (or absence) of zinc(II)-containing scaffolds.[41] Indeed, easily-accessible zinc(II)-porphyrin **A** and zinc(II)-salphen **B** were used, respectively, for Mizoroki-Heck reactions between chloro- and bromo-pyridines with styrene. In the presence of these zinc(II)-containing scaffolds higher yields and higher reaction rates were obtained in these cross-coupling reactions except for the combination of the 2-halopyridine derivatives and zinc(II)-porphyrin **A**, in which no binding event occurs due to steric shields. The yields and reaction rates were roughly correlated with the binding strength between the zinc(II)-containing scaffolds and the halopyridines, being higher with the zinc(II)-salphen **B** than with zinc(II)-porphyrin **A**. A less pronounced effect was found in Suzuki-Miyaura cross coupling reactions between the halopyridines and phenyl boronic acid in the presence of **A** (**B** was found unstable under the reaction conditions). Importantly, the active palladium catalyst was the same in all the cases, i.e. $Pd(OAc)_2/PPh_3$, which clearly shows that the reactivity of a trivial palladium catalyst can be indirectly controlled by this remote Zn···N interaction, even at high temperatures (80 ºC). In other words, the zinc(II)-containing scaffolds inhibit to some extent the undesired pathway of over-coordination to palladium by the pyridine derivatives (substrates and/or products). Such observations were made possible only in the presence of one equivalent (at least) of the zinc(II)-containing scaffold using the non-coordinating toluene as the solvent.

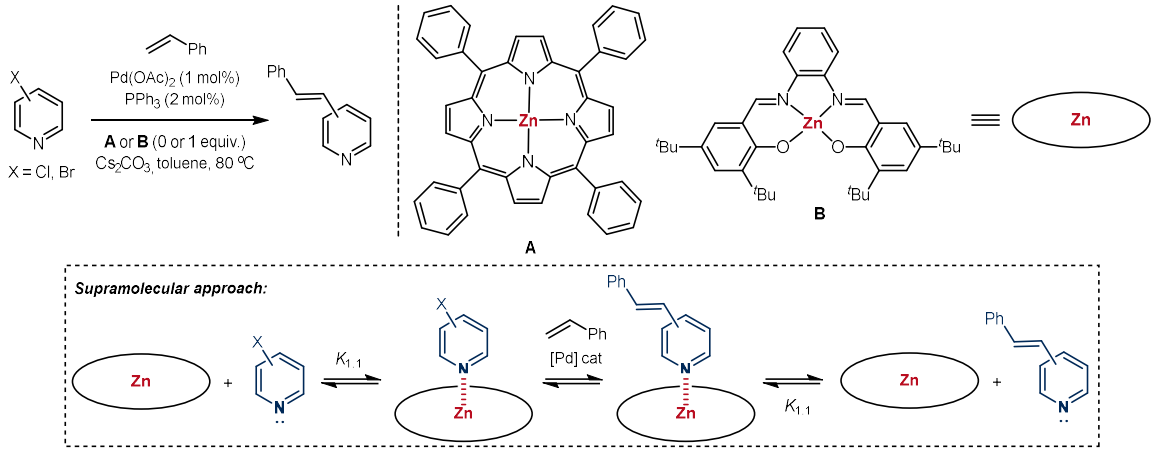

Figure 5. Palladium-catalyzed cross-coupling reactions with halopyridine derivatives controlled by remote Zn···N interactions.

In subsequent studies, we were attracted to the design of a truly catalytic system, that is, the incorporation of the active palladium site to a ligand comprising a substrate recognition site build around a zinc(II)-porphyrin.[42] As such, we synthesized in a single-step operation porphyrin **L** that is appended with nitrile groups in the *ortho* position of the *meso* phenyl groups. In this way, different metal cations (Zn, Cu, Ru) can be embedded in the porphyrin core, thereby changing the binding ability towards pyridine derivatives as substrates; whereas the nitrile groups are available for binding catalytically active palladium cations. From the many metals incorporated inside of the porphyrin, zinc(II) revealed the most pertinent for representative Suzuki-Miyaura reactions. With this supramolecular ligand (**L1**), a unique substrate-selectivity was observed since 3-bromopyridine as the substrate reacted preferentially with phenyl boronic acid over the 2- or 4-bromopyridine ones. In addition, the catalytic system displayed remarkable substrate selectivity even in the presence of bromobenzene in competition experiments. This is a complete reversal of reactivity when compared to classical palladium catalysts that do exhibit higher reactivity for bromobenzene. A careful assessment of the origin of this unique reactivity revealed that the ideal substrate pre-organization provided by the porphyrin pocket as well as the distance and geometry between the active site and the substrate-recognition site were key parameters on stabilizing the different intermediates from the catalytic cycle. Furthermore, in depth NMR and X-ray diffraction studies indicated that the binding of palladium to the nitrile groups increased the binding strength of the substrate to the zinc(II)-porphyrin. This is not a mere allosteric effect, but it also shows that it is possible to fine-tune the strength of the Zn···N interaction in a remote fashion through coordination chemistry.

