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ORGANOMETALLIC CATALYSIS WITHIN
SELF-ASSEMBLED SUPRAMOLECULAR
STRUCTURES

SETTORE SCIENTIFICO-DISCIPLINARE DI AFFERENZA: CHIM04

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“It is a sort of molecular sociology!”

Jean Marie Lehn in “Supramolecular Chemistry”, 1995

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1. INTRODUCTION

1.1 ENZYMES RULE!

First came Brønsted acids, as reported by Kirchhoff in 1812, who succeeded in decomposing starch into glucose by adding acid to a refluxing solution of the bio-polymer. Then Davy demonstrated in 1816 that platinum powder is an effective additive to produce water from hydrogen and oxygen. Berzelius, in 1835, went deeper in the work of Kirchhoff on starch and coined the term *catalyst* to indicate something that accelerates a chemical reaction. Finally Ostwald rose an articulated discussion on catalysis and, studying Gibbs considerations on thermochemistry, he came up with the theory of a complex formation between the catalyst and the substrate to form an intermediate that decomposes releasing the final product and the unmodified catalyst.¹ In the same years, biologists were discovering the natural version of this phenomenon and Schwann isolated the first enzyme- pepsin- in 1836. Berzelius was the first one to recognize the direct correlation between inorganic catalysts and enzymes and to understand that thousands of catalytic reactions take place in living systems.² Slowly this concept became universally accepted and now catalysis is considered a fundamental characteristic of life, while enzymes remain examples of excellence worth of imitation. Why did enzyme performance appear so unreachable for years? The answer is probably held within the multiple functions that they fulfill at the same time. They bring together the substrates in proper orientations within the active site; then they usually promote proton transfers from and to the substrate by means of acid and basic groups present in the active site. The pre-orientation of the substrate and its interaction with the protein surface is of primary importance for the catalysis and is ensured by a network of non-covalent interactions spanning from hydrogen bonds to much weaker Van der Waals forces. In addition to these, covalent interactions may also take place between the substrate and groups within the enzyme (usually nucleophilic groups) to form structures that are more reactive than those originally present in the substrate.

Moreover, the protein often surrounds the substrate to hold it in an organic pocket where hydrophobic forces take place. Most enzymes are also able to make small readjustments of their tridimensional structure to provide good complementarity to the substrate and especially to the transition state, following the *induced fit* mechanism. This means that the traditional idea of the *key-lock* principle should be modified in favor of a more sophisticated model in which the lock changes its conformation with the entrance of the key, providing a best binding compared to the very initial enzyme-substrate complex. After the reaction, the enzyme recovers its original conformation as a consequence to new weak interactions occurring between the binding pocket and

the product structure and is ready to accommodate again another substrate molecule. In some cases this conformational change involves a whole enzyme domain, as for aspartate aminotransferase, for which all the hydrophobic side chains of the aminoacids next to the active site are packed towards the substrate to enhance the hydrogen bonds and the electrostatic interactions between the charged groups of the substrate molecule and the aminoacids residues around it (Figure 1). Other enzymes experience a minor distortion, involving just a single side chain or a limited part of a secondary structure.

Finally, the enzyme may be able to induce strain or distortion in the substrate to facilitate the reaction of a defined portion of the molecule contributing to the chemo-, regio- and stereoselectivity of the reaction.

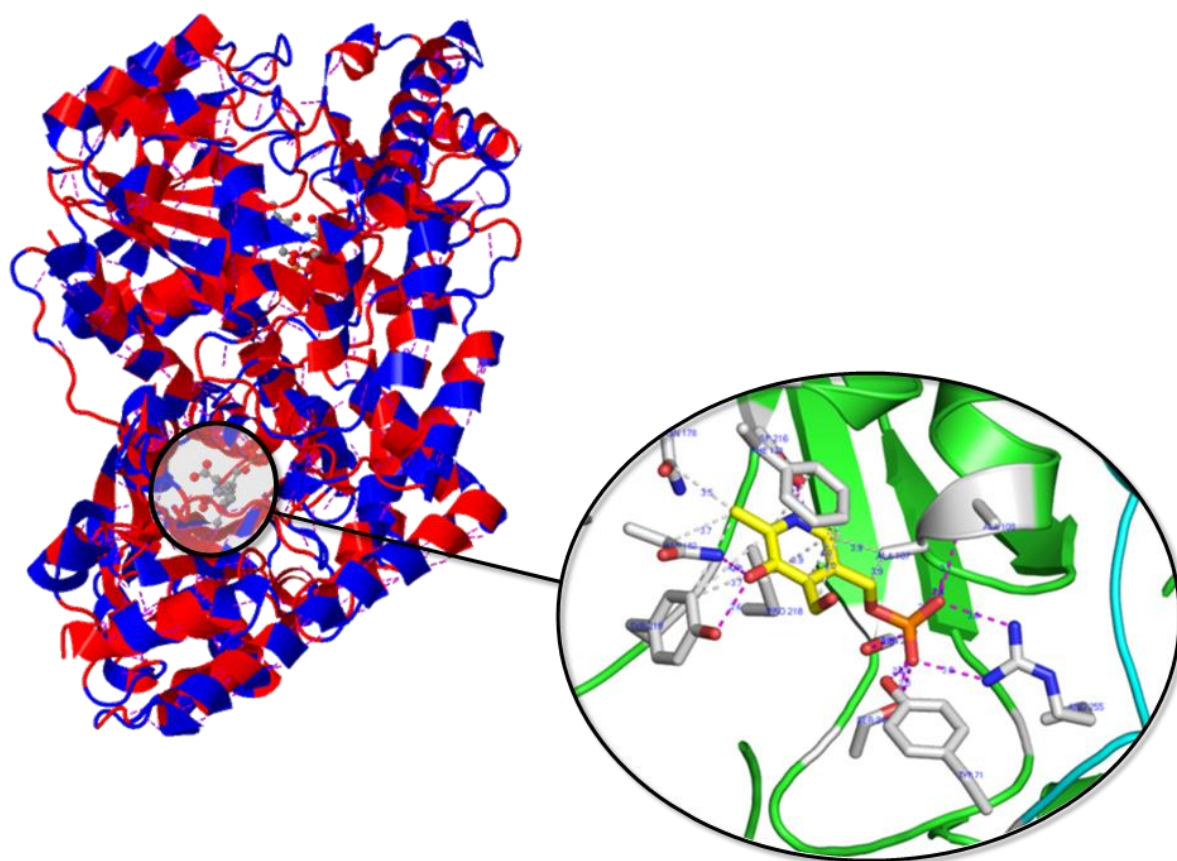


Figure 1: the crystal structure of *escherichia coli* aspartate aminotransferase, a dimeric enzyme that facilitates the conversion of aspartate and alpha-ketoglutarate to oxaloacetate and glutamate (and vice-versa) is represented on the left. The active site of this enzyme is completely based on non-covalent interaction between the peptide scaffold and the cofactor, that have the capacity to bind the substrate. Hydrophobic parts are rendered in red, while the blue color belongs to hydrophilic groups. The circular zoom on the right shows the active site with the coenzyme pyridoxal phosphate PLP (yellow sticks) interacting *via* electrostatic forces and H-bonds (dotted lines) with aminoacidic residues provided by both chains in the dimer (rendered in grey sticks). Residue Tyr 72, at the bottom part of the figure, comes from the other chain and interacts with the phosphate group of PLP. The aldehyde group of the cofactor PLP reacts readily and reversibly with amino acids to form Schiff bases which react further to give products.

All these tasks are assolved by the same molecule and therefore we shouldn't be surprised if a single enzyme can implement more than 2500 amino acids residues; an enzyme constitutes definitely a complete microenvironment comprehending a surface complementary to that of the substrates (especially of the transition state of the reaction) connoted by a certain rigidity imparted by the complex protein backbone.

It is evident the challenge in artificially reproducing such a complex machine that took ages to evolve to this stage, but it seems that the key for the success resides in cooperation between multiple weak forces instead of one strong covalent bond. The impressive structure of enzymes suggests the need of large surfaces of interaction between the catalyst and the reagents, beyond the high affinity with the active site, to obtain better and better selectivities. Biochemistry is thus changing the way of thinking a catalyst encouraging the use of innovative strategies such as supramolecular ligands, micellar aggregates, hydrogen-bonded structures and metal-ligand scaffolds (Figure 2) to complement traditional highly active catalysts, imparting additional selectivity.

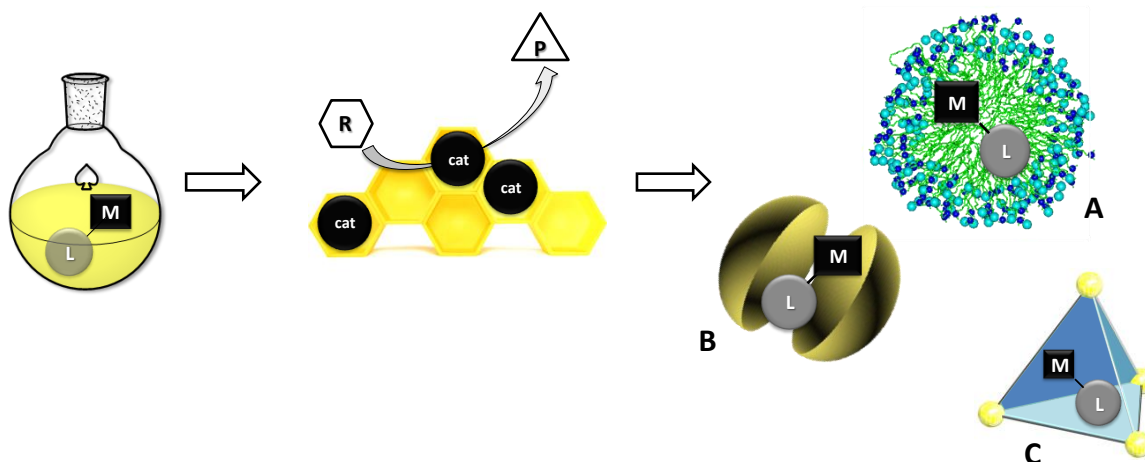


Figure 2: evolution of organometallic catalysis. Organometallic catalysts of increasing complexity used in solution were further improved by anchorage to a support to facilitate recovering and to impart changes in activity and selectivity. A step further is constituted by new micro- and nanostructures surrounding the organometallic complex like a *second-sphere* ligand to mimic enzymes' peptide backbones. Examples of this new trend in catalysis are A) micelles, B) capsules and cavitands held together by non-covalent interactions and C) metal-ligand based capsules.

1.1.1 SUBSTRATE SELECTIVE SUPRAMOLECULAR CATALYSTS

In living systems, chemical reactions must proceed with high specificity in order to control the concentration of certain compounds within a complex mixture of molecules. Every molecular structure is deputed to a certain role and often enzymes must select a certain reagent among several others all bearing the same functional

groups. This means that biological catalysts are extremely selective not only on products but, unlike traditional organometallic catalysts, also on substrates. Natural catalysts are therefore able to pick the right reagent among others and this peculiarity is crucial when considering the elaborated cellular matrix (Figure 3).

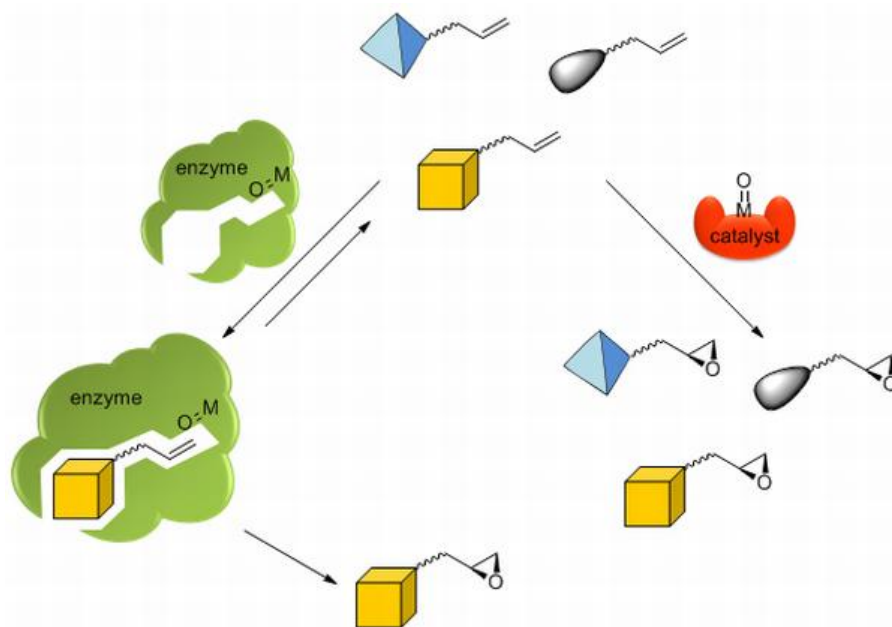


Figure 3: Schematic representation of the high substrate selectivity in the epoxidation of terminal alkenes displayed by an enzyme compared to a traditional unselective homogeneous organometallic catalyst.

A typical example of enzymatic substrate selectivity is given by serine proteases that catalyze the hydrolysis of amide bonds following a three-steps mechanism: (i) combination of the substrate with the enzyme to form the Michaelis complex; (ii) generation of an acyl-intermediate involving an OH group of the enzyme backbone and release of the amino fragment; (iii) hydrolysis of the acyl compound liberating the acidic product and regenerating the original enzyme (Figure 4). The characteristic features of some serine proteases are reported in Table 1 and Table 2.

Table 1: specificity of common protein-hydrolyzing enzymes (serine proteases).

Enzyme	Cleavage Position	Restrictions
Trypsin	Lys-X, Arg-X	X ≠ proline
Chymotrypsin	<i>rapid</i> : Phe-X, Tyr-X, Trp-X <i>slow</i> : Leu-X, Asn-X, Gln-X, His-X, Met-X, Ser-X, Thr-X	X ≠ proline
Thermolysin	<i>rapid</i> : Ile-X, Leu-X, Val-X, Ala-X, Phe-X, Met-X <i>slow</i> : Tyr-X, Gly-X, Thr-X, Ser-X	

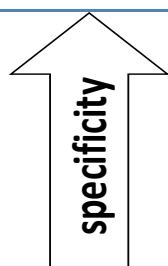
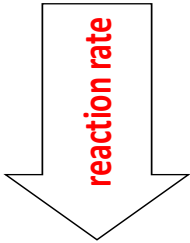


Table 2: substrate selectivity based on chain length for chymotrypsin.

$$\text{E-OH} : \begin{array}{c} \text{O} \\ \parallel \\ \text{R}-\text{C}-\text{N}-\text{R}' \\ | \\ \text{H} \end{array} \xrightarrow{k_2} \begin{array}{c} \text{O} \\ \parallel \\ \text{E}-\text{O}-\text{C}-\text{R} \end{array} + \text{H}_2\text{N}-\text{R}'$$

Michaelis complex

	Substrate	k_2
	Suc-Phe-pNA	0.094
	Suc-Ala-Phe-pNA	0.91
	Suc-Ala-Ala-Pro-Phe-pNA	<u>98</u>

The overall rate of the catalyzed reaction is extremely dependent on the length of the substrate peptidic chain and this global effect derives from a dramatic increase of the kinetic constant of the acylation step: for α -chymotrypsin, for instance, the rate constant of the acylation step increases by a factor of 2500 as the model substrate is extended from Suc-Phe-pNA* to Suc-Ala-Ala-Pro-Phe-pNA for the hydrolysis of the C terminal amide bond.³ This denotes a fine selection of the substrates, that is expressed in the faster cutting of longer peptide chains with an extra contribution if the carbonyl group of the amide linkage belongs to basic amino acids like lysine or arginine.² The global effect is an impressive substrate specificity that makes serine proteases (and especially endo-peptidases like trypsin and α -chymotrypsin) a powerful tool to discriminate the single components of a complex proteic mixture. The fine substrate recognition is related to the high complementarity between the active site, held together by an articulated net of hydrogen bonds, and the substrate. In particular, in the case of chymotrypsin (Figure 4), substrate recognition is provided by the presence of a sort of “hydrophobic pocket” 10–12Å deep that has just the right dimensions to accommodate the aromatic ring of phenylalanine.

* pNA= *p*-nitroanilide. An unspecified amino acid is commonly addressed with the letter X, while everyone of the 20 standard amino acids has a specific code, as reported by IUPAC Comm. Nomenclature Org. Chem. and IUPAC-IUB Comm. Biochem. Nomenclature in “Nomenclature of α -amino acids. (Recommendations, 1974)” *Biochemistry* **1975** *14*, 449-462.

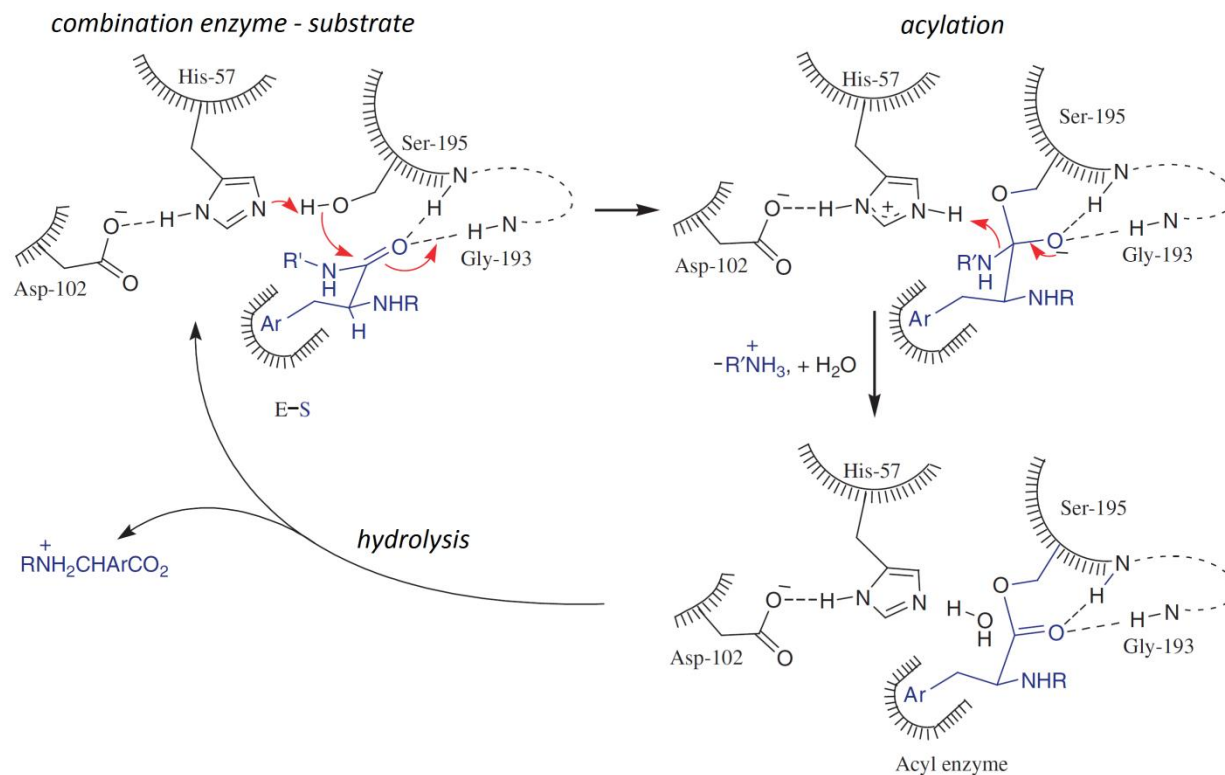


Figure 4: Key steps in the cleavage of a peptide bond by α -chymotrypsin. The substrate (blue) is orientated in the Michaelis complex E-S by binding interactions involving its functional groups and in particular the aromatic side-chain CH_2Ar in the hydrophobic binding site.

The above cited well defined tridimensional topology is traditionally associated to heterogeneous instead of homogeneous catalytic systems, thanks to the continuous development of solid materials with controlled porosity. Zeolites,⁴ for instance, are industrially applied in the petrochemical industry to convert selectively determined components of the complex feedstock chosen on the basis of the steric constraints imposed by the shape and dimension of the zeolite's micropores (pore diameter < 2 nm). This type of substrate selectivity is commonly addressed as *shape selectivity* and is typical of porous heterogeneous systems⁵ that are commonly employed as supports for other catalytic species, such as metal complexes or nanoparticles.⁶⁻⁸ An example of a substrate selective reaction based on a zeolitic catalyst is the one developed by Herron and Tolman⁹ for the oxidation of hydrocarbons by *in situ* generated H_2O_2 . A zeolite 5A (which is a Ca, Na-ionic form of zeolite A) was treated with a Pd(II) solution that gave, after calcination, the formation of highly dispersed Pd(0) particles within the zeolite's pores. The competitive oxidation experiment with cyclohexane and n-octane proved that, poisoning the external catalytic sites in order to consider just the oxidation inside the pores, the catalyst converted selectively the linear hydrocarbon while cyclohexane was too bulky to penetrate inside the micropores.

Unlike these heterogeneous systems, artificial homogeneous catalysts generally express their function in a much less selective way, showing even high product selectivity but converting all the substrates of a mixture in the same way, unless they bear different functional groups. This poor substrate selectivity is particularly anti-economical considering the need of one or more purification steps on the reactant mixture in order to avoid the formation of byproducts with the same functionality of the desired compound.

A possible homogeneous compromise between the highly regular zeolite's framework and an enzyme was identified in polymers, used either as a support¹⁰ or as catalytic species themselves. Breslow^{11,12} for instance developed a polymeric transaminase mimic operating in water and thus exploiting the hydrophobic pockets formed by the polymer chain to simulate the hydrophobic interactions occurring within an enzymatic catalyst. Similarly to polymers, dendrimers was considered to create biomimetic catalysts by virtue of the opportunity to prepare them with controllable topology and with specific functionalities located at predetermined positions within the dendritic matrix.

A pertinent example was provided by Chow¹³ who developed a Cu-bis-(oxazoline)-based catalyst bearing dendritic appendages observing a little but significant substrate selectivity in the Diels Alder reaction depicted in Figure 5. In competitive kinetic studies involving two dienophiles of different steric sizes, the so-called "third generation dendrzyme G3", differently to the lower ones G2 and G1, showed a 1.18 times higher reaction rate for the shorter substrates (Figure 5).

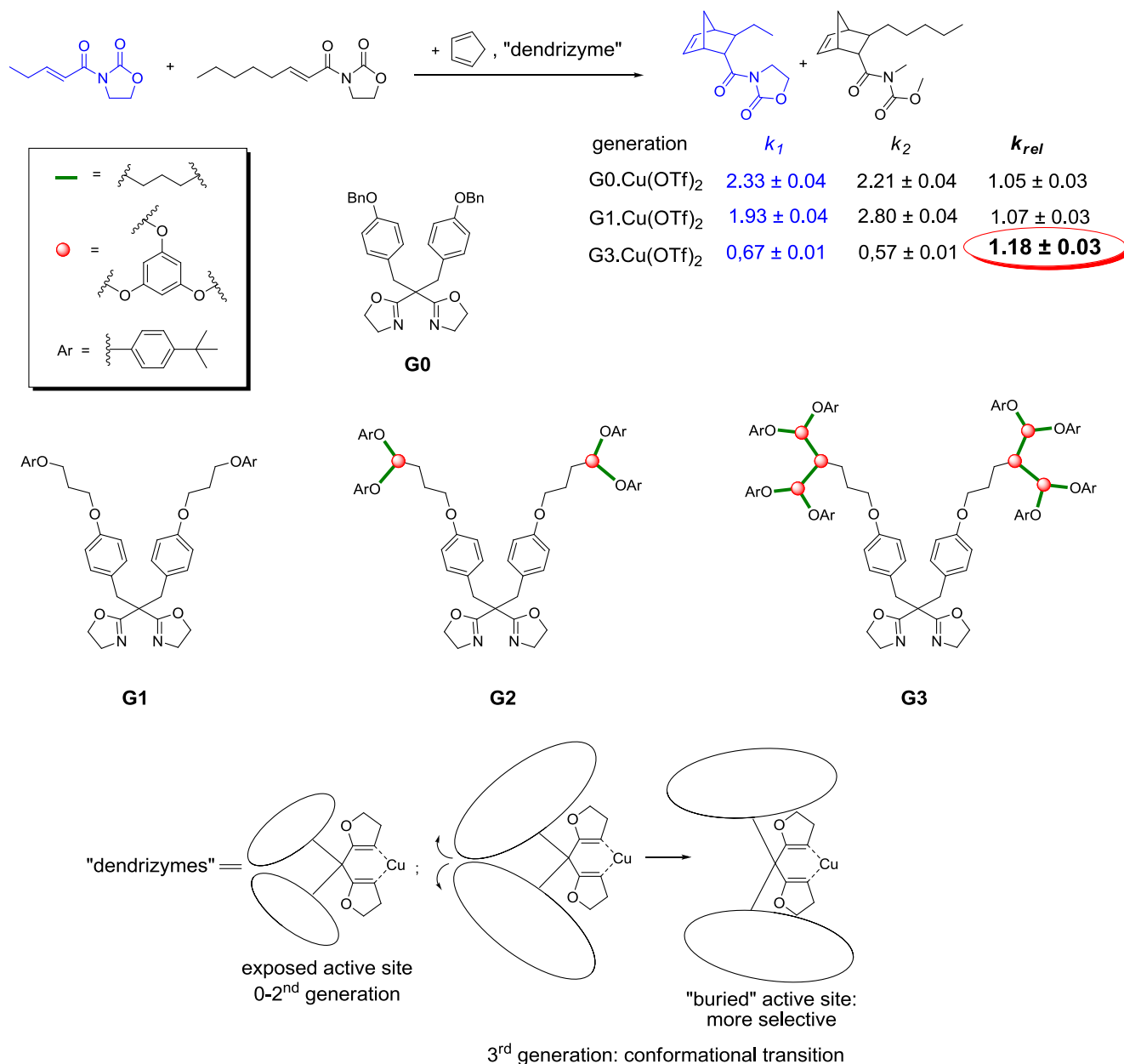


Figure 5: substrate selectivity expressed by dendritic bis(oxazoline)copper(II) catalysts of increasing generation in the Diels Alder reaction between cyclopentadiene and crotonylimide.

The realization of a selective organic reaction performed in water represents an important challenge to win. The peculiar features of this solvent, especially hydrophobic effect, stimulated the application in catalysis of a well known class of supramolecular hosts, namely cyclodextrins (CDs).¹⁴ Particularly relevant is the substrate selectivity displayed by the system developed by Monflier¹⁵ where six CD derivatives were evaluated in the palladium catalyzed cleavage of a series of similar substrates belonging to the groups of biphenylmethylallylcarbonates and N-alkyl-O-allylurethanes (Figure 6). The selection of the substrates in the

competitive experiments depended strongly on the chemical substitution of the host and on the size of the substrate itself. Smaller α -cyclodextrins proved to be more selective thanks to the narrower cavity where only few substrates were admitted, especially in the case of rigid biphenylmethylallylcarbonates. The substrate selectivity was quantified by comparison of the ratio between reaction rate carried out with and without CD for the different reagents. As reported in Figure 6, a decrease of catalytic activity of about eight times was observed comparing *para* biphenylcarbonate with the *ortho* isomer.

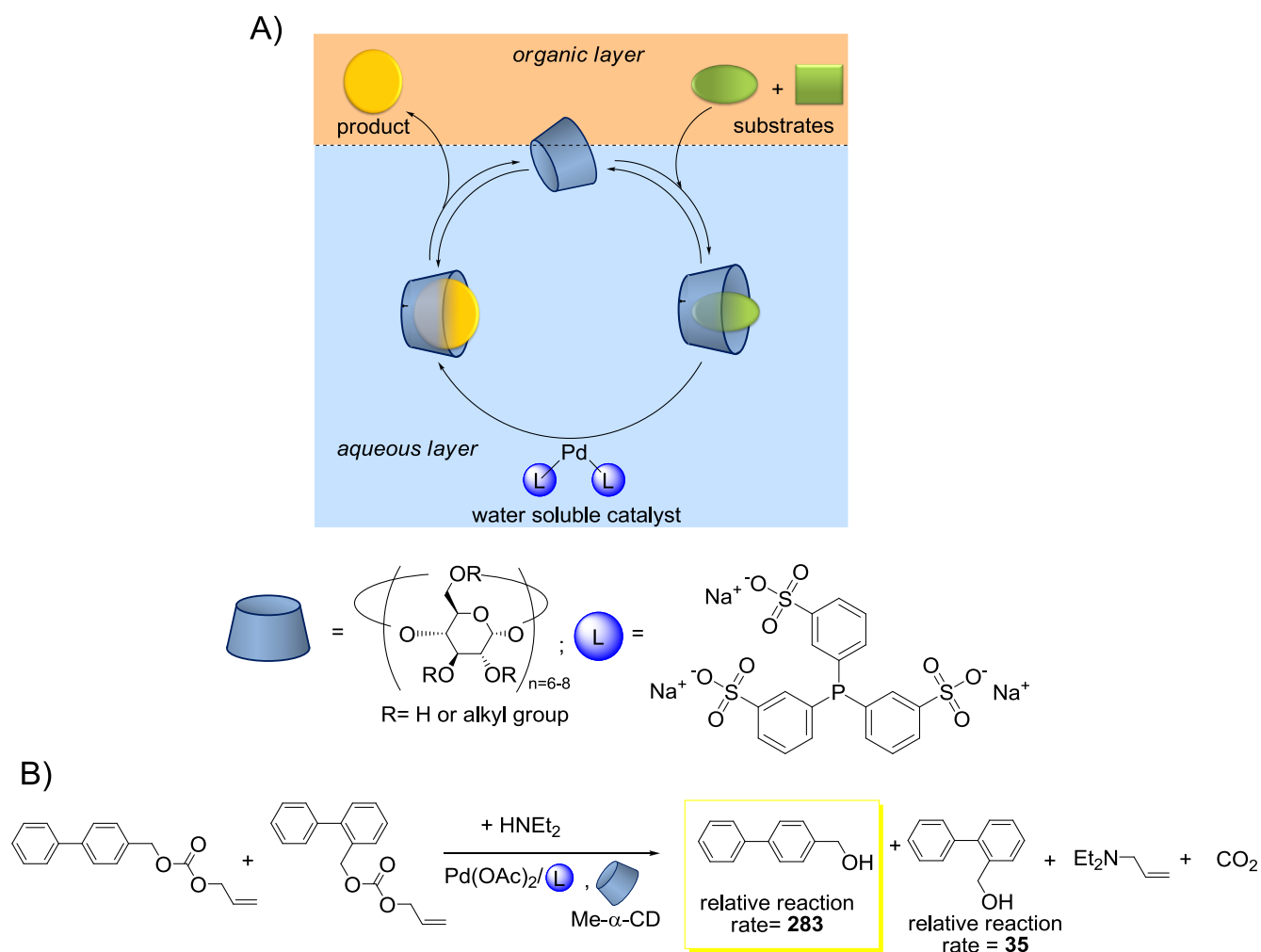


Figure 6: A) substrate-selective aqueous organometallic catalysis mediated by cyclodextrin derivatives. Preferentially one of the substrates (green oval) fits properly the host cavity of the cyclodextrin and consequently reacts with the water soluble catalyst to give the product.

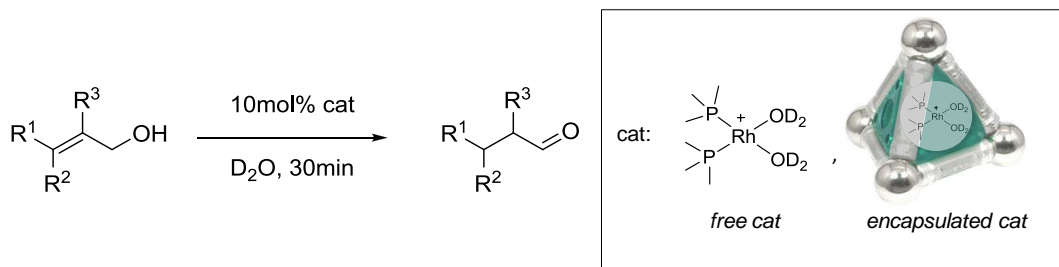
B) Substrate selectivity observed with *p*-biphenylmethylallylcarbonate and *o*-biphenylmethylallylcarbonate in the presence of methylated α -CD and a Pd water soluble catalyst.

An innovative alternative to cyclodextrins for enzyme mimics operating in water was recently developed by Raymond using a self-assembled tetrahedral metal-ligand capsule to build a supramolecular box in which substrates can be selected depending on their shape, analogously to what observed for zeolites. The capsule is

constituted by Ga(III) centers connected by means of polydentate organic ligands and is represented in Table 3 as a green tetrahedron, where Ga centers are the spherical corners.

Raymond and coworkers were able to encapsulate in this tetrahedral cage small Rh(I) complexes of the general formula $[(P-P)Rh(diene)][BF_4]$ ($P-P = 2 PR_3$ or 1,2-bis(dimethylphosphino)ethane, $diene = 1,5$ -cyclooctadiene or norbornadiene) that they further tested on allylic alcohols isomerization, chosen as an ideal model involving a single water soluble substrate reacting on the metallic catalytic site. The $(PMe_3)_2Rh(COD)^+$ precursor enclosed in the Ga_4L_6 tetrahedron in aqueous solution was treated with 1 atm of H_2 to generate the active species $(PMe_3)_2Rh(OD_2)_2^+$ (**1**): this is kinetically formed inside the capsule, but slowly dissociates to return in solution where it is highly solvated (complete dissociation after 12 hours). Under these circumstances, the reaction catalyzed by this system should be characterized by a short reaction time and fast in/out exchange of the substrate within the capsule. Anyway, compared to the free complex, the encapsulated one showed remarkable substrate selectivity, choosing only the smallest alcohols and leaving the other ones totally unreactive in the same conditions (Table 3).

Table 3: Allylic alcohol isomerization mediated by a Rh(I) complex encapsulated in the tetrahedral cage developed by Raymond.



substrate	Yield% _{free cat}	Yield% _{encaps}	substrate	Yield% _{free cat}	Yield% _{encaps}
	95	95		0	0
	95	0		0	0
	95	0		95	95
	0	0		95	0

Branched molecules, in particular, are prevented from reaching the active site by the limited opening of the tetrahedron walls. Finally, if crotyl alcohol, a catalyst inhibitor, is added to the reaction mixture, the catalyst is

completely poisoned in the bulk, but no poisoning is detected if the Rh complex is enclosed in the Ga₄L₆ host where the inhibitor cannot enter. These results clearly demonstrate how an artificial supramolecular environment can control the catalytic performance of a system in terms of high substrate selectivity, similarly to what happens for natural catalysts.

1.2 THE FUTURE IS GREEN

Alchemy began to exist in the past as the science of understanding, deconstructing, and reconstructing matter, but economically speaking, the idea of the opportunity to turn common metals into gold was so attractive for human nature, that any other discovery in this field was shaded by the “golden goal”. During the XVII century chemists abandoned the search of the philosopher’s stone, but economical reasons still remain the principal driving force for nearly all the scientific research sponsored by industry. This led often to undervalue health and environmental consequences of chemical processes in favor of high productivity with the cheapest feedstock, but nowadays pollution prevention and workers safety cannot be ignored anymore and the way of environmentally benign chemical syntheses have been taken following the dictate of a new discipline called *green chemistry*. The *Green Chemistry Program* was established in the US in 1991, following the passage of the Pollution Prevention Act the previous year.¹⁶ The ultimate aim of this trend is to develop elegant and efficient chemical processes reducing the risks and the guidelines to achieve it are summarized in the *12 principles of green chemistry*,¹⁷ some of which are reported below:

2 - Atom Economy

Synthetic methods should be designed to maximize the incorporation of all materials used in the process into the final product.

5- Safer Solvents and Auxiliaries

Use of auxiliary substances (e.g., solvents, separation agents, etc.) should be made unnecessary wherever possible and innocuous when used.

6- Design for Energy Efficiency

Energy requirements of chemical processes should be recognized for their environmental and economic impacts and should be minimized. If possible, synthetic methods should be conducted at ambient temperature and pressure.

9 - Catalysis

Catalytic reagents (as selective as possible) are superior to stoichiometric reagents.

12- Inherently Safer Chemistry for Accident Prevention

Substances and the form of a substance used in a chemical process should be chosen to minimize the potential for chemical accidents, including releases, explosions, and fires.

The 2nd principle deals with atom economy¹⁸ concerning the incorporation of the highest percentage of the starting material into the final products to avoid wastes that have to be discarded or recycled spending energy, time and resources. The concept is quantified in the simple equation reported below ($m = \text{mass}$):

$$\text{Atom Economy \%} = \frac{m_{\text{desired product}}}{\sum_{i=1}^i m_{\text{reagents}}^i} \cdot 100$$

Atom Economy is now a new criterion to judge the efficiency of a synthetic methodology and is related to biological systems in the way that every chemical reaction has preferentially no byproducts unless they are reused for another consecutive reaction or to produce another useful compound through another synthetic pathway. The evolution of chemical processes towards high atom economical ones can be clearly exemplified analyzing the hydrogen peroxide to propylene oxide (HPPO) process developed by the Dow Chemical Company (Dow) and BASF, for which they received a 2010 Presidential Green Chemistry Challenge Award.¹⁶ This new technology improves the production process of a key chemical intermediate, propylene oxide, used in a variety of applications from home insulation, appliances, automobiles and furniture to aircraft de-icers, paints, brake fluids and pharmaceuticals. The precedent synthetic method was characterized by a definitely low atom economy, correspondent to about 1/3 of that calculated for the new process (Figure 7).

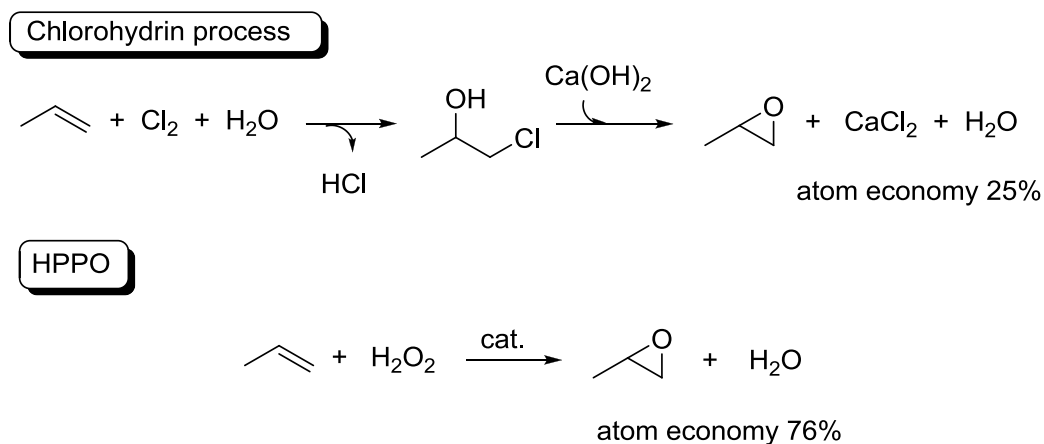


Figure 7: evolution of propylene oxide production: from the stoichiometric process via chlorohydrin and calcium hydroxide to the modern HPPO catalyzed process using hydrogen peroxide as terminal oxidant. the new HPPO process reduces wastewater by 70 to 80 percent and energy use by approximately 35 percent, compared with the old technology. Moreover, no by-products are produced besides water. Finally, PO plants using the HPPO technology require up to 25 percent less capital to build than conventional technologies, as they have reduced infrastructure, a smaller physical footprint and simpler raw materials integration.

One of the secrets for atom economical successful procedures is the turn of stoichiometrical syntheses into catalytic ones, as showed for HPPO process, somehow implying that all scientists dealing with catalysis are potentially “green chemists”. But remembering that enzymes can be considered a paragon in catalysis, one important feature of biological systems often ignored for industrial applications is the ability to perform highly efficient organic reactions in aqueous systems. This introduces the 5th green chemistry principle and the parameter called E-factor defined by Sheldon¹⁹ and described by the formula:

$$E \text{ factor} = \frac{\text{total waste (Kg)}}{\text{product mass (Kg)}}$$

“Total waste” comprises everything but the desired product, including byproducts, solvents and non-converted reagents, while recycled solvents and re-used catalysts are excluded from the count. An important exception is made for water. Water, thanks to its availability, cheapness, low volatility and non-toxicity is assumed to give no contribution to the E-factor becoming the most environmentally friendly solvent (with the exception of NO solvent) from this specific point of view.

The combination of all these factors means, for instance, performing an organic reaction in water, at ambient temperature and pressure, minimizing the number of steps and the use of toxic compounds. A clear representation of this concept is given by Lipshutz and coworkers in the scheme reported in Figure 8, taken from the recent review “Greening Up Cross-Coupling Chemistry”.²⁰

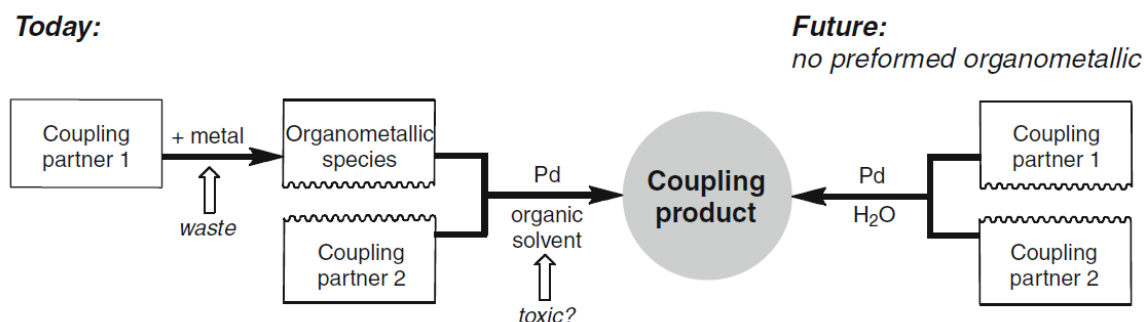


Figure 8: Evolution of cross coupling processes following the principles of green chemistry as described by Lipshutz.²⁰ In the future we should be able to perform couplings in a one-pot procedure bringing together directly the two coupling partners without the need of preforming the organometallic species. Practically two (or more) electrophilic species should co-exist in the reaction medium, wherein one of them ultimately becomes the *in situ*-derived nucleophile. Avoiding traditional moisture- and air-sensitive organometallic species it would then be possible to operate in water, eliminating toxic organic solvents.

Lipshutz’s work in aqueous C-C coupling spans almost all types of couplings and is tightly related to the development of a new Vitamin E derived neutral surfactant called PTS (polyoxyethanyl α -tocopheryl sebacate). He developed in 2008 a room temperature process by using PTS²¹ to form micellar nanocapsules in which both

catalyst ($[\text{Pd}(\text{dtbpf})\text{Cl}_2]$ was found to be the most effective one) and substrates were included providing high local concentrations. What is interesting about this system is the possibility of a facile recovery of the catalyst by nanofiltration or extraction, thus allowing recycle of the aqueous phase and separation of products. Similar technologies were applied for Suzuki, Negishi and other couplings, like Fujiwara-Moritani and Sonogashira, extensively explained in the above cited review paper.

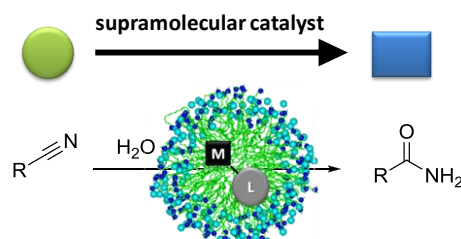
“Going green” appears as the main imperative for chemists of the third millennium and “elegant” procedures mediated by highly active catalysts, neat or using non-toxic solvents, seem to represent the industrial chemistry of the future. The goal is ambitious, but deepening the knowledge on every aspect of this panorama, it becomes easier and easier to cross the line.