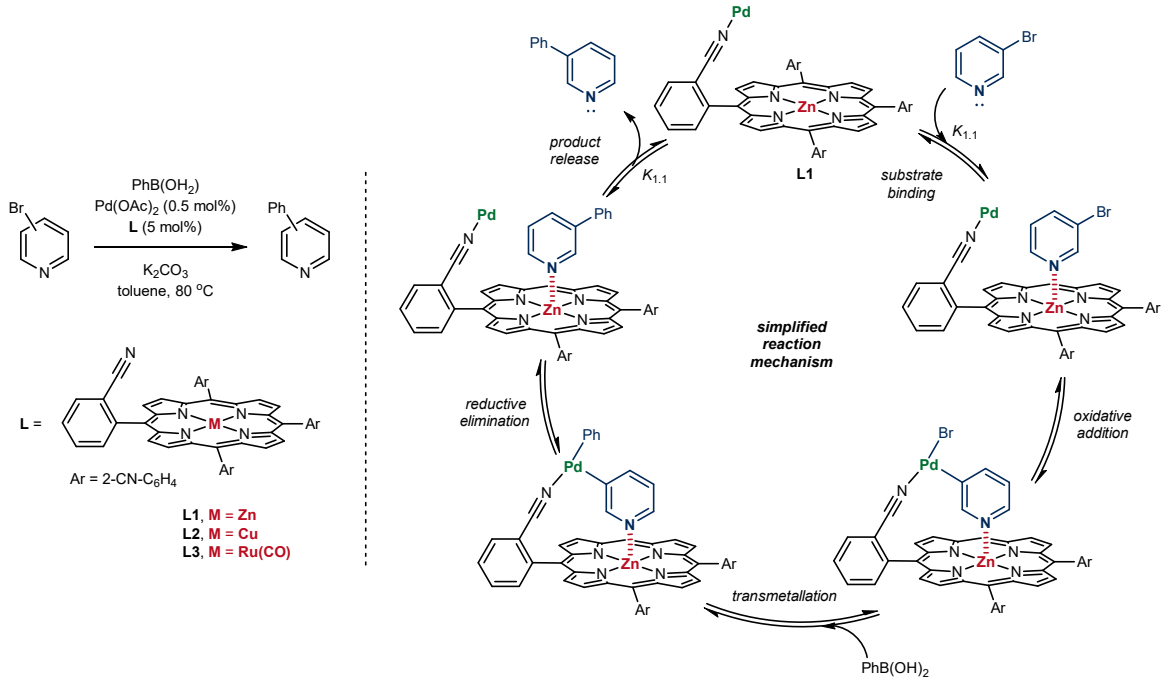

Figure 6. A supramolecular catalyst with a catalytically active palladium site and a substrate recognition site enabling Zn···N interactions between substrate and catalyst, together with the postulated catalytic cycle.

4. Conclusion

The last three decades have witnessed the birth and progress of the rational use of Zn···N interactions between substrates and catalysts in organic reactions as well as in transition metal catalysis. Although this type of interaction is rather unconventional compared to the ones more studied, i.e. hydrogen bonding, it has already shown that unique type of reactivities and selectivities can emerge. The interaction strength associated to Zn···N interaction is rather strong (when compared to a single hydrogen bond for example) and kinetically labile with non-coordinating solvents, even at high temperatures. All these aspects are relevant for future implementations. At this stage, this interaction has been exploited between pyridine derivatives as substrates and ligands (or catalysts) derived from zinc(II)-porphyrin or zinc(II)-salphen derivatives. Owing to the chemical robustness and synthetic versatility of these and other zinc(II)-porphyrinoids, many of them will be readily accessible for the generation of new supramolecular catalysts featuring Zn···N interactions. For instance, many zinc(II)-porphyrins containing metal-appended fragments are known,[43-46] but their substrate recognition properties in catalysis remains to be addressed, not to mention the possibilities to design novel ones. Overall, one would expect further developments to design supramolecular catalysts based on Zn···N interactions to mimic enzymatic features in man-made catalysts.

Acknowledgements

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