2. AIM OF THE THESIS

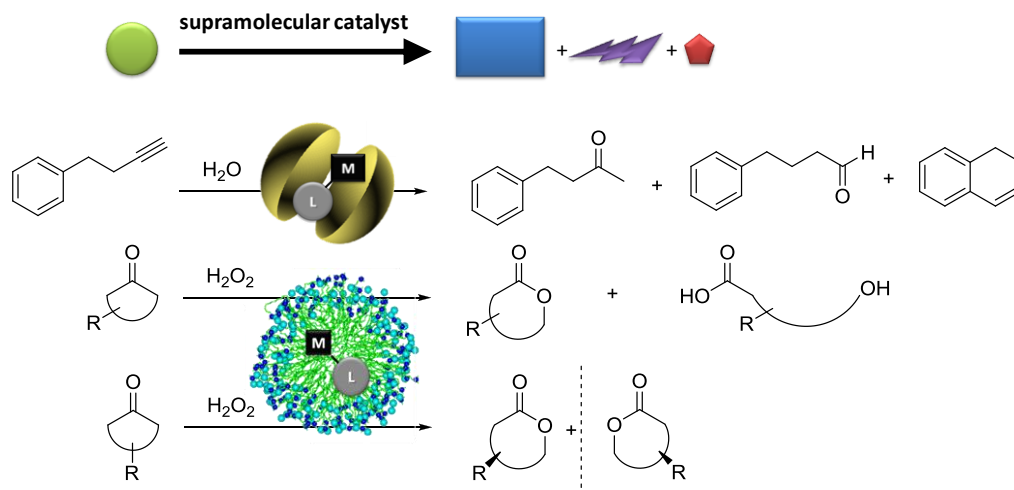
At the beginning of this work, the aim was to substitute traditional solvents, having high environmental impact, with more environmentally benign and health compatible aqueous media. This approach belongs to a recent trend of green chemistry, applied to industrial production. The transfer in water of processes, normally performed in organic solvents, was realized by means of solubilizing agents such as surfactants that are cheap and extensively used chemicals, first of all in detergents formulation. The use of surfactants is of great interest to make a chemical process water compatible, as catalytic reactions in water are mostly performed by modifying catalysts with water soluble tags to make them soluble, a procedure that involves energy, money and time consuming syntheses. Moreover the modified catalyst could display different sterics and electronics compared to the original one, not always favorable. The use of surfactant-based nano-aggregates (micelles) entails also other innovative aspects such as the tuning of the selectivity of a chemical reaction exploiting the tridimensional scaffold built by the micelles around hydrophobic catalysts and substrates. The objective was therefore expanded to a comprehensive study on the effects on selectivity of supramolecular self-assembled hosts, such as micelles, in reactions mediated by organometallic catalysts. The inclusion of organometallic complexes within nanometric supramolecular aggregates would allow, in fact, a fine tuning of the selectivity on the basis of shape, dimensions and substrates affinity with the host, with some similarities to the interaction between a substrate and the complex peptide backbone of an enzyme. At the beginning the attention was focused on hydration reactions, in order to take advantage of the aqueous medium, avoiding the co-solvent approach when water is necessarily present as a reactant. The example of choice was the hydration of nitriles mediated by Ru^{II} catalysts, for which the goal was the development of a highly active system without modifying the catalyst structure and using milder conditions than the traditional ones (Figure 9A).

Subsequently the work continued with the application of micellar systems to the Baeyer-Villiger oxidation of cyclic ketones, extensively studied in our lab in ordinary solvents,²² but poorly studied in aqueous medium, except in the enzymatic version.²³ This oxidation reaction presents both activity and selectivity issues: high activities are generally difficult to achieve especially for intrinsically less reactive six-membered ring cyclic ketones, while selectivity is a general problem to overcome in oxidation. Micellar systems were tested in order to solve both challenges by virtue of the confinement of catalyst and substrates inside the supramolecular structure (Figure 9B).

A) catalytic activity



B) product selectivity



C) substrate selectivity

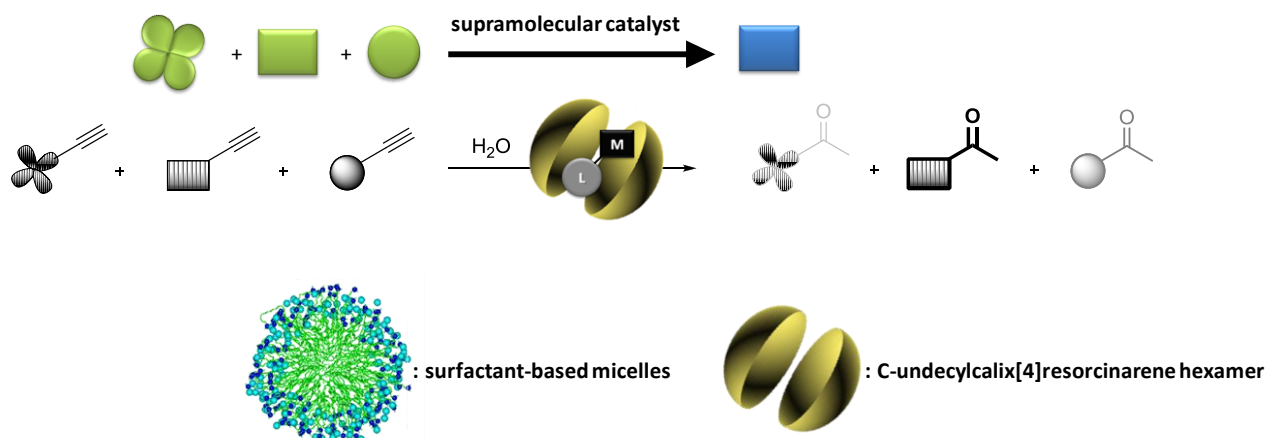


Figure 9: characteristic features of organometallic complexes encapsulated in supramolecular self-assembled structures with selected examples.

Following the idea of a comprehensive study on supramolecular hosts combined with organometallic complexes, the use of a self-assembling capsule was evaluated during a six-months stage in the research group of prof. Joost Reek at the Van't Hoff Institute of Molecular Sciences at the University of Amsterdam. The capsule of choice was the C-undecylcalix[4]resorcinarene hexamer, for which no examples of organometallic

catalyst encapsulation are known so far. This particular work was started considering the great interest in understanding new biomimetic catalytic moieties and to develop innovative processes in which the catalyst is able to impart both product and substrate selectivity (Figure 9B and C).

The formation of a supramolecular catalyst, exploiting the large cavity of this capsule to encapsulate a suitable metal complex was the first objective, followed by the application of this new system on the hydration of alkynes as a model reaction. Water is vital for the formation of the nano-capsule (Chapter 6) and this led again to hydration reactions.

The results obtained are the first step towards the optimization of this unusual catalytic system and to scale up micellar processes. Some principles to develop innovative chemical processes have been proved that may be implemented in the design of better performing, more selective catalysts.

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3. STATE OF THE ART

3.1 SUPRAMOLECULAR CATALYSIS IN AQUEOUS MEDIUM WITHIN UNIMOLECULAR HOSTS

This chapter deals with catalytic activity displayed by cyclic unimolecular water-soluble species characterized by a well defined cavity where a guest can be accommodated. Within this group, derivatized calixarenes and cyclodextrins are examined in their use as supramolecular ligands for organometallic complexes. These two classes of hosts represent the first and most investigated tool to non-covalently modify organometallic species in aqueous medium, in order to change their catalytic properties. The number of studies involving these concave molecules constitutes a good starting point to understand the potential of the supramolecular approach to perform organometallic catalysis in water and to develop a new generation of catalysts.

3.1.1 DERIVATIZED CALIXARENES

In 1940s Alois Zinke, a professor of chemistry at the University of Graz in Austria, and his coworker Erich Ziegler were working on the phenol-formaldehyde process, developed some forty years before by Adolf Von Baeyer. A typical experiment in the Zinke and Ziegler study is described in a 1944 paper as follows: “When 50 g of the resin which is obtained by heating 100 g of p-tert-butylphenol, 100mL of 3N NaOH, and 97 g of a 35% formaldehyde solution is heated with stirring with 200 g of linseed oil, it dissolves at 100–120 °C. At 140–160 °C there is a vigorous foaming, and turbidity appears which increases greatly upon further heating at 200–220 °C. The resulting brown waxy paste is stirred with ethyl acetate, washed thoroughly, and reprecipitated from CCl₄ with alcohol to give a crystalline product as platelets or rosettes that decomposes above 300 °C.” The same scientists had already reported some years earlier the same product of empirical formula C₁₁H₁₄O. The poor reactivity of this compound and the comparison with resorcinol-aldehydes reaction lead in 1944 to the understanding of the structure of this mysterious product as the cyclic tetramer depicted in Figure 10. In 1970s, when the new area of bioorganic chemistry relating to enzyme mimics was emerging, Zinke’s cyclic tetramers came on the scene as good candidates for molecular baskets, thanks to their easy synthesis and the non-planar structure that, except for cyclodextrins, was unique in those years. This particular shape inspired David Gutsche, who, perceiving a similarity between the shape of a Greek vase and a space-filling molecular model of

Zincke cyclic tetramer-(Figure 10), coined the name “calixarene”, derived from the Greek *calix* meaning “vase” or “chalice”; and arene which indicates the presence of aryl residues in the cyclic array.²⁴

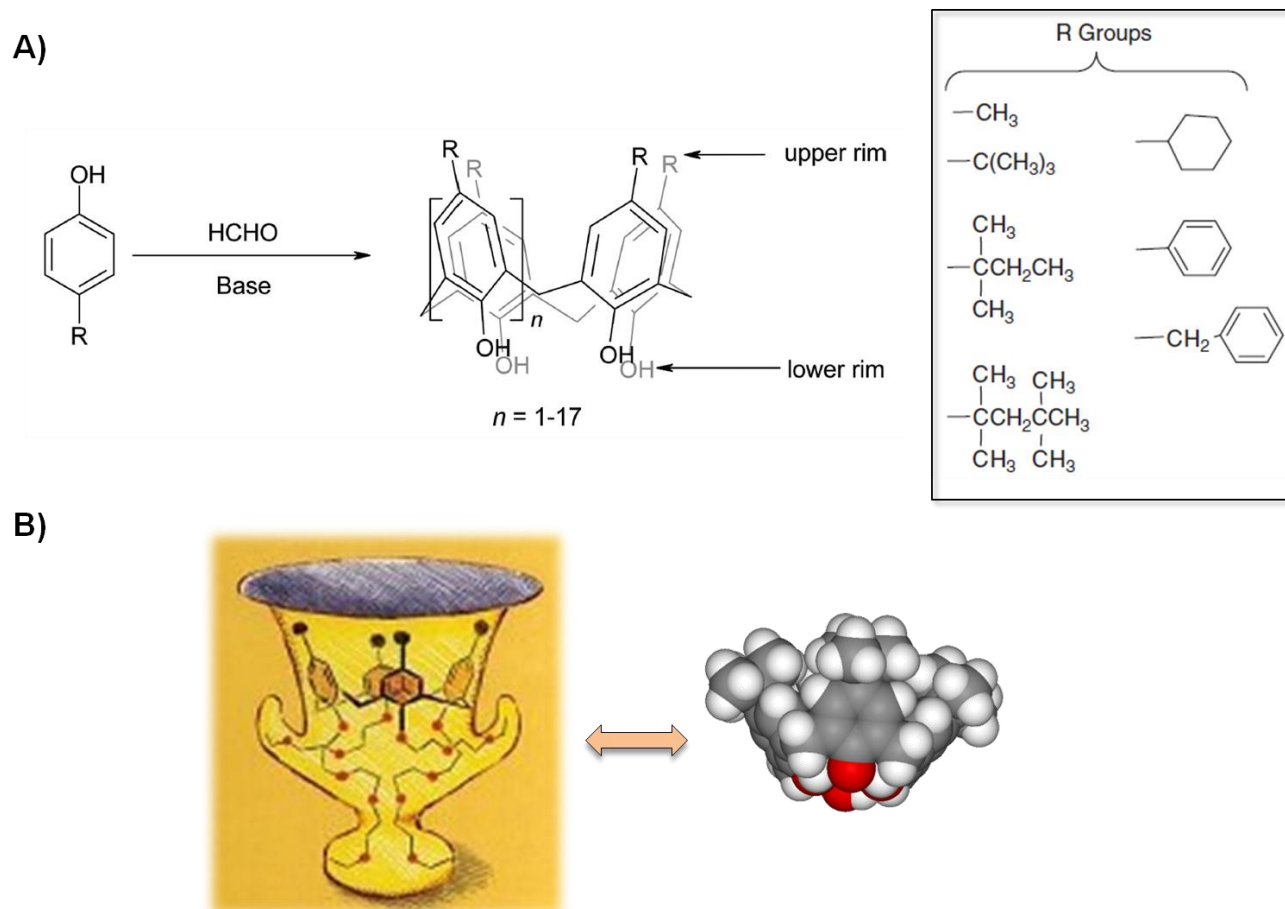


Figure 10: A) the generic synthesis of calixarenes with an example of the R groups that can be attached to the upper rim; B) a cartoon representing the analogy between calixarenes and a greek chalice²⁵ and the related 3D model of the molecule (with methyl groups as R substituents).

Organic functionalization of calix[n]arenes²⁶ is nowadays a well established method to build fluorescent probes and sensors,^{27,28} phase-transfer agents, separation media,^{29,30} nano-capsules³¹ and especially catalysts.^{30,32} In fact, the same challenge that made calixarenes become famous still constitutes the major field of research where these compounds are applied, namely biomimetic catalysis. The first example was reported by Shinkai and coworkers in 1986³³ performing the hydration of 1-benzyl-1,4-dihydronicotinamide catalyzed by p-sulfonatocalix[6]arene, mimicking the action of the enzyme glyceraldehydes phosphate dehydrogenase (Figure 11). In this pioneering work these authors first solved the problem of solubilisation of calixarenes in water by adding sulfonic groups to a six-membered macrocycle, using then the new host in the hydration reaction. The latter is efficiently accelerated and proceeds according to the Michaelis-Menten kinetic model, opening the

way to the employment of sulfonated calixarenes, as well as surfactants, and other host molecules, as a new class of biomimetic catalysts. It was indeed the first example for host-guest-type behavior of calixarenes observed in an aqueous system.

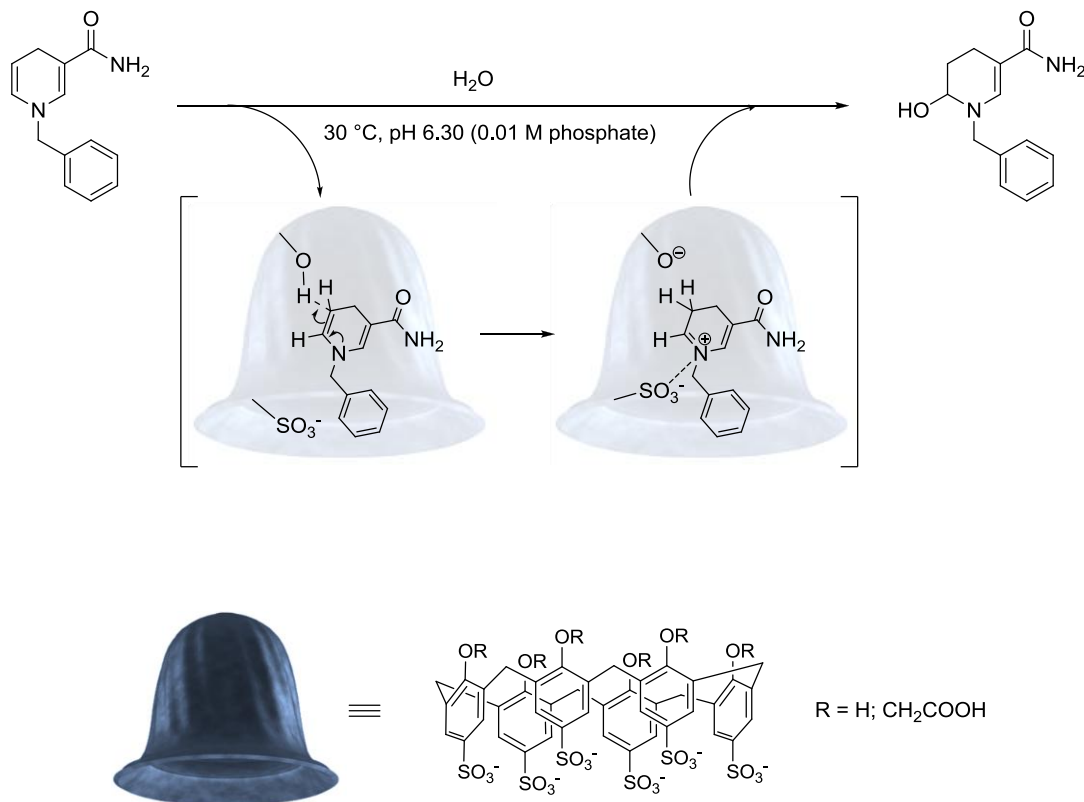


Figure 11: Proposed reaction mechanism for the hydration of 1-benzyl-4-dihyronicotinamide, in which protonation of 1,4-dihyronicotinamide is involved in the rate-determining step. The *p*-sulfonatocalix[6]arene has both acidic protons and anionic groups to stabilize the intermediate.

Some years later the same research group achieved the regioselective cleavage of the P–O(2') bond of cytidine 2',3'-cyclic phosphate, an intermediate in RNA hydrolysis, by use of water-soluble calix[4]arene-5,11,17,23-tetrasulfonate, "the first totally man-made mimic for the regioselective catalysis of ribonuclease".³⁴ The cleavage of phosphodiester bonds by artificial nucleases is particularly interesting from a biological point of view and recently the group of Ungaro provided several excellent results in this field. Artificial ribonucleases need two moieties to work properly: a catalytic group and a probe for sequence recognition. The catalytic site is the place where the ester bond cleavage occurs and traditionally promoted by metal ions.³⁵ Therefore, among the chemical models of ribonucleases, a special place is occupied by metallonucleases, and Reinhoudt and Ungaro groups reported on the synthesis of a series of water-soluble copper(II) and zinc(II) complexes of calix[4]arene-based nitrogen ligands, showing high cooperativity between the metal centers (Figure 12).³⁶⁻³⁸

The calix[4]arene scaffold, blocked in the *cone*-conformation[†] by proper derivatization of the hydroxyl groups in the lower rim, are versatile scaffolds for this type of catalysts keeping the functional groups and the metals in a preorganized, semi-rigid shape. The success of this type of structures in comparison with other artificial metallo-enzymes comes from the combination between the catalytic activity of the metal itself and the structure provided by the ligand unit, together with the hydrophobic effect within the *calix* that enhances the binding of aromatic nucleobases, something really similar to natural enzymes' behavior. The same type of systems, optimized on RNA models like HPNP (2-hydroxypropyl *p*-nitrophenyl phosphate), were tested in 2007 as cleaving agents of 6-, 7-, and 17-meric oligoribonucleotides, observing a high selectivity by copper(II) complexes, that resembles closely the one shown by natural RNase A (cleavage rates exceeding the rate of spontaneous RNA cleavage by $>10^8$ -fold).³⁹

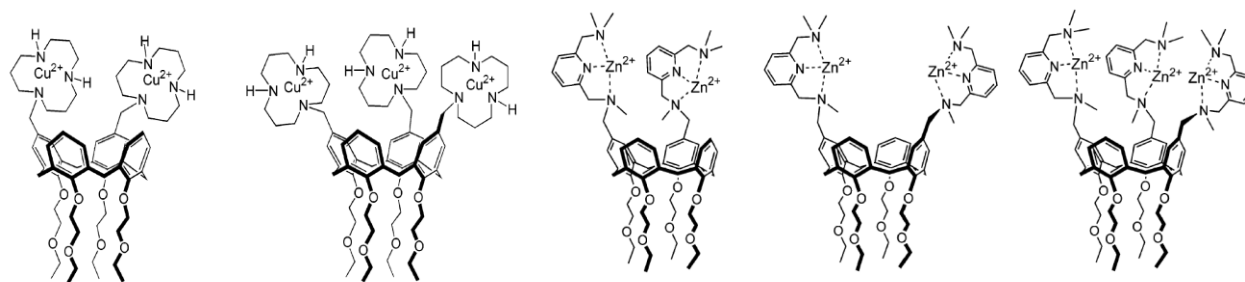


Figure 12: Most active di- and tri-nuclear complexes bearing derivatized calixarenes scaffolds synthesized by Ungaro, Reinhoudt and coworkers.

The closest calixarenes' cousins, namely resorcinarenes, are much less studied as catalysts and one of the rare examples was provided in 2008 by Zakharova and coworkers, combining amphiphilic sulfonatocalix[4]resorcinarenes, polyethyleneimine and lanthanum ions to form a supramolecular catalyst that permitted the enhancement of the catalytic effect (k_{app}/k_0) of about two orders of magnitude compared to the alkaline hydrolysis of *O*-ethyl *O*-*p*-nitrophenyl chloromethylphosphonate.⁴⁰

Water soluble calixarenes and their derivatization products have been further tested as inverse phase-transfer catalysts, in close analogy with cyclodextrins. In particular, Wacker oxidation of olefins to methyl ketones have been performed using both CDs and *p*-sulfonated calixarenes by Karakhanov and coworkers. For the oxidation of 1-octene to octanone they achieved 80% yield using *p*-sulfonatocalix[6]arene as water soluble phase-transfer catalyst, while β -CD provided just 20%yield.⁴¹

[†]When calixarenes are in solution, two opposing aromatic units rapidly move inward to or outward from the hydrophobic cavity, resulting in interconversion between conformations with either two diverged (flattened) or parallel (pinched) aromatic units via a cone-shaped symmetrical intermediate.

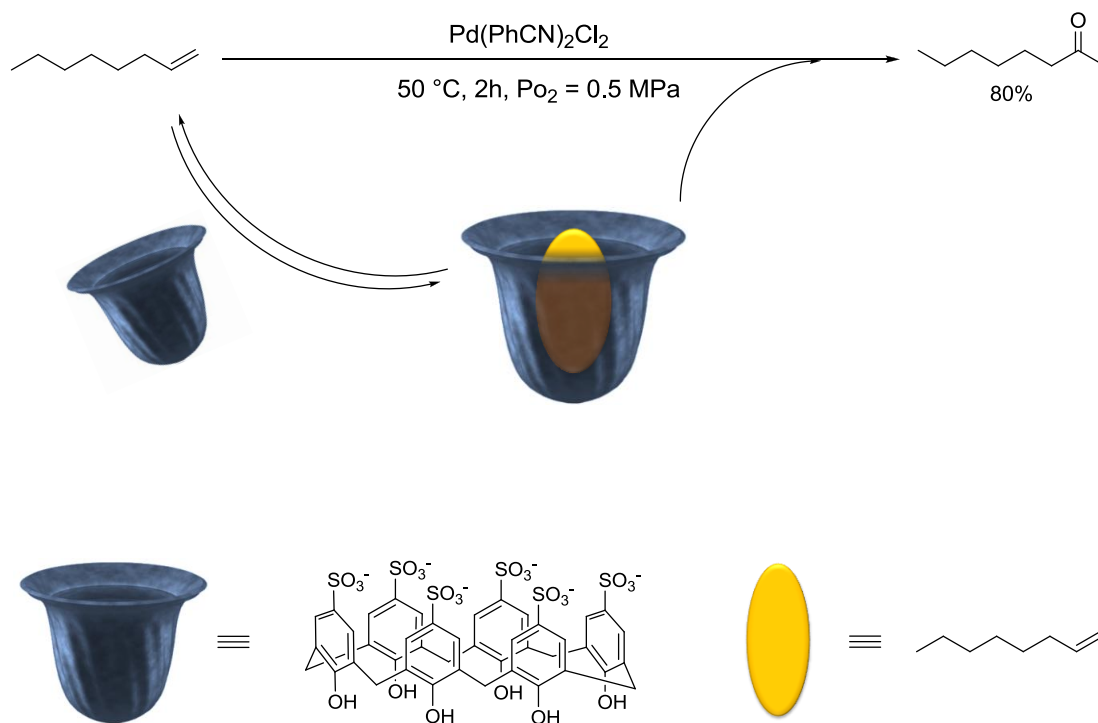


Figure 13: Wacker oxidation of 1-octene using a catalytic systems based on palladium dichloride dibenzonitrile combined with the water-soluble *p*-sulfonato-calix[6]arene. This substrate provided the highest yield with this specific system thanks to its optimal length that perfectly complemented the calixarene, leading to the formation of a stable inclusion complex. For shorter olefins, a smaller calixarene, such as *p*-sulfonato-calix[4]arene, was preferred.

3.1.2 CYCLODEXTRINS

Cyclodextrins^{14,42} are a class of chiral cyclic oligosaccharides characterized by a defined tube-like shape provided by the hydrogen bonds network between the hydroxyl groups on the rims. They are readily available semi-natural compounds that can accommodate organic substrates into their hydrophobic cavity in water solution. The two rims can be easily functionalized in order to attach spacers, catalytic groups or other functional groups. These advantages are the reason why these are the most widely used hosts in industry. Tons of cyclodextrins are produced every year *via* enzymatic degradation of starch. The major part of this large production is used as stabilizing or solubilizing agents, in which CDs do not play any catalytic role. But, as a consequence of their hydrophobic cavity, that permits the formation of inclusion complexes with several organic hosts, cyclodextrins (in particular β -cyclodextrin) are also used in many catalytic applications,⁴³ often similar to natural enzymatic processes. Considering hydrolysis reactions, most CD-mediated systems operate following the Michaelis-Menten model, thus representing good artificial enzymes examples. Breslow and Campbell provided in the 70's the first examples of α -cyclodextrin acting as catalyst in the chlorination of anisole,^{44,45} for which complete selectivity towards para-substitution was obtained in conjunction with increased rates and changed kinetic models (Figure 14). This is even more of what enzymes do for this reactions and demonstrate how the right combination of host and substrate can even improve natural catalysts performance. Similar examples were also reported, where simple CDs promoted the rate or the selectivity of reaction, but without all the striking effects observed in Breslow's work.

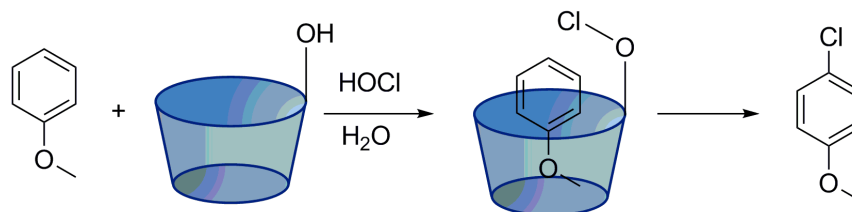


Figure 14: Anisole is selectively chlorinated in para position when it binds into α -CD and the chlorine is delivered from a cyclodextrin hydroxyl group

The hydrophobic effect also makes CDs particularly suitable to increase mass transfer in reactions performed in biphasic systems: CDs form indeed host-guest complexes with the substrate at the interface between aqueous and organic phase, where the reaction occurs usually mediated by a water soluble catalyst. The product formed is released in the organic phase due to complexation of another substrate molecule and the catalytic cycle starts again.^{46,47} The reactions in which CDs are employed as phase-transfer catalysts are mainly biphasic Wacker-type oxidations and hydroformylations,^{48,49} where the host binds a substrate molecule (in these two

cases an olefin) and the better the binding, the higher the yield. The binding constant depends on CD's size and on the shape of the guest molecule, but most of the times to improve affinity of the CD with the substrate, solubility and selectivity of the reaction, derivatization on hydroxyl groups on the host is performed. This leads to several changes in host properties: using sulfonated groups the CD becomes negatively charged losing its neutrality; some substituents can broaden the pH range of solubility (this is the case of sulfobutyl ether- β -CDs) and, for specific catalytic systems as the one reported in Figure 15, substitution can be useful to create spacers and preorganize the host.

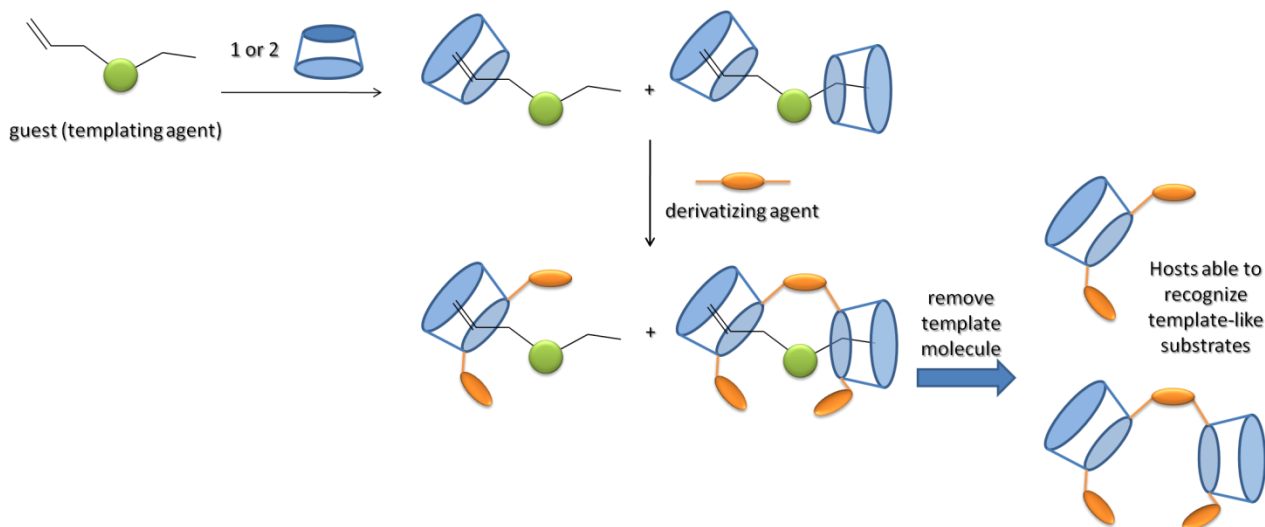


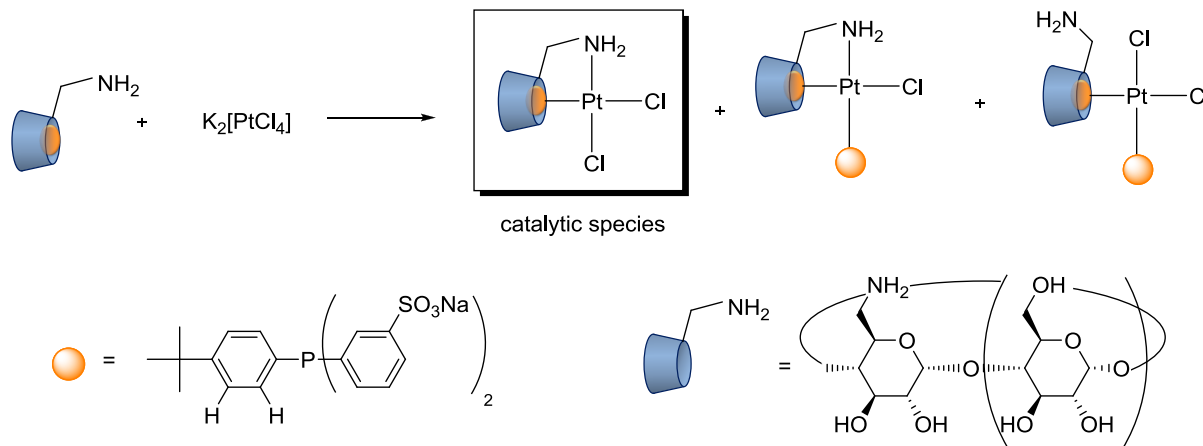
Figure 15: modification of CDs using molecular imprinting method

More recently, CDs came back on the scene as useful second sphere ligands for traditional metal complexes in order to assemble supramolecular catalysts in a straightforward way, exploiting the affinity between phosphorous containing ligands and the CD's cavity. This binding affinity came out for the first time with the use of CDs as phase transfer catalysts for hydroformylations and the effect of the formation of phosphine ligands-CD inclusion complexes was assessed observing dramatic changes of activity and selectivity performing the reaction in presence of CDs.^{46,47,49}

The employment of β -CDs for complexation of organic ligands was exploited successfully in other contexts to create innovative water-soluble catalysts, as the ones in Figure 16 and Figure 17.^{50,51} Monflier developed a supramolecular catalyst based on the complexation of the species disodium bis(3-sulfonatophenyl)(4-tert-butylphenyl)phosphane with an amino-CD (6'-amino-6'-deoxycyclomaltoheptaose). Once combined with $K_2[PtCl_4]$ the inclusion complex acted as chelating P-N ligand coordinating Pt both with the phosphorous ligand and the nitrogen of the amino group attached to the β -CD and interestingly three different complex structures (Figure 16) were identified dependently on the substitution of one of the two chlorine atoms coordinated to Pt.

The hydrogenation of 2-methyl-3-buten-1-ol in water was performed adding *in situ* the three components (modified CD, phosphane ligand and platinum salt) with different amounts of phosphane ligand, but just one of the three complexes was found to be active with an initial TOF of 2600 h⁻¹.

A



B

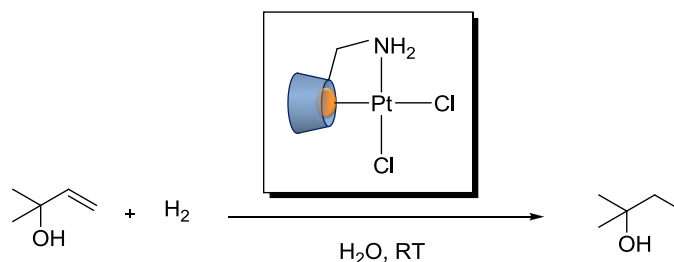


Figure 16: A) An N,P heterobidentate supramolecular ligand was synthesized in water by mixing a monoamino- β -cyclodextrin with an appropriate phosphane. The resultant assembly was combined with a platinum(II) salt in aqueous medium and led to the formation of three supramolecular complexes. B) One of them, isolated from the mixture as a brown precipitate, proved to be an effective catalyst for the hydrogenation of the allyl alcohol 2-methyl-3-buten-1-ol.

The same approach was applied to form a Rh(acac)(DABP[‡])₂/methylated- β -CD complex, that was evaluated by Leclercq and Schmitzer as catalyst for the homogeneous hydroformylations in homogeneous and biphasic medium. Both di- and tri-methylated β -CDs (DIME- and TRIME-CD) were employed as a supramolecular host for the phosphine ligand, in order to tune the hydrophilicity of the resulting complexes. DIME-CD complexes, for instance, were preferentially dissolved in water, while TRIME-CD enhances the solubility in the organic phase, transferring to the complex the intrinsic solubility properties of the host. For hydroformylation of allyl alcohol in water, DIME- β CD proved to be the best supramolecular host with CD/Rh = 2. The conversion obtained with this system is significantly increased compared to the CD-free system (from <1% up to 76%) and the selectivity towards the linear aldehyde is also enhanced. Mechanistically, the methylated cyclodextrin most probably

[‡] di(1-adamantyl)benzylphosphine

induces the formation of more active catalytic species trapping the DABP in solution and enhances the steric effects around rhodium coordination sphere, acting as a catalyst promoter Figure 17B.

As showed by these examples, cyclodextrins represent a powerful tool in the fast growing field of supramolecular catalysis.

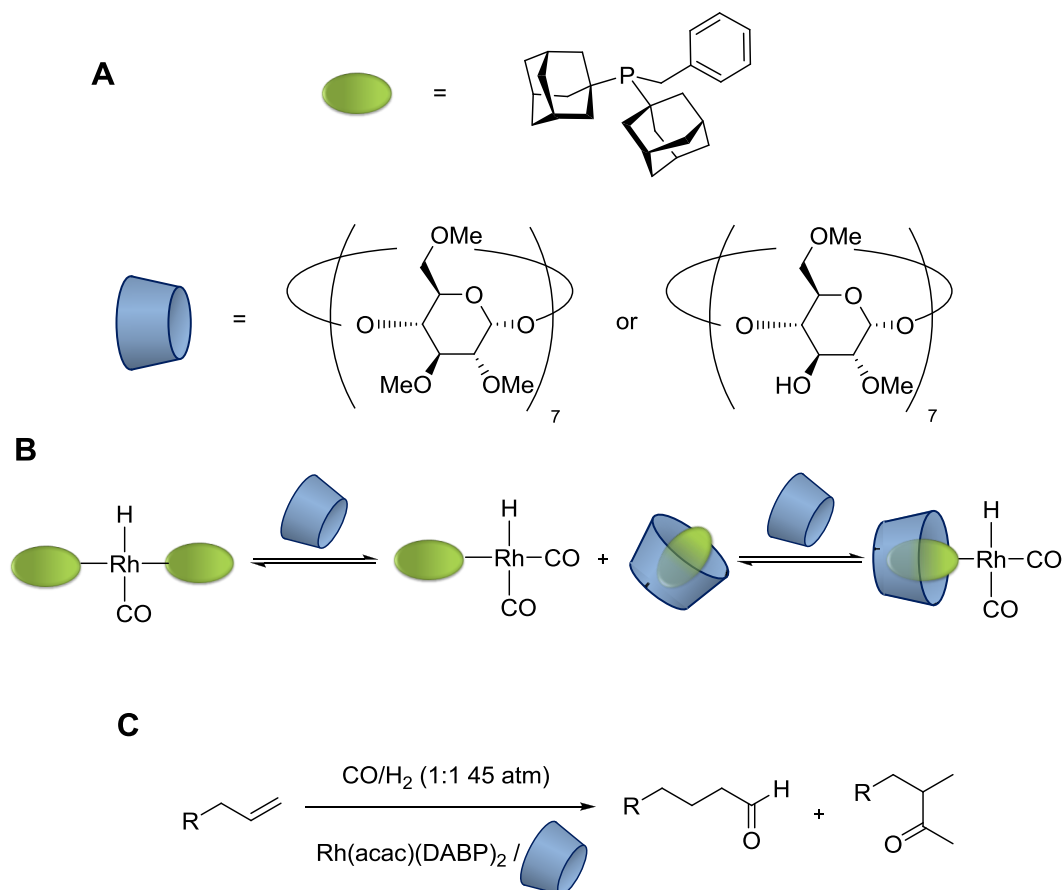


Figure 17: A) DABP (green), TRIME-CD and DIME-CD (blue). B) proposed equilibria for the formation of the active catalytic species in presence of syngas pressure before substrate coordination. C) catalytic hydroformylation catalyzed by Rh complexes with supramolecular DABP/CDs ligands. The reaction was performed either in water (substrate = allyl alcohol) and in dichloromethane (substrate = 1-octene) using DIME- or TRIME-CD changing the CD/Rh ratio.

3.2 SUPRAMOLECULAR CATALYSIS IN AQUEOUS MEDIUM WITHIN SELF-ASSEMBLED HOSTS

Self-assembly lies at the base of vital biological processes, such as the replication of DNA and the folding of proteins. If these complex architectures were formed by covalent bonds they would require an enormous amount of energy to be built and broken and this is evidently incompatible with a large biological system like our body, in which thousands of chemical reactions occur continuously. The secret of self-assembly is the employment of specific building blocks where the information towards the final assembly is already coded and the aggregation occurs spontaneously in specific conditions. This powerful tool adopted by Nature is becoming more and more popular nowadays to artificially build complex structures, otherwise hardly accessible, such as supramolecular polymers, knots, polygons and capsules or nanoreactors. The latter species is extremely interesting for the development of catalysts within which chemical reactions take place experimenting steric constraints that are unusual in homogeneous catalysis. One of the simplest and first studied example of self-assembly is the formation of micelles by using surfactant molecules in aqueous solutions. Micelles are nanometric tridimensional objects extensively studied in their solubilizing ability, but less considered in combination with organometallic complexes to tune activity and selectivity of a homogeneously catalyzed reaction. In this chapter some example of this specific application are reported, together with a general introduction to the theory of micellization, in order to give an overview on this particular type of supramolecular aggregates on which the first part of the experimental work of this thesis is based. Additionally, the description of some metal-ligand capsules is also included, with the aim of underlining the important role of these self assembled aggregates in the development of biomimetic systems by means of encapsulation of traditional organometallic complexes in supramolecular scaffolds. These topics are particularly relevant to this thesis.

3.2.1 MICELLES

Imagine how could James William McBain have felt when, right after the lecture he presented at the Royal Society of Chemistry in London, the chairman replied “Nonsense McBain”.⁵² We don’t know whether, once at home, he decided to check again all his data and theoretical deductions about surfactant containing solutions and micelle formation, but his subsequent career showed that he continued successfully in this field. McBain’s scandalous assertion was about surfactant molecules aggregation in aqueous solution above a certain concentration (CMC) and temperature (Krafft point) to form micelles (from the latin word mica(a)= grain + ella, diminutive suffix); nowadays this concept is universally accepted and called micellization process. Taking a step back, to understand why these molecules self-assemble in water, we have to consider what a surfactant is.

The name stands for “surface active agents”⁵³ pointing out that the main feature is the ability to absorb at the interface between two immiscible phases and lower the interfacial tension between them. Generally speaking there can be 5 possible interfaces (liquid/liquid, solid/solid, liquid/solid, liquid/gas, solid/gas) but in this chapter we’re talking just about the liquid/liquid and liquid/gas ones. In principle, the higher is the tendency to absorb at the interface, the better the surfactant, and the lower the interfacial tension. To optimize the action at the surface, all surfactant molecules should be distributed along the phase boundary, therefore a good surfactant should have low solubility in the bulk phase. But at higher concentrations another phenomenon occurs when an *amphiphile* (from Greek words *amphi-* meaning *dual* and *philia* meaning *loving*, then an amphiphile is a molecule that likes both phases) is dissolved in a - usually aqueous - solution: the monomers start to aggregate to form polymeric self-assembled structures without causing any further variation of the surface tension γ ($d\gamma=0$) and the shape of the aggregate is closely related to the shape of the molecule itself.

Surfactants molecules are constituted by two parts, connected by a rigid linker, each of them showing affinity for a different medium. Common amphiphiles bear a hydrophilic “head”, usually a polar functional group and a lipophilic “tail”, alkylic and either linear or branched. The “head” gives the criterion on which they are classified, therefore we have *anionic*, *cationic*, *non-ionic* and *zwitterionic* surfactants (Figure 11) and the choice depends tightly on the application and the function they have to carry out

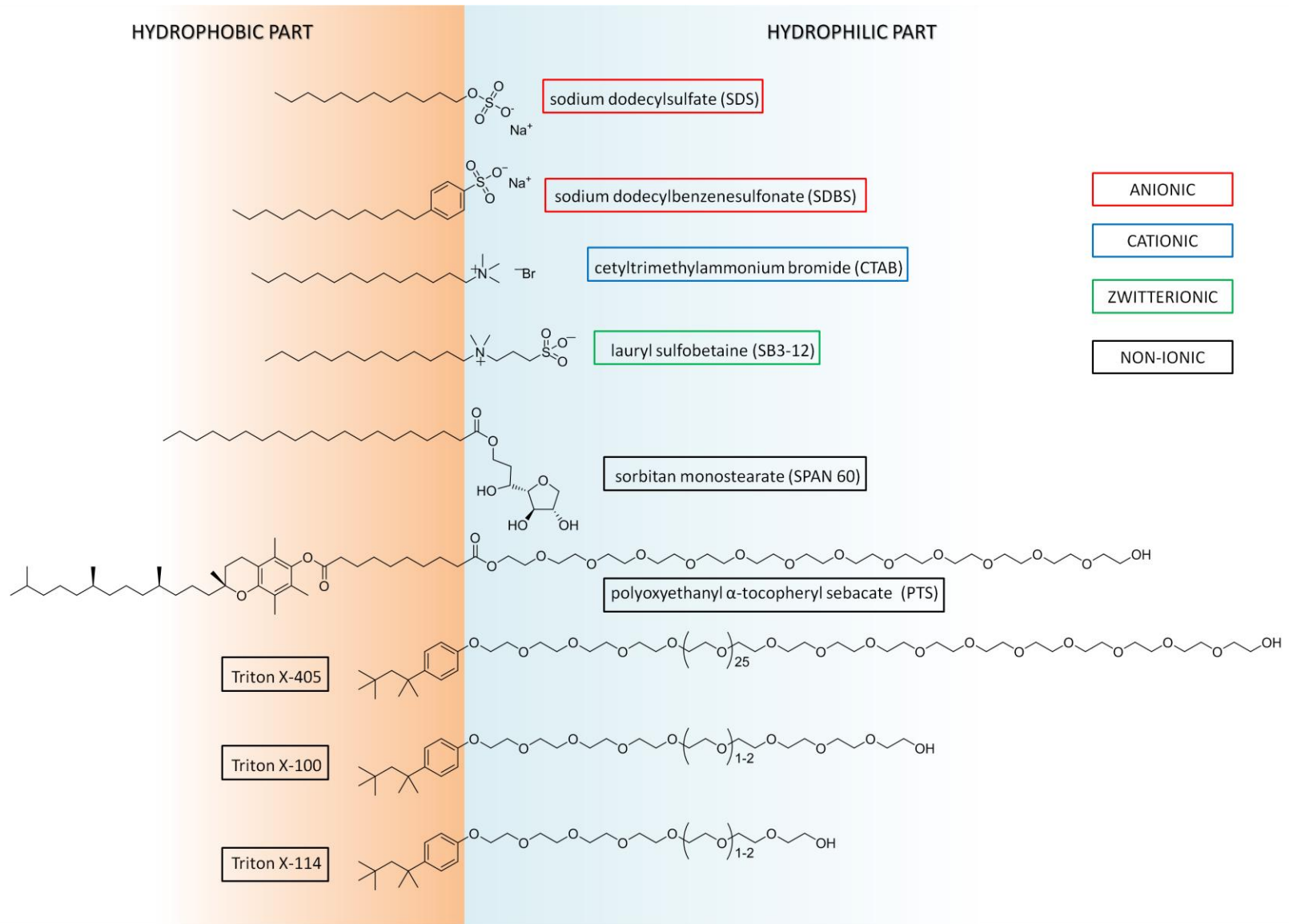


Figure 18: structures of surfactants belonging to different classes.

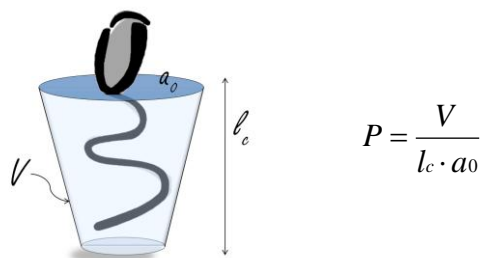
Once dissolved in solution, part of the surfactant molecules are going to align on the surface with the heads pointing to the water phase and the tails to the other phase (that can be an organic liquid or air) but the rest of them will assemble, either in a *synkinetic* – fast involuntary contemporary movement of single components leading to the formation a bigger structure – or in a *programmed* way giving rise to a well defined supramolecular self-assembly. Programmed assemblies in chemistry are totally analogous to computer programs, in the way that components and algorithms are the storage medium for all the information necessary to build the entire process.⁵⁴

What forces the molecules to aggregate is the lowering of the total Gibbs energy derived from the release in solution of several water molecules that otherwise would have been engaged in solvation of every single alkylic chain with a significant loss in hydrogen bonds due to reorientation of the dipoles. Indeed, as the “tail” of the amphiphile is hydrophobic, it tends to reject water and if at low concentrations this results in the migration of the molecules to the surface, when the concentration goes over the *critical micellar concentration* the combination of three different terms gives a ΔG value for supramolecular assembly lower than the one for dispersion of single molecules in solution. This tendency of the hydrophobic substances to segregate, excluding water, constitutes the so called hydrophobic effect, that at the macroscopic level is evident when oil and water are mixed together and form separate layers and at the molecular level drives, besides micellization, protein folding, formation of lipid bilayers, and protein-substrate interactions.

When surfactants are dispersed in water, a clustering process occurs providing: 1) a favorable entropic contribution to the free energy due to the formation of a hydrophobic pocket within the polar heads that, compared to water clathrates formation⁵, leads to a more disordered system; 2) a repulsive force deriving from the electrostatic interaction between the heads (especially the charged ones) balanced by the aggregation tendency (hydrophobic interaction) to aggregate and minimize the interaction alkane-water. If the repulsive contribution is significantly smaller than the hydrophobic interaction the macroscopic consequence is a complete phase separation; the contrary will lead instead to a complex or dimer formation: in micellization process the two contributions are then comparable. The decrease in entropy is the main contributor to the hydrophobic effect, being 85% or more of the total ΔG . The third term to be considered for the total Gibbs energy of this process is 3) a packing term that implicates the total exclusion of water molecules from the hydrophobic core of the aggregates: this means that depending on the shape of the single molecule only a few specific supramolecular architectures are possible.

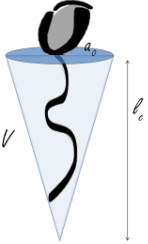
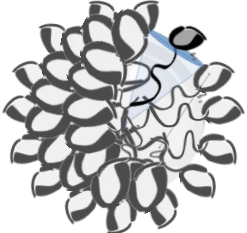
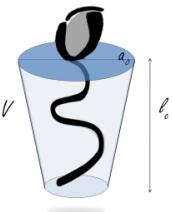
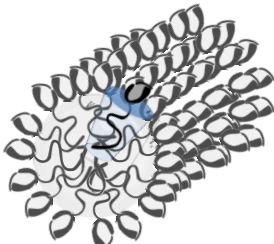
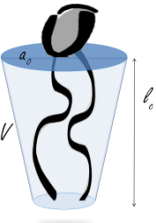
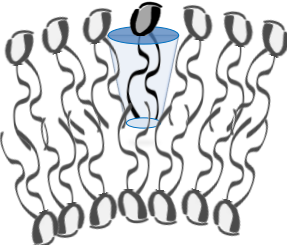
⁵ In presence of apolar solute molecules, water molecules form a cage or *clathrate* around the apolar species. The hydrogen bonds involved in the clathrate formation are weaker than in the liquid bulk, but more ordered.

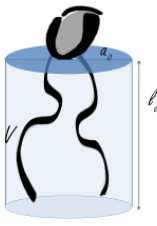
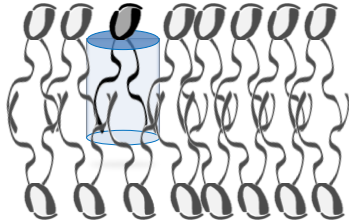
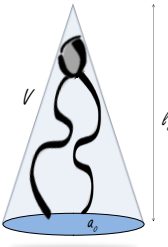
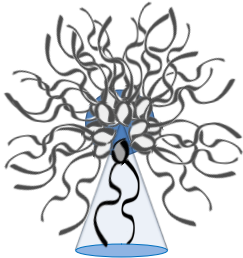
The latter effect was studied extensively by Israelachvili,⁵⁵ who explained the correlation between the structural features of the single surfactant molecule and the global architecture of the resulting supramolecular assembly. This simple model is still used (although important deviations were reported, especially for molecules containing aryl moieties affected by π -stacking between the phenyl rings) to predict the final shape and characteristics of a micellar medium, and is based on the *packing parameter* of the surfactant, defined as follows:



If $0 < P < \frac{1}{3}$ the surfactant is going to form spherical aggregates; a cylindrical shape, corresponding to a packing parameter $\frac{1}{2} < P < 1$ will lead instead to the formation of wormlike micelles up to linear bilayers when the cylinder is perfect. If the head diameter is smaller than the tail one the cone is inverted and the micelles formed are *inverted* too, meaning that the polar heads form a hydrophilic core surrounded by all the hydrophobic tails (Table 4). Non ionic surfactants represent a specific case compared to the other classes: their packing shape can vary not only with the length of polyoxoethylene chain but, depending mainly on temperature, the same molecule can form different kinds of aggregates, sometimes all of them.

Table 4: packing shape of different types of surfactants and related supramolecular structures

<i>surfactant shape</i>	<i>packing parameter</i>	<i>supramolecular assembly</i>
	$0 < P < \frac{1}{3}$	<i>spherical micelles</i> 
	$\frac{1}{3} < P < \frac{1}{2}$	<i>cylindrical micelles</i> 
	$\frac{1}{2} < P < 1$	<i>flexible bilayers, vesicles</i> 

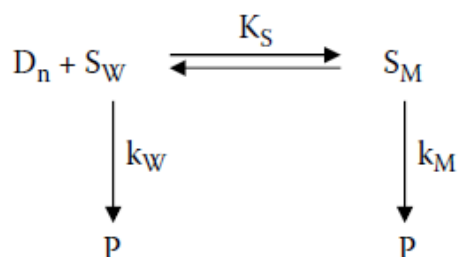
surfactant shape	packing parameter	supramolecular assembly
	$P \approx 1$	<p data-bbox="1170 300 1333 329"><i>planar bilayers</i></p> 
	$P > 1$	<p data-bbox="1159 621 1347 651"><i>inverted micelles</i></p> 

Considering an aqueous solution of a single-tailed surfactant above the CMC value, the phase formed is defined a *pseudophase*, namely something in between two distinct phases and an homogeneous one. When a reaction takes place in presence of micelles, a substrate can be positioned either inside the hydrophobic core, on the micelle surface or in the aqueous bulk. The core is similar to a liquid hydrocarbon, therefore it is able to host poorly water soluble organic substrates or organometallic compounds. The pseudophase kinetic model for reactions occurring in micellar media is also called the *two-domain pseudophase model*, because of the distinction between the micellar part (core and surface together) and the bulk of the solution. The assumptions on which the model is based are:

1. Distinction between micelles and bulk solvent (two different regions or domains)
2. The reactions rates and equilibria are not dependent on micellar size and shape
3. Micellar ingress and egress of the substrates is much faster than the reaction rate, meaning that the reaction in and out the micelle proceeds under chemical regime ($k_{in} \gg k_W$ and $k_{out} \gg k_M$ and $k_{in}/k_{out} = K_s$ in Scheme 1).
4. Different substrates are independently considered

5. The rate constants for formation and disruption of the micellar aggregates are higher than the reaction rate constants inside and outside the micelle ($k_f \gg k_w$ and $k_d \gg k_M$), then the micelle is considered integer for all the reaction time monitored, or, at least, destructing and recomposing without influencing the position of the substrate in the pseudophase.

The model describes micelles as ideal nanoreactors without diffusion restrictions in which concentrations of reactants are altered compared to the bulk. This results in compartmentalization of the substrates (and possibly of the catalyst) that enhances the collision frequency of the molecules favoring for instance C-C couplings or Diels-Alder reactions. Despite the hyper-simplification of this theory and the lack of unambiguous validations for some of the assumptions, the pseudophase model is still used as a starting point to determine kinetics in micellar media in the absence of cross-interface reaction phenomena. Another limit of this model concerns photochemical reactions, being these usually faster than solute uptake in the micelle.



Scheme 1: representation of rate constants involved in a micellar catalyzed reaction. D_n , S_w and S_m stand for micelle, substrate in the bulk and substrate inside the micelle respectively. k_w and k_M are the reaction rate constants outside and inside the micellar phase. K_S is the association equilibrium constant for the inclusion of the substrate within the micelle.

When a micellar aggregate is formed by surfactant molecules with an ionic polar head another important phenomenon has to be taken into account when using such a medium for catalysis. Every ionic group has a corresponding counterion to ensure electrical neutrality and more than half of them are positioned in close proximity to the micellar surface, in the so-called Stern or Helmholtz layer, while the rest is localized in the diffused electric double-layer in continuous motion.⁵⁶ The Stern layer is approximately the same width as the surfactant head group and constitutes something in between water and hydrocarbons, with unexpected pH values and catalytic properties. The latter consideration gave rise to an extended pseudo-phase model called PIE (pseudophase ion exchange) model, in which reactive charged species compete at the surface with surfactant counterions similarly to what they do for a loosely cross linked ion-exchange resin. An example of this exchange capability is the displacement of highly hydrated ions, like OH^- or F^- , by poorly hydrated species, like halogen anions.⁵⁶ This is not the only model existing in literature for micellar aggregates (*e.g.* the Poisson-

Boltzmann Expression model PBE is widely used too), but it works well in many cases, providing qualitative and, for simple systems, also quantitative results.⁵⁷ The bottom line is the need of a careful choice of the surfactant and the counterion with respect to the reaction to be catalyzed in order to enhance reaction rate and avoid unwanted acid/base catalysis or side reactions. Furthermore, a high concentration of reactants and/or catalyst on the surface is ensured if they can substitute the original surfactant counterions and this can be the case of anionic nucleophiles like OH^- on the surface of cationic micelles, or organometallic cationic catalysts forming an ion pair with the heads of anionic surfactants.

An example of surfactant tuning potential was reported by Iglesias for ethylcyclohexanone-2-carboxylate,⁵⁸ for which different pathways can be observed for the reaction in Figure 19.

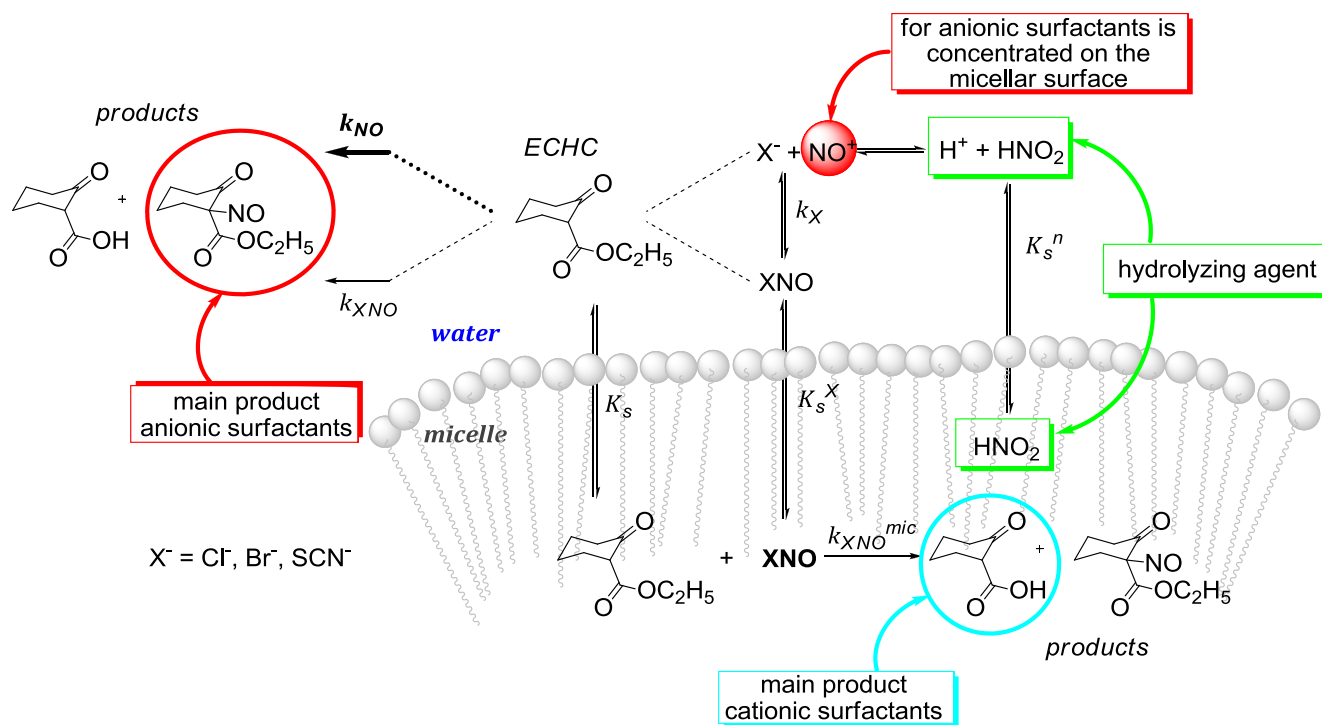


Figure 19: Reaction mechanism and equilibria for nitrosation of ethyl-2-cyclohexanone carboxylate (EHC) in the water-micelle pseudophase system. For anionic surfactants the nitrosation agent is NO^+ on the micelle surface, while cationic surfactants keep this species away due to electrostatic repulsion. This implicates the only presence of XNO as reactant, with a dramatic activity drop.

Under acid conditions provided by *in situ* generated nitrous acid, the use of anionic surfactants, like SDS (Figure 18) or HDS (hydrogen dodecylsulfate), results in inhibition of ester hydrolysis favoring the nitrosation as depicted in Figure 19, with a further enhancement of this effect by increasing amphiphile concentration. In the

same acidic medium, cationic surfactants like DTABr or TTACl** led mainly to the hydrolysis product with no evident effect of concentration changes.

3.2.1.1 Micellar and metallomicellar catalysts: the beginning of a long story

An overview on reactions in micellar media begins with phosphonic esters saponification, that came to the fore as one of the first investigated reactions, used among others in 1967 to validate the pseudophase model. In this case the effect of the micellar medium is to inhibit hydrolysis using anionic surfactants. The ester stays inside the hydrophobic core being protected from hydroxide ions confined in water; the inverse effect is observed using cationic surfactants that attract anions on the surface and provide an enhancement of the reaction rate.⁵⁹ After these first attempts research focused on micellar catalyzed solvolyses, primarily because surfactants permit the direct solubilization in water of a huge number of organic compounds, making possible the transfer of organic hydrolysis reactions in an aqueous medium and resulting in a significant gain in environmental compatibility of these chemical processes.

Among the numerous examples, in the beginning several researchers applied the non-toxicity of micellar catalysis for decontamination from lethal nerve agents used in the past as chemical weapons.⁶⁰⁻⁶³ Moss et al.⁶⁴ were able to hydrolytically cleave the diastereomeric dialkyl *p*-nitrophenyl (PNP) phosphates in Figure 20 at pH 10 with a rate enhancement of more than 2000 folds, with respect to the uncatalyzed reaction, using micellar CTAOOH (cetyltrimethylammonium hydroperoxide). The same catalyst proved to be highly active also at lower pH, opening the way to environmental detoxification.

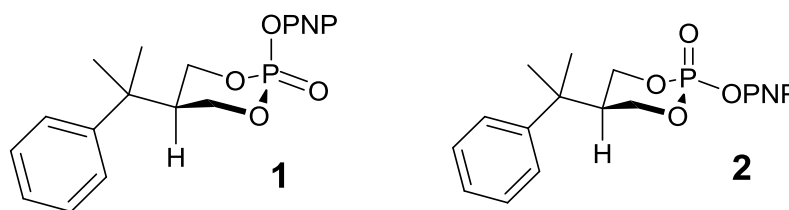


Figure 20: diastereomeric phosphate triesters cleaved by CTAOOH micellar catalyst.

The comparison with metalloenzymes induced researchers to focus on metal-containing systems to push the phosphate ester hydrolysis to higher levels of activity and selectivity. In a recent review paper by Bhattacharya and Kumari⁶³ numerous examples are reported, starting from the first attempt made in 1986 by Gellman⁶⁵ and coworkers, who demonstrated the existence of a combined micellar and metal catalysis for the hydrolysis of

** DTABr = dodecyltrimethylammonium bromide; TTACl = tetradecyltrimethylammonium chloride

diphenyl p-nitrophenyl phosphate DPPNPP using a tetracoordinated Zn(II) complex bearing an hexadecyl group (Figure 21).

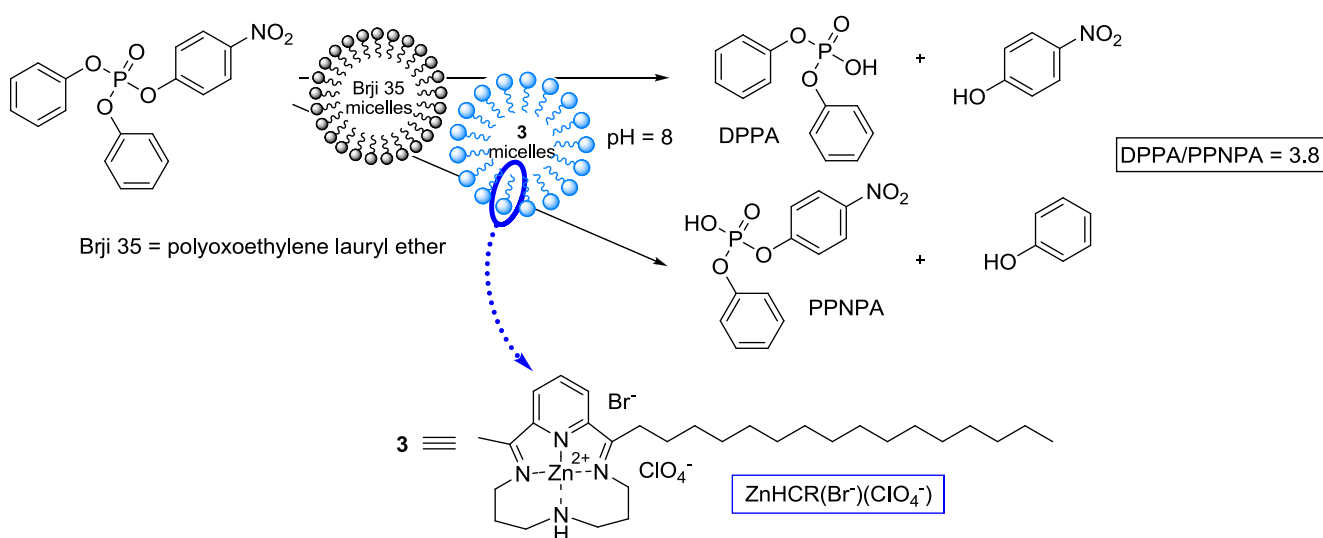


Figure 21: Catalysis of DPPNPP hydrolysis by ZnHCR in aqueous micellar Brij 35. An enhancement of k_{obs} with pH was observed, implicating the formation of ZnHCR-OH (or a kinetic equivalent) as the active species. The apparent second-order rate constant for the ZnHCR catalyzed reaction at pH =8, in micellar solution, increases dramatically with complex concentration, suggesting that ZnHCR aggregates can perform hydrolysis through some higher order mechanism and this alternative mechanism resulted highly effective.

Changing type of substrate, it is worth noting the work of Khan and coworkers, who studied deeply the effect of salts and organic solvents addition for the alkaline hydrolysis of 4-nitrophthalimide in presence of CTAB (Figure 18) micelles.⁶⁶ Increasing the concentration of NaX (with X = Br and Cl) results in a decrease of reaction rate of the hydrolysis most probably for anion exchange at the micelles surface and the same effect is provided by consecutive addition of CH₃CN aliquots up to 15% v/v, when the binding constant of the ionized substrate is lowered from 3650 to 370M⁻¹ (Figure 22).

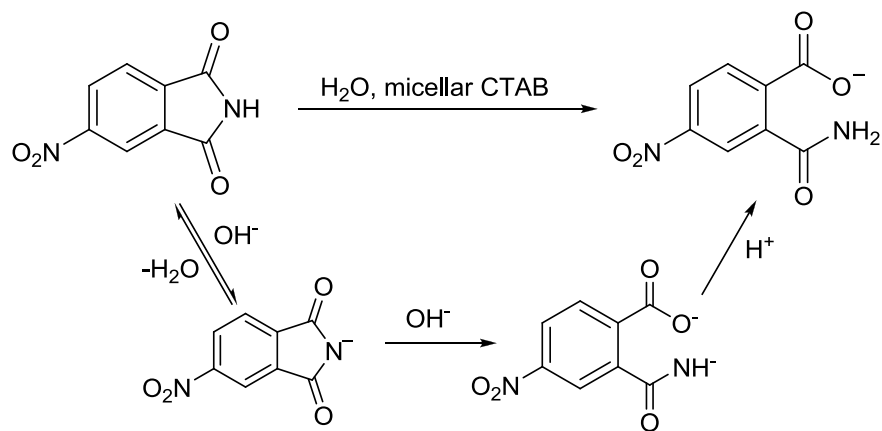


Figure 22: alkaline hydrolysis of 4-nitrophthalimide in aqueous micellar media.

Throughout this chapter some highlights on metal catalysis in micellar media will be given, and attention will be focused on organometallic complexes *within* micelles instead of metal-amphiphile complexes.

3.2.1.2 Pericyclic reactions: Diels Alder

As previously remarked, the hydrophobic environment inside the micelles core is particularly favorable to intra and intermolecular reactions involving hydrophobic organic substrates like in cycloadditions.⁶⁷ Thanks to the work of Breslow and coworkers, water was brought to the scene as a not only suitable, but even desirable solvent for Diels-Alder reactions in the 80's.⁶⁸ Cycloaddition between cyclopentadiene and butenone, was found surprisingly accelerated (more than 700 folds) by simply using water as solvent.^{††} By switching to an aqueous medium, two scenarios are possible: if the concentrations of the organic substrates are low enough to allow their solubilization in water, a homogeneous reaction medium is employed and this corresponds to the so called *in water* approach. But most of the times substrates are insoluble in water and by stirring they form an emulsion composed by oily droplets in which reaction takes place.⁶⁹ This corresponds to *on water* conditions.^{70,71} In both cases the hydrophobic effect plays a key role on reaction's rate acceleration. By measuring activation parameters for Diels-Alder *in water* it turned out that the major contribution to the reaction rate is given by a favorable entropic change in the total energy of the process, identifying hydrophobic effect as the main responsible for reaction acceleration.⁷² Another important effect of hydrophobicity *in water* is the local increase of pressure for substrates "squeezed" together by the water molecules. The Diels-Alder transformation proceeds with a consistent *volume of activation* contraction (ΔV^\ddagger) related to the formation of the transition state.^{‡‡} For this kind of equilibria the direct reaction is known to be favored by increasing pressure and this is what happens locally in the hydrophobic droplets formed when operating *on water*.⁷³ Moreover, as the higher ΔV^\ddagger is usually associated with the endo adduct, unusual selectivities towards this product are observed.

It has been known for many years that pericyclic reactions are accelerated by Lewis acids, thanks to the coordination of these with the polar group of the dienophile, lowering the LUMO energy and consequently stabilizing the transition state: water molecules provide a similar effect thanks to hydrogen bonding. In the present case, the combination of two promoters, water and cationic metal species, allows even better results and a further improvement could be obtained with the addition of micellar aggregates.

^{††} Compared with the reaction in isooctane ($k_{\text{water}}/k_{\text{isooctane}} = 722$ at 20 °C).

^{‡‡} The values of ΔV^\ddagger for Diels-Alder reactions are between -20 and $-45 \text{ cm}^3 \text{ mol}^{-1}$

The first complete study on the real influence of combining micellar and Lewis acids catalysis in Diels-Alder reaction was reported by Otto and coworkers in 1998,⁷⁴ including kinetic studies, substrate scope, surfactant screening and determination of the metallic cation position in the system. The reaction between cyclopentadiene and all the possible **4** species in Figure 23 is inhibited when using both charged and neutral surfactants without Lewis acids contribution, but the formation of micellar aggregates of copper dodecylsulfate $\text{Cu}^{\text{II}}(\text{DS})_2$ causes an up to 1.8 million folds acceleration (using the nitro-dienophile), compared to the uncatalyzed transformation, because of the concentration of the catalytic species on the micellar surface, where the dienophile is located. The presence of **5** on the surface formed with the copper-containing amphiphile is higher than the other surfactants tested and this results in higher proximity between the two substrates, eliminating the negative effect of distance between cyclopentadiene dissolved in the hydrophobic core and the corresponding dienophile coordinated to copper.

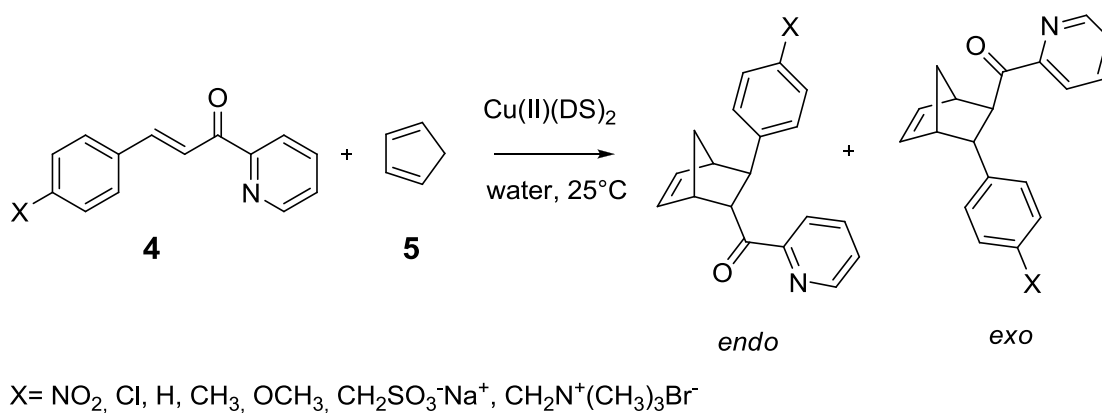


Figure 23: Diels-Alder reaction catalyzed by copper in micellar media. $[\text{Cu}(\text{II})(\text{DS})_2] = 7.8 \text{ mM}$ above the cmc of the particular compound under reaction conditions. Endo/exo ratio, reported for the non-substituted dienophile is generally higher when using surfactants than in pure water or in organic medium.

The above reported was the only successful example of improved activity by micellar catalysis on a Diels-Alder reaction until the beginning of the third millennium. Engberts later demonstrated how reaction rate acceleration is made possible by carefully combining the substrates and the micellar medium. In a 2007 paper⁷⁵ the reaction between the 4-nitrophenyl-1-(2-pyridyl)-2-propen-1-one dienophile and cyclopentadiene was performed using acidified anionic surfactants such as sodium dodecyl sulfate (SDS) and linear alkylbenzene sulfonic acid (LAS) with a rate enhancement of 40 and 170 times respectively.

3.2.1.3 Hydroformylations

Since the discovery of Otto Roelen in 1938, hydroformylation has been both a landmark for the progress of homogeneous catalysis and a multi million tons process. In 1976⁷⁶ Ruhrchemie and Rhône-Poulenc (RCH/RP) patented a revolutionary biphasic process where the Rh(I) catalytic species was modified with three TPPTS (triphenylphosphine tri-sulfonated) water soluble ligands, thus allowing catalyst recovery and recycling by aqueous phase separation from the product containing organic phase. This bright idea entails one major problem i.e. the generally low solubility of the olefinic substrates in the aqueous phase where the rhodium complex is dissolved. The consequence of this is the practical applicability of the system just to C₂-C₄ alkenes, while longer chain olefins provide an unacceptably low conversion for industrial purposes. Many solutions have been proposed over the years, surfactant addition among others,⁷⁷⁻⁷⁹ to either increase the solubility of longer homologues in the catalyst containing aqueous phase or increase the contact surface between the two phases to enhance catalyst accessibility. An additional complication for practical purposes is the following: most organic liquids possess a certain water saturation concentration, meaning that water is always present in the organic medium and this may result in water soluble catalyst migration into the wet organic phase and additional purifications steps needed for products and solvent (this is the reason why RCH/RP process is not applied for fairly water miscible propanal). This phenomenon is present especially when single components concentrations are high, as it happens in industry.

Calixarene derived surfactants combined with rhodium complexes containing the same macrocycle served well the purpose for hydroformylation of 1-octene, ensuring high regioselectivity towards the corresponding linear aldehyde.⁸⁰ The unusual surfactant employed for this study holds a tetrasulfonated calixarene as hydrophilic head and medium/long alkyl chains starting from the lower rim (*vide calixarenes* §3.1). Without surfactant addition the bulky hydrophobic rhodium complex is dissolved in the 1-octene layer formed over the water phase and the reaction proceeds analogously as in toluene. Calixarene based surfactants instead form supramolecular aggregates, that bring the hydrophobic catalyst in the aqueous phase together with the substrate, resulting in the formation of a sort of nanoreactor containing high concentrations of both reagent and catalytic species. This leads to higher activity compared to the organic phase reaction and maximum TOF is reached by tuning surfactant tails length (n-butyl was found to be the best hydrophobic group in terms of conversion: 63.1% after 2.5h). Furthermore, the same reaction medium allows higher linear/branched selectivity than the organic medium (*l:b* = 62 vs 24) still maintaining low levels of olefin isomerization. The choice of surfactants chain length strongly influences the aggregation number and assembly shape in solution. The best results were indeed reported with the C₄-chains, that are required for effective micelle formation. Longer chains (>C₆) lead to dimer or trimers, while shorter ones prevent aggregation. This consideration

suggests the micellar environment as an important factor, still able to modify activity and selectivity even of a high sterically hindered catalyst as the one used in this study. Unfortunately, no mention is made about the possibility to recycle the catalytic species, and this constitutes, from an industrial point of view, one of the most important problems to overcome.

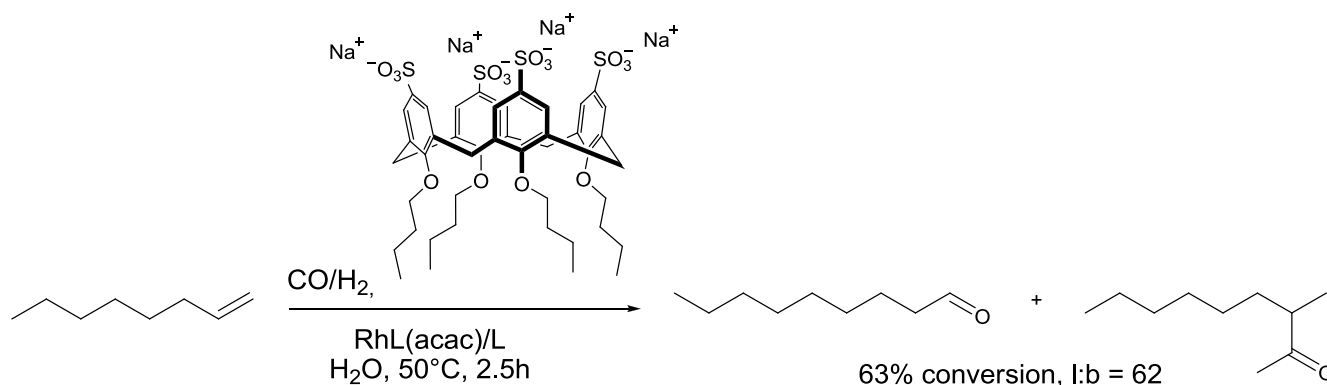


Figure 24: hydroformylation of 1-octene catalyzed by a hydrophobic Rh complex in presence of n-butyl tetrasulfonated calixarene aggregates.

In a recently published work carried out by Strukul and Scarso,⁸¹ the hydroformylation of various olefins was performed by an innovative catalytic approach combining Pt(II) catalysts with cheap, commercially available surfactants and the catalytic phase could be easily recycled.

Monomeric Pt(II) complexes (Figure 25) were dissolved in water by mean of anionic surfactants like SDS, SDBS (sodium dodecylbenzenesulfonate), SDSU (sodium dodecylsulfonate) and SHSU (sodium hexadecylsulfonate), that interact with the cationic complex via electrostatic attraction on the micellar surface. The aqueous medium provides an improvement in catalytic activity, in some cases reaching quantitative conversions (with complex $[(\text{dppb})\text{Pt}(\text{OH}_2)_2](\text{OTf})_2$ styrene conversion is around 10% using organic solvents and goes up to 100% and $\text{H}_2\text{O}/\text{SDS}$). Moreover, the possibility to solubilize a wide range of traditional organometallic complexes allows catalyst screening that revealed, in this particular case, the direct correlation between the phosphine ligand *bite angle*⁸² and catalyst activity and selectivity. For most terminal linear alkenes tested the selectivity to the linear aldehyde is extremely high, complete in some cases, and no olefin isomerization products are detected. For styrene, the unusual formation of benzaldehyde is reported for the first time in literature and the amount of this byproduct can be modulated by changing the surfactant. Finally, recycling tests have been performed for vinylcyclohexane hydroformylation, demonstrating good stability of the catalytic system, that maintains yields >90% and the same l:b ratio (99:1) even after four recycles.

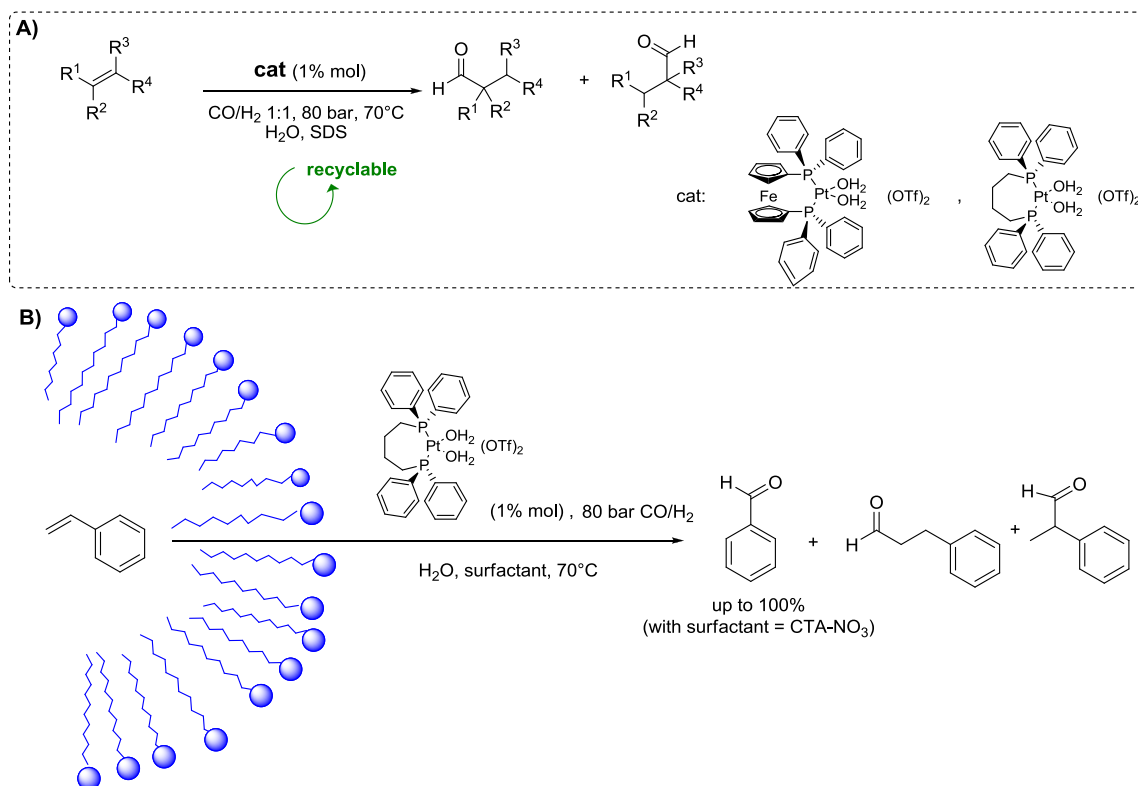


Figure 25: A) Alkenes hydroformylation in aqueous medium catalyzed by Pt(II) complexes bearing bidentate phosphines with different bite angles B) unusual selectivity for styrene hydroformylation in water catalyzed by Pt(II) complexes. The amount of benzaldehyde can be modified by using different micellar media: with SDS benzaldehyde:linear:branched = 9:82:9, while using a cationic surfactant like CTA-NO₃ benzaldehyde is the only product formed.

3.2.1.4 Oxidations

As hydrogenation was one of the first reactions investigated in aqueous medium, the literature concerning this field is extremely rich, while switching to oxidations the number of articles is definitely much lower. Oxidation catalytic systems are less common and stoichiometric oxidants based on high valence metals such as chromium or manganese are still widely used in industry as well as in laboratories, generating large amounts of toxic waste. This makes oxidation a challenging testing ground for green chemistry, especially in fine chemicals productions where oxidations using air, pure oxygen or aqueous hydrogen peroxide are rarely considered. The main problem in pharmaceuticals and natural products syntheses is represented by the several different functional groups of the building blocks that can be all potentially oxidized. Therefore, highly selective oxidation catalysts are required to avoid protections and hydrogen peroxide is generally the “green oxidant” of choice in terms of selectivity. Anyway hydrogen peroxide is sold in aqueous solution and produces water as a by-product, while organometallic catalysts are usually water sensitive. Environmentally speaking performing oxidations with hydrogen peroxide directly in water, similar to what occurs in nature for peroxidases would be

the best choice, but, as it appears clearly from these considerations, this approach entails many hurdles to clear.

Among the available oxidants, both molecular oxygen and hydrogen peroxide allows reactions to be carried out with high atom economy, but from an industrial point of view, the second is preferred because liquid, easier to handle and more selective. Anyway, commercial hydrogen peroxide solutions present a concentration of about 35% v/v and being most of the catalysts not enough active with such a diluted oxidant, more concentrated solutions are required, economically impeding the industrial application of such systems (solutions containing higher concentrations of H₂O₂ are much more expensive than the 35% one). Evidently there is a need for green oxidation methods employing diluted hydrogen peroxide. Titanium silicalite was the first efficient oxidation catalyst working with diluted hydrogen peroxide for several different substrates spanning from olefins to ketones. The system was developed and patented by ENI in the eighties and employed for epoxidations, hydroxylation of aromatics and for the synthesis of cyclohexanone oxime.⁸³ It works in polar solvents, water included (albeit with poor activity), but organic solvent are still preferred for practical applications.

As far as homogeneous catalysts are concerned, MTO (methyl trioxorhenium) was found to form with H₂O₂ an efficient oxidant for the epoxidation of a broad range of olefins, but the best results using diluted aqueous hydrogen peroxide solutions were obtained in dichloromethane⁸⁴⁻⁸⁶ and trifluoroethanol⁸⁷ and no homogeneous process in water has been reported, even if MTO is water soluble. Another successful approach to epoxidations was reported by Beller's group in 2006,^{88,89} wherein Ru(pybox) complexes were employed as asymmetric catalysts for aromatic olefins observing medium-high *ees* (up to 84%), but also in this case a solvent different from water was used. Even the catalyst developed by Mizuno, a Keggin-type di-vanadium-substituted silicotungstate ensuring high selectivities under very mild conditions, was dissolved in CH₃CN/*t*-BuOH.⁹⁰ The use of Pt(II) complexes allowed finally, as reported by Strukul and Scarso in 2007,⁹¹ the development of a high regio- and stereoselective catalytic system operating in water as the only solvent for epoxidation of terminal alkenes. The cationic Pt complexes of general formula [(P-P)Pt-(C₆F₅)(H₂O)]⁺ employed for this reaction are soft Lewis acids characterized by a high air and water tolerance and capable to activate hydrogen peroxide avoiding decomposition and consequently without the need to use over-stoichiometric amount of the oxidant. The epoxidation of terminal olefins was earlier optimized in an organic medium obtaining high stereo- and regioselectivity and the system was subsequently made "green" by switching to a micellar medium. Remarkably, there is no need to modify the catalyst when operating in water, but just the addition of an appropriate surfactant as a solubilizing agent. In this case, Triton X-100 was found to be the best surfactant to ensure solubilization of both catalyst and substrates and in some cases it provides significantly

higher selectivities compared to the organic medium. The aqueous medium allows also catalyst recycling for at least three cycles (Figure 26).

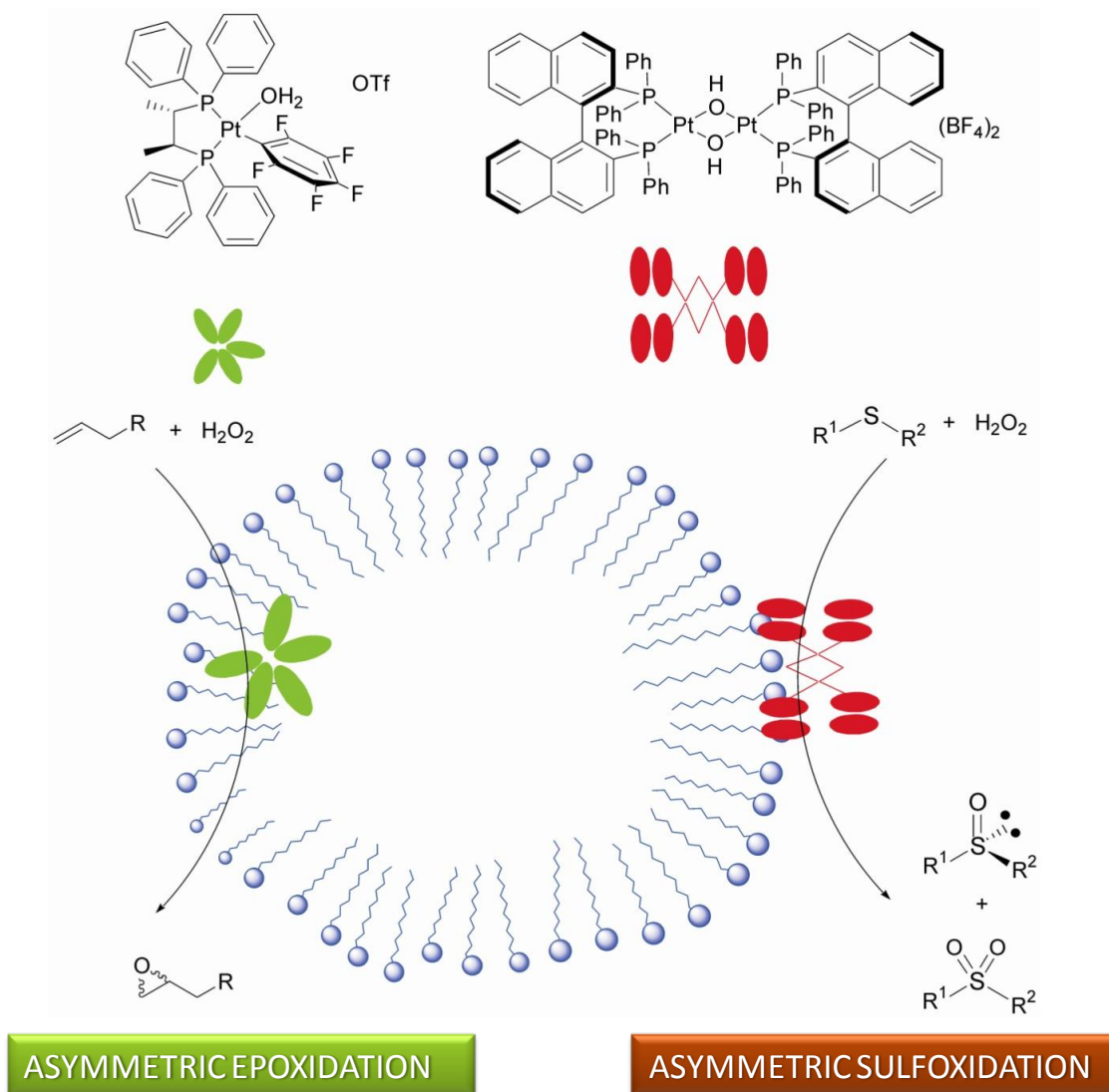


Figure 26 left: switching from traditional chlorinated solvents, like DCE, to micellar Triton X-100, enantioselective epoxidation of terminal olefins was performed with a significant ee enhancement (from 58% up to 84% for 4-methylpentene). On the right side: using anionic surfactants, enantioenriched sulfoxides are obtained with good chemoselectivity and moderate ee, both generally higher than the reaction performed in chlorinated solvent.

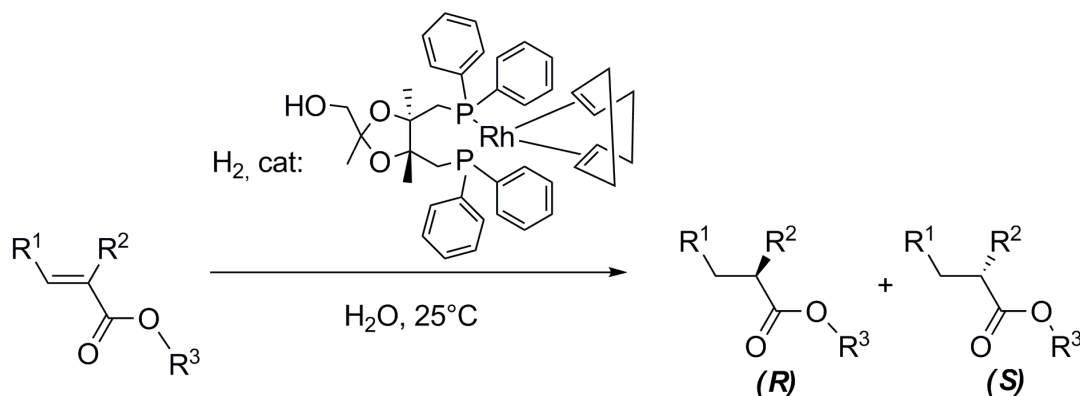
The same group provided in 2005 the first example of asymmetric catalytic sulfoxidation in water (Figure 26) using a dimeric Pt(II) catalyst bearing a traditional chiral bidentate phosphine ((*R*)-BINAP). The synthetic methodology reported therein represented a viable way for carrying out asymmetric sulfoxidation in water. Catalyst loading was low, yields and sulfoxide/sulfone selectivity were from good to excellent (no other products were formed) and, as was previously remarked for epoxidations, the aqueous medium allowed a

significant improvement in the asymmetric induction, compared to the use of organic solvents, although ees were moderate, with only one case over 80%. Searching through the literature, other examples of asymmetric sulfoxidations, even with higher ees can be found, but they invariably work in organic (chlorinated) solvents and require either a higher catalyst loading, or different oxidants, or low temperatures with consequent slow down of rates.⁹²⁻⁹⁵

Another important oxidation, dating back to the 19th century, is the Baeyer-Villiger oxidation, that has been reviewed a few times in the last 20 years^{96,97} and, thanks to its versatility, is widely used for lactones manufacture. This reaction is commonly carried out with expensive and/or hazardous peracids, such as *m*-chloroperbenzoic acid, leading to the formation of at least one equivalent of the corresponding carboxylic acid as waste. Efforts have been made to develop catalytic systems employing aqueous hydrogen peroxide as a much more environmentally friendly oxidant, but in addition to other previously cited problems (like decomposition caused by the metal catalyst and the lower activity compared to other common oxidants enhanced by the dilution) the presence of water as a byproduct can cause the hydrolysis of esters formed by the oxidation reaction. This is also an additional drawback of water as a reaction medium for the Baeyer-Villiger that added to the others prevented chemists from using this solvent for years. Several metals are known for activating hydrogen peroxide to perform BV oxidations, for instance Cu,⁹⁸ Co,⁹⁹ Pd,¹⁰⁰ Pt,¹⁰¹⁻¹⁰⁴ Zr,¹⁰⁵⁻¹⁰⁷ Hf,¹⁰⁸ and Re.^{109,110} Good results in water, especially in the asymmetric version, were achieved by using enzymatic systems, either with isolated enzymes or whole cells containing lipases or BV monooxygenases (BVMOs), operating on traditionally challenging, intrinsically poorly reactive six-membered rings ketones. Entire cells are often the preferred choice in order to provide the regeneration of cofactors (usually NAD(P)H) via fermentation processes.⁹⁶ There's evidently the need for new biomimetic BV catalyzed processes operating in water with H₂O₂ as the terminal oxidant, similar to enzymatic ones, as chlorinated solvents become less and less tolerated for industrial purposes. Metal catalyzed asymmetric Baeyer-Villiger is more recent than other asymmetric oxidations and the number of active organometallic catalysts for this reaction is still very limited. This stimulated numerous studies using enzymes, either pure or as whole cells, but their moderate stability, difficulties in handling and the need of biochemical background has so far limited their use for practical purposes. Therefore the BV challenge remains open.

3.2.1.5 Other reactions

Nowadays, asymmetric synthesis catalyzed by chiral soluble complexes is a common technology employed in several industrial processes and in the synthesis of lots of drugs¹¹¹ and food additives, herbicides and pesticides. Historically the first and most successful enantioselective reaction studied was hydrogenation; the simplicity of this reaction led quickly to full mechanistic understanding disclosing a variety of elementary steps that were subsequently useful also for other reactions. Water as a reaction medium appeared first as a negative choice, mainly due to the low solubility of H₂ in such a polar solvent. But some hydrogenation catalysts, e.g. Ru chloride complexes, and substrates, e.g. carbohydrates or acids, are insoluble in common organic solvents and require water to be brought into solution. This prompted to study hydrogenation in biphasic media and/or water. Selke, for instance, provided a viable method for the hydrogenation of aminoacid precursors using rhodium complexes and SDS as additive.^{112,113} The addition of SDS led to a general increase of enantioselectivity, explained by a combination of different effects, including high local concentration of catalyst and substrate in the micellar phase and less catalyst solvation resulting in stabilization of the active species. In a test performed on unsaturated prochiral acids derivatives using the precatalyst [Rh{(R,R)-OH-diop}{cod}]BF₄ the effect of the micellar medium was such that the ee's went up to 40-80% from the 2-30% of the same reaction without SDS. The importance of micelles formation was confirmed by the dramatic decrease in enantioselectivity caused by the addition of MeOH, known for disrupting SDS aggregates. The striking effect of amphiphiles addition is most probably related to the coordination of the surfactant to rhodium, forming a highly selective metallomicellar catalyst. Thanks to Oehme and coworkers the micellar approach optimized in the early 90's became more industry-friendly and recycling was possible using a membrane reactor wherein the micellar-encapsulated catalyst was entrapped.¹¹⁴



R ¹	R ²	R ³	ee% water	ee% SDS micelles
Ph	NHCOCH ₃	Me	1.5	76.6
Ph	NHCOCH ₃	H	34.4	72.8
H	CH ₂ COOMe	Me	26.4	40.3 (S)
H	CH ₂ COOH	Me	11.7 (S)	69.7 (S)



Figure 27: enhancement of the enantioselectivity for a hydroxy-containing Rhodium(I) bisphosphine catalyst (the species in figure is the precatalyst $[\text{Rh}\{(R,R)\text{-OH-diop}\}(\text{cod})]\text{BF}_4$) in aqueous solution by micellar SDS.

When the hydrogenation agent is not molecular hydrogen, but a synthetic analogous, the reaction is addressed as (asymmetric) transfer hydrogenation, ATH and highly enantioselective Ru catalyzed versions of this reaction were studied in micellar media.¹¹⁵⁻¹¹⁷ Anyway, in order to enhance environmental and human sustainability of these chemical processes, more bio-compatible metals, like iron or copper, are today preferred to toxic metals such as ruthenium. In this respect, it is worth citing a 2008 work by Lipshutz about Cu catalyzed reductive aldol addition creating three stereocenters in one pot.¹¹⁸

The surfactant recently introduced by Lipshutz, PTS, gained its main glory in non-asymmetric cross-coupling reactions (Chapter 1, Section 1.2). However, it was quite satisfactorily applied also in the intramolecular asymmetric reductive aldol reaction of (Z)-4-methylnon-3-ene-2,8-dione, catalyzed by an active species made of copper hydride stabilized by one of the ligands of the Josiphos family and the desired cyclic product was obtained in high yields and 94% ee, comparable with the organic system in toluene (Figure 28).

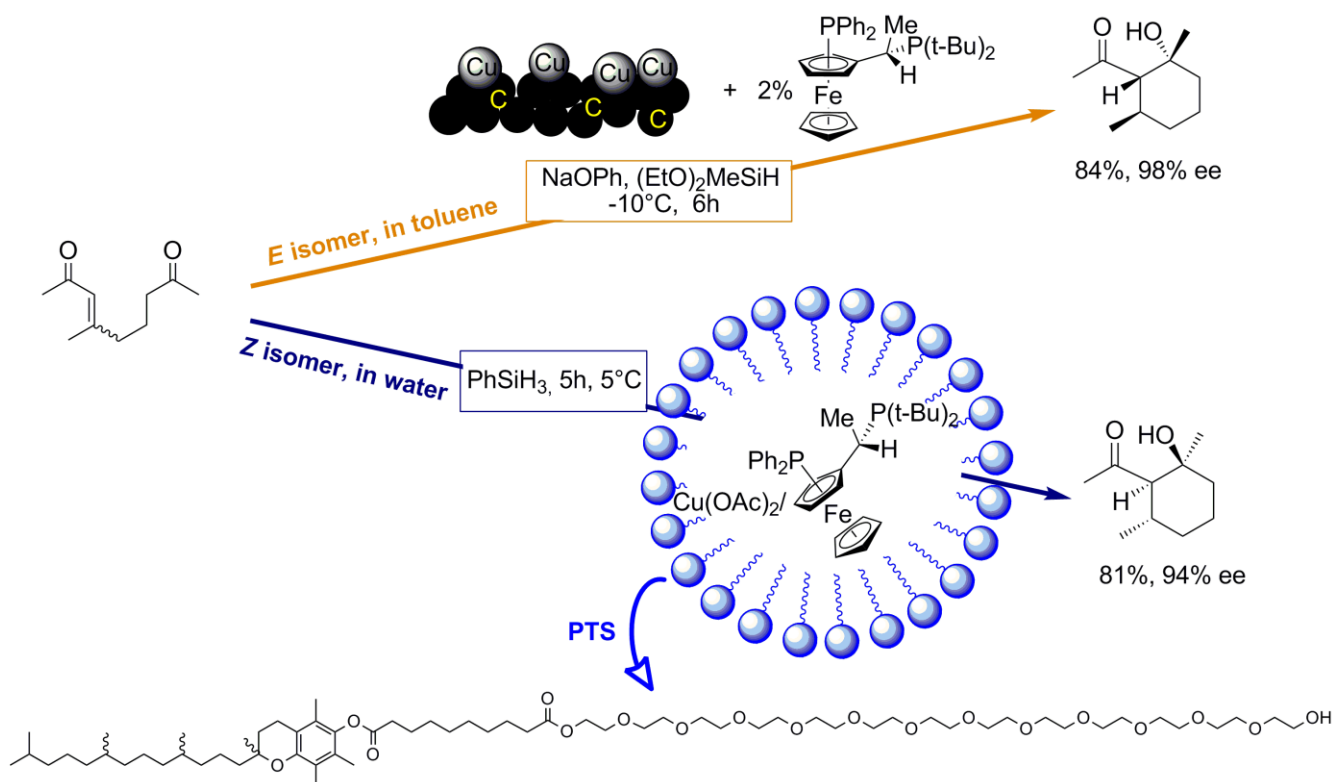


Figure 28: comparison between heterogeneous and aqueous asymmetric reductive aldol reaction. The greener aqueous system, based on micellar PTS to solubilize the chiral Cu catalyst, gave competitive yields and ee's compared with the organic one.

Another prominent example of asymmetric reaction in micellar medium was provided by Kobayashi in 2004.¹¹⁹ He observed a notable enhancement in activity and selectivity for asymmetric Mannich-type reactions in water by adding CTAB to the reaction mixture including water, ZnF₂ as the Lewis acid catalyst, a chiral diamine and the substrates. In addition of the increase in enantioselectivity, the micellar medium shows the unusual possibility to convert (*E*) or (*Z*) silicon enolate to the *anti* and *syn* adduct respectively, while other catalysts usually preferably provide just one of the two. The only drawback of this system is the use of stoichiometric amounts of ZnF₂ with respect to the acylhydrazone ester **6** (Figure 29A). One year later,¹²⁰ employing dodecyl sulfate bearing Sc(III) as counterion and a chiral bipyridine ligand in water, Kobayashi achieved the catalytic asymmetric ring-opening of *meso*-epoxides with aromatic amines to produce β-amino alcohols in high yields (up to 91%) with enantioselectivities up to 96% (Figure 29 B). In both reactions selectivities proved to be significantly higher than in dichloromethane.

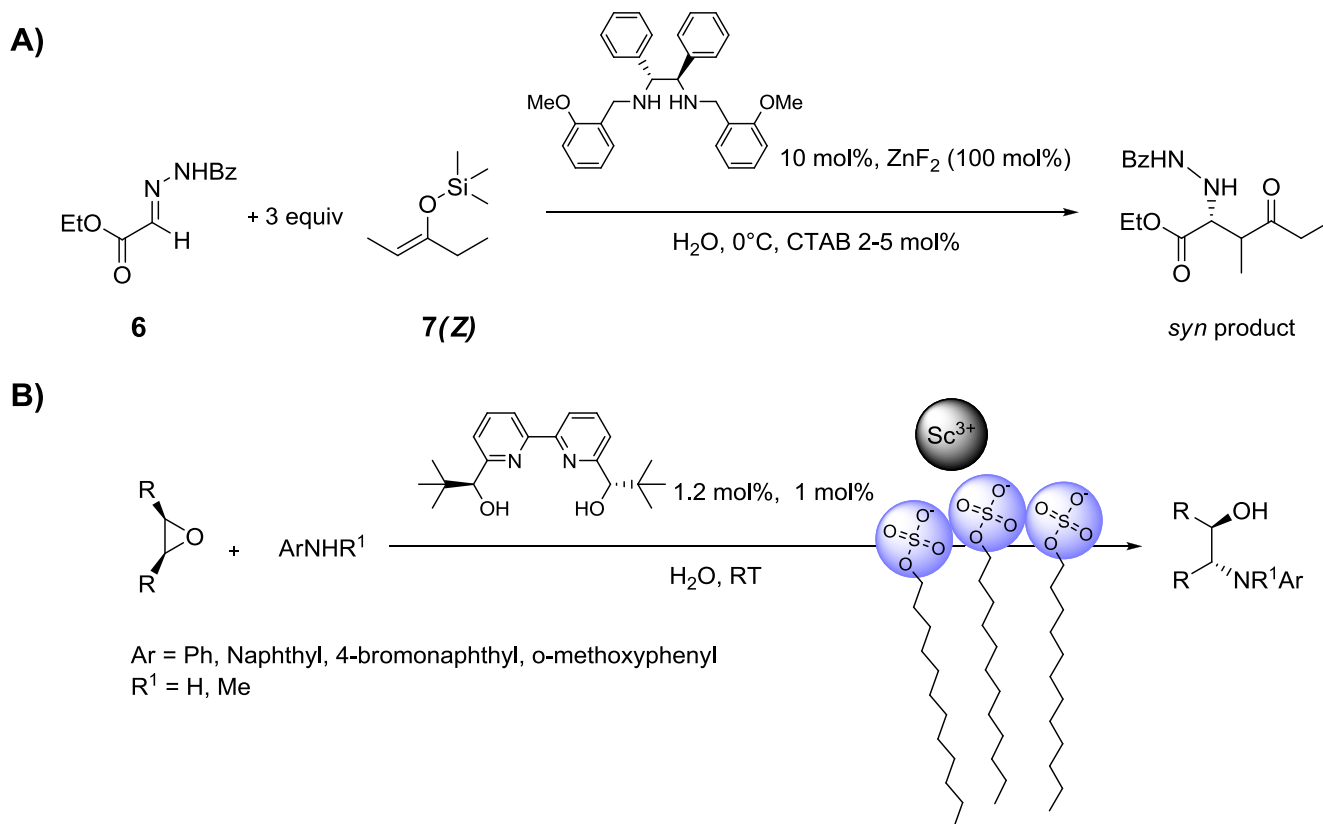


Figure 29: Asymmetric syntheses in aqueous medium catalyzed by A) ZnF_2 combined to CTAB micelles and B) scandium dodecylsulfate micellar aggregates. The Mannich-type reaction A) can be directed towards the *anti* instead of the *syn* product by changing the starting 4 diastereomer.

In all the selected examples the asymmetric induction is ensured by a chiral ligand coordinating the metal, but another possible approach could be the use of chiral surfactants combined with achiral complexes. Studying surfactant-based organo-catalytic systems, some chiral amphiphiles were developed,¹²¹⁻¹²⁶ potentially representing a good starting point to test this alternative approach, but no examples of the combination of these molecules with organometallic complexes are known yet.

3.2.2 METAL-LIGAND BASED CAPSULES

In 1998 a swiss company put on the market a new toy construction system (GEOMAG™), based on nickel-plated steel balls (spheres) and short connecting sticks with a magnet on each end (rods). With these two basic elements, a huge number of geometric shapes and structures could be built (Figure 1a). Three years before, Fujita and coworkers published an article with the title “Self-assembly of ten molecules into nanometre-sized organic host frameworks”,¹²⁷ in which the structure of Figure 30b was reported. Most probably Fujita did not imagine how his work could have been so similar to a toy, but the concept he applied to create such cages was exactly the same as GEOMAG™: taking linear (organic ligands) and angular (metal complexes with free coordination sites) subunits of appropriate shape and size you can create defined molecular polygons held together by non-covalent bonds.

A)



B)

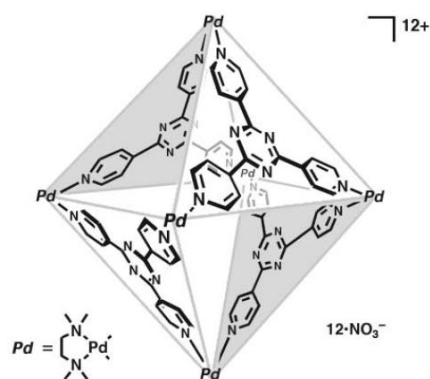


Figure 30: A) regular octahedron built using the GEOMAG™ construction set; B) nano-container synthesized by Fujita's group using ethylenediamine palladium(II) dinitrate complexes (spheres) in combination with a tridentate aromatic ligand (walls)

This octahedron and all the other polygons synthesized by Fujita can be prepared quite easily by means of self-assembly using the information “stored” in the building blocks. In a seminal work in 1998,¹²⁸ Stang and coworkers assessed the design strategies for metallocycles and polyhedra to ensure a closed structure instead of an open, polymeric one. In general ligands are classified as one-dimensional and two-dimensional whether they are bi- or multi-dentate, like those bridging between more than 2 metals centers that can form the faces of the final polyhedron. Starting from metal complexes and one-dimensional ligands (the spheres and the rods of GEOMAG™) to form structures as in Figure 31 the process is called *molecular scaffolding*; when the ligands are two-dimensional (the green faces in Figure 30A) the same process is called *molecular panneling*. In both

cases the final result is the creation of an *artificial void* where a guest can be accommodated: for instance the poly-cationic hydrophobic nature of Fujita octahedrons (in Figure 30B between the ligand's aromatic rings there can be either no spacer or an aryl spacer) makes it suitable to host either anionic or neutral organic species in aqueous medium.

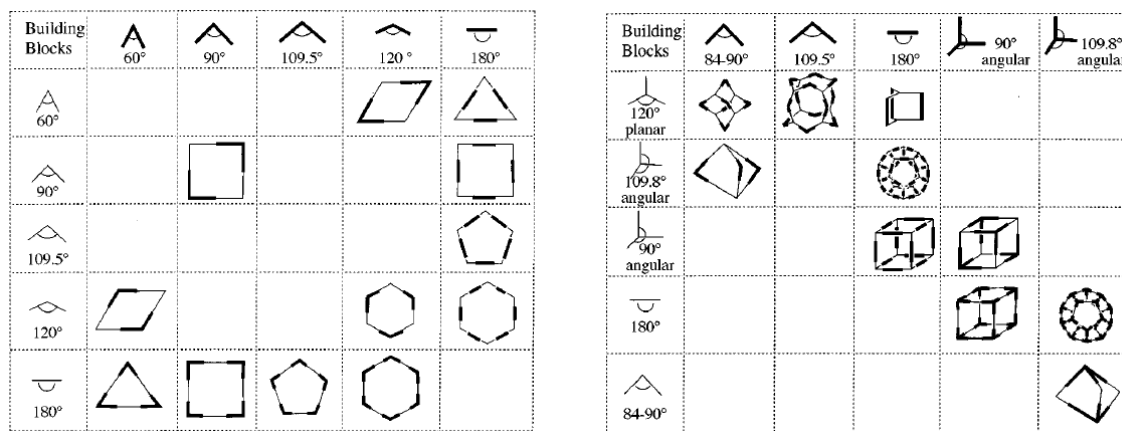


Figure 31: molecular scaffolding of planar and tridimensional structures using metal-ligand interactions.

The compartmentalization of organic species inside a cavity provided by a big supramolecular surrounding is one distinctive feature of enzymes' catalytic action in living systems, and chemists have been trying for years to create a similar environment; metal-ligand cages seem to be the most promising approach to this aim so far. Ten years after its creation, Fujita's octahedral cage was used as supramolecular nano-reactor for the Diels-Alder reaction between 9-hydroxymethylanthracene and N-phenylphthalimide in water.¹²⁹ Usually anthracenes react preferably at the central ring, preserving the aromaticity of the two side rings, but in this case unusual selectivity and higher yields were observed, leading to the formation of the 1,4-*syn* adduct in quantitative yield. This is most likely due to the parallel orientation, assessed by force-field calculations, of the guests inside the cage before reacting, with the C=C bonds of the phtalimide in close proximity to the terminal ring of the anthracene: this is one of the rare examples where pre-orientation of the substrates, forced by a confined space, can lead to a product different from the energetically favored one. The main problem in this kind of enzyme-like systems is the turnover of the catalyst that makes the real catalytic nature of the species doubtful when, like in the latter example, the amount of nano-cage is almost stoichiometric. Product inhibition in Diels-Alder reactions is, for most of the synthetic capsules,¹³⁰⁻¹³³ a dramatic problem arising from the entropically favored binding of one product molecule instead of two substrate ones in the cavity. Using a cavity bearing a wider opening, like the pyramidal bowl in Figure 32, the same reaction suffered the loss of the 1,4 selectivity, but gained a moderate turnover (the optimal amount of supramolecular catalyst is 10 mol%), permitting the formation of the Diels-Alder product quantitatively in 5 hours at room temperature.

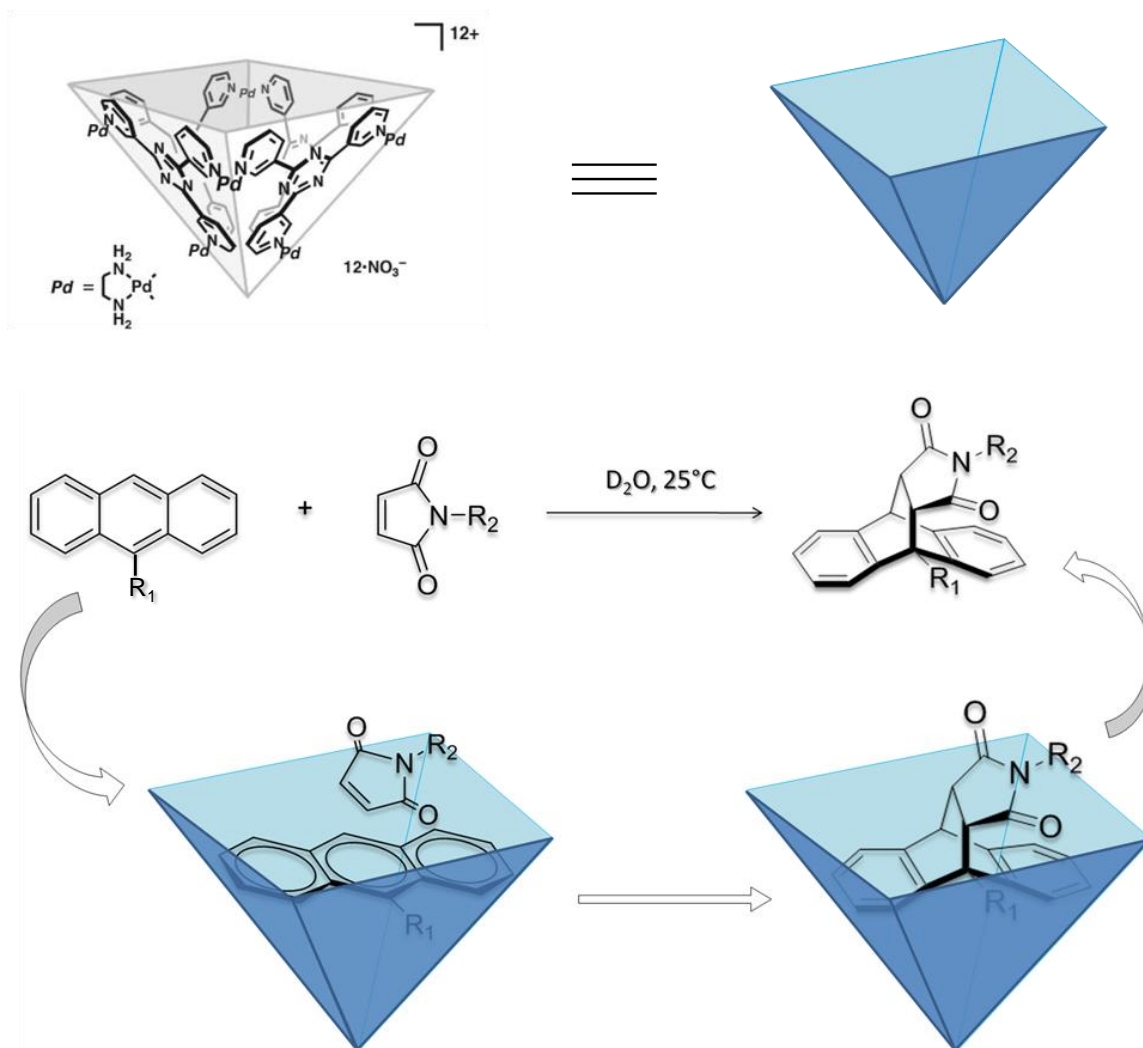
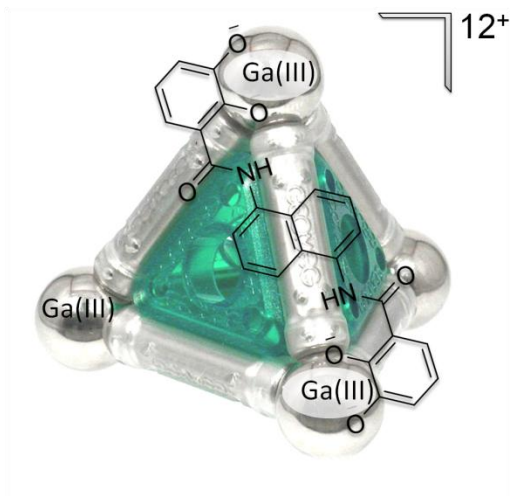


Figure 32: Schematic representation of the catalytic Diels-Alder reaction of anthracenes and phthalimide in the presence of the bowl-shaped host. The catalytic action of the cage is ensured by the autoinclusion and autoexclusion step depicted in the scheme.

Other examples of capsules acting as true catalysts are known in literature, first of all the tetrahedral cage developed by Raymond in 1999 using for the first time a rational synthetic approach to the synthesis of high-symmetry clusters based on the metal–ligand coordinative bond. The capsule is an example of molecular scaffolding employing four metal vertices coordinated to six organic ligands. Each cluster could theoretically present either C_3 ($\Delta\Delta\Delta\Delta/\Delta\Delta\Delta\Delta$) S_4 ($\Delta\Delta\Delta\Delta$) or T ($\Delta\Delta\Delta\Delta/\Delta\Delta\Delta\Delta$) symmetry, depending on the chiralities at each metal center; practically just the homochiral T-symmetric assemblies are formed.⁵⁵ The dodeca-anionic charge of the cage render it soluble just in water or other polar solvents and allows the inclusion in the hydrophobic

⁵⁵ The symbol Λ (*lambda*) is used as a prefix to describe the left-handed propeller twist formed by three bidentate ligands. Similarly, the symbol Δ (*delta*) is used as a prefix for the right-handed propeller twist.

cavity (300-500 Å³) of cationic guests like alkylammonium ions or organometallic complexes. In addition, it “protects” reactive guests that suffer from decomposition in water or are only stable under anhydrous or extremely acidic conditions.



All these characteristics permitted the employment of the tetrahedron as a nanoreactor for a plethora of different reactions, both in stoichiometric and catalytic quantities, e.g., the isomerization of allylic alcohols,¹³⁴ acetals hydrolysis,¹³⁵ 3-aza-Cope rearrangement of allyl enammonium cations¹³⁶ and Nazarov cyclization,¹³⁷ the first one reported. One striking example of this host at work is the catalytic action on the acidic hydrolysis of orthoformates HC(OR)₃ (where R is an alkyl or aryl group) in basic solutions (Figure 33),¹³⁸ made possible by the formation of a cationic transition state stabilized by the anionic pocket even in a unfavorable environment (pH=11 in the bulk). Protonation of the orthoformate is thermodynamically driven by stabilization of protonated species, as observed for other cationic intermediates such as tropylium ion, phosphine-acetone adducts, and iminium cations. Catalytic amounts (1 mol%) of the tetrahedral assembly gave acceleration of the reaction up to 890-fold, showing an enzymatic behavior characterized by Michaelis-Menten kinetic, substrate size selectivity and competitive inhibition by NPr₄⁺. Completely analogous to this is the aza-Cope rearrangement of allyl enammonium ions, performed using 13 mol% of the same capsule with similar rate enhancement and enzymatic features.

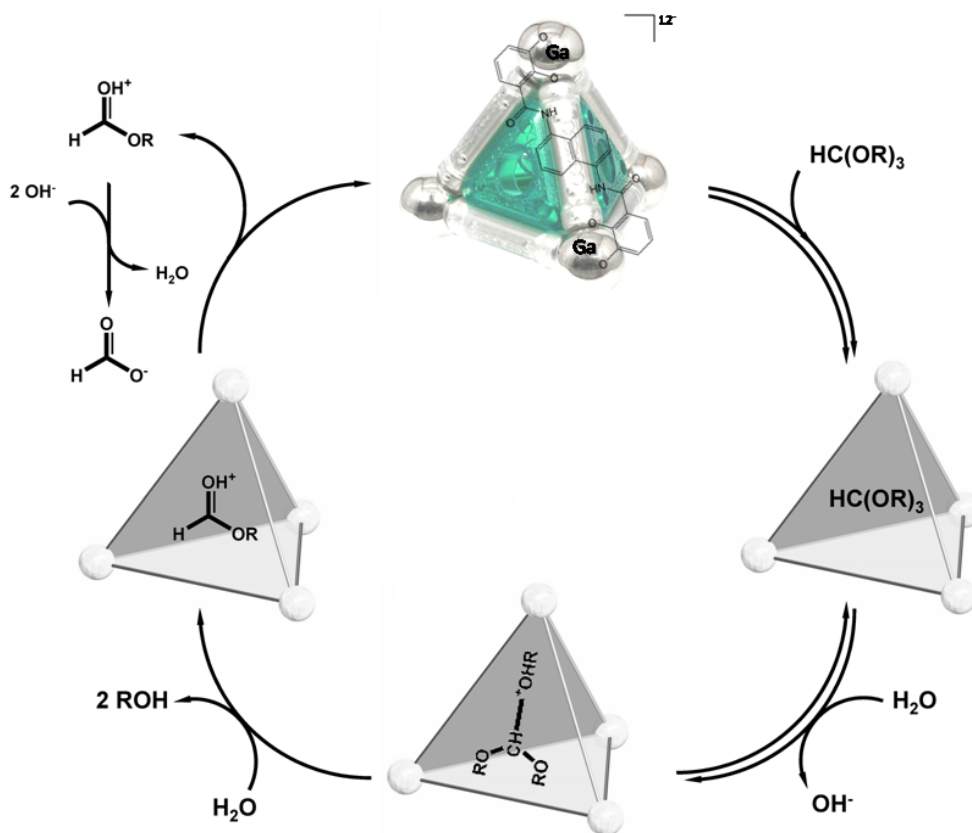


Figure 33: orthoformate hydrolysis in water within the tetrahedral host developed by Raymond.

The hosting ability of this cage was used not only for substrates or reactions intermediate, but also for organometallic cationic complexes, creating artificial metallo-enzymes, in some cases with great substrate selectivity. Besides the example reported in Chapter 1, the capsule was also used to host the chiral racemic monomeric Ir(III) complex $\text{Cp}^*(\text{PMe}_3)\text{Ir}(\text{Me})(\text{CH}_2\text{CH}_2)$ leading to two diastereoisomeric complexes with modest diastereoselectivity. The organometallic species readily reacted with aldehydes R-CO-H leading to C-H activation of the carbonyl compound with ethylene elimination and formation of chiral $\text{Cp}^*(\text{PMe}_3)\text{Ir}(\text{CO})(\text{R})$ species where the R residue of the aldehyde was now connected to the metal center. For the encapsulated organometallic precursor the reaction with the aldehyde was highly substrate sensitive, both in terms of size selectivity (*n*-pentanal did not react while *n*-butanal did) as well as shape selectivity (2-methyl-butanal did not react while 3-methyl-butanal did). The chiral products were formed in a chiral cavity, therefore diastereoselective formation of the two stereoisomeric Ir(III) complexes occurred, with selectivity that could be as high as 70:30. This is a clear example of cavity directed substrate and product selectivity, where the surrounding of the catalytic site with a supramolecular structure influences the pathway of the reactions also from a stereochemical point of view.

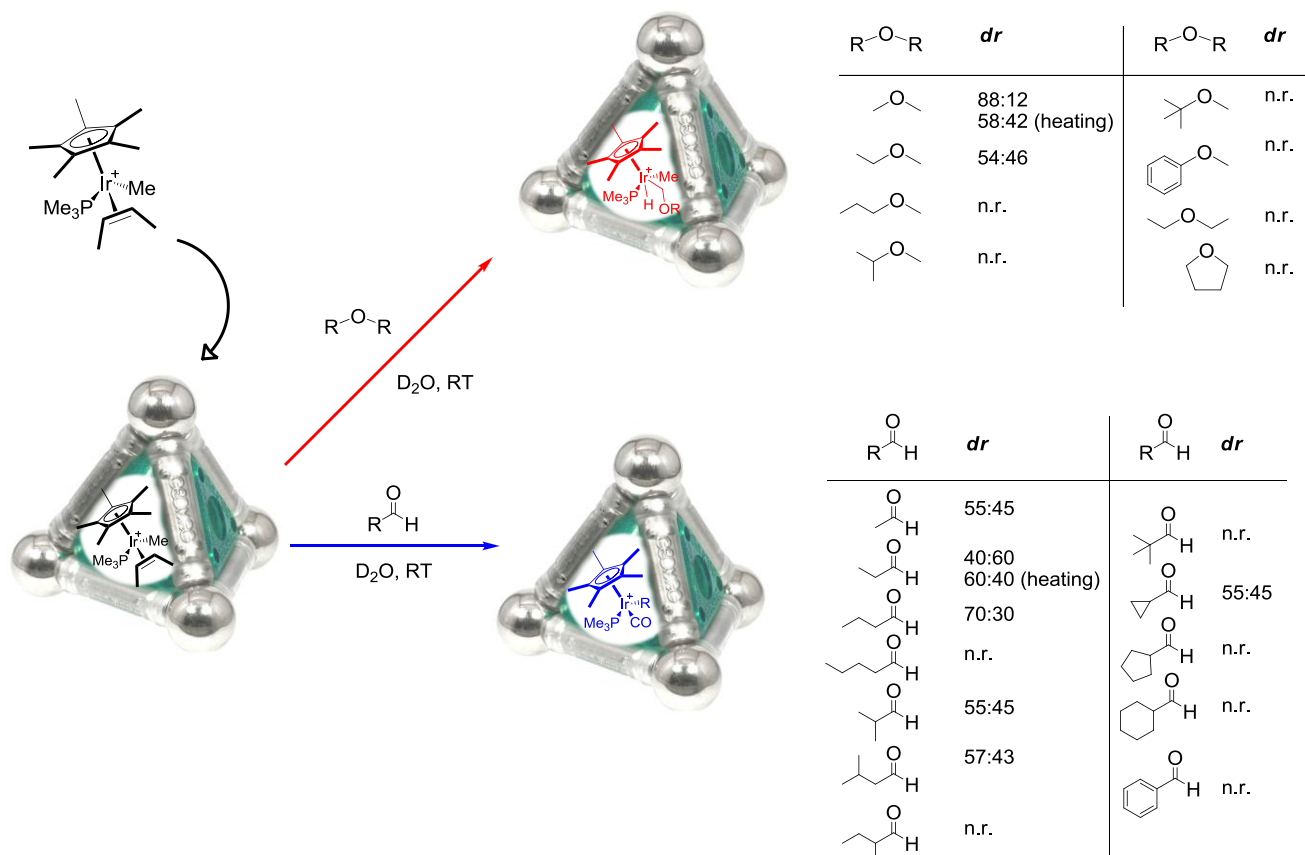


Figure 34: C-H bond activation within a supramolecular host catalyzed by an encapsulated chiral iridium complex. The reaction of the encapsulated species with both aldehyde (blue arrow) and etheral (red arrow) substrates led to different kinetic diastereomeric ratios depending on the host-guest affinity. In some cases (dimethylether and propionaldehyde) heating up to 75°C resulted in equilibration to the thermodynamic diastereomeric ratio.

3.3 SUPRAMOLECULAR CATALYSIS IN ORGANIC MEDIUM WITHIN HYDROGEN BONDED STRUCTURES

“Hydrogen bonds are like human beings [...]. As an individual they are feeble, easy to break, and sometimes hard to detect. However, when acting together they become much stronger and lean on each other.”

Prins, L. J.; Reinhoudt, D. N.; Timmerman, P. *Angewandte Chemie - International Edition* **2001**, 40, 2382-242

Francis Crick and James Watson's names are bound together since 1953, when they deduced from models and X-ray diffraction data the helical structure of DNA. The molecule on which our genetic code is written was found to be a supramolecular assembly of two linear strands, held together by weak intermolecular interactions, namely hydrogen bonds. The combination of all the single weak bonds provides a linkage between the two DNA (or RNA) strands that are strong enough to keep them together in normal conditions but allows also the separation needed for the duplication process. This is one of the most famous examples of hydrogen bonded structure, given us by nature, continuously inspiring chemists in search for innovative synthetic tools. Supramolecular chemistry in particular was defined as “the chemistry of the noncovalent bond” and reporting the words of J.M. Lehn, Nobel Prize in 1987, “The design of artificial, abiotic systems capable of displaying processes of highest efficiency and selectivity requires the correct manipulation of the energetic and stereochemical features of the non-covalent, intermolecular forces”,¹³⁹ like van der Waals forces, electrostatic interactions, π - π stacking and especially hydrogen bonding. All these interactions are much weaker than covalent bonds (0,1-5 Kcal mol⁻¹ vs 50-100 Kcal mol⁻¹) but play a fundamental role in biological systems, like in protein folding and enzymatic catalysis, contributing to the stabilization of the transition state and to substrate recognition. In order to understand the forthcoming examples, it is important to underline the tight correlation between the existence of H-bonds in solution and the solvent used: polar solvents like alcohols or water are strong competitors for H-bonding and tend to disrupt the intermolecular interactions between the solute molecules, therefore most of the supramolecular structures based on non-covalent syntheses are dissolved in apolar solvents, either chlorinated or aromatic ones. Nature provides many examples of hydrogen bonds in water, but usually these are embedded in lipophilic pockets having the double role of protecting the H-bonded part and enforcing the interaction thanks to the hydrophobic effect (*vide* §2.2.2). In enzymatic catalysis, the presence of a pocket or cavity ensures a large area of interaction between the substrate and the catalyst, and this plays a key role in improving activity and selectivity of the reaction. Anyhow, this interaction should not be too tight and certain flexibility is required to permit substrate ingress and products egress in an easy way. An

excessive rigidity of the catalytic environment may lower the turnover, but on the other hand when the substrate is too loosely bound, the lack of selectivity may become the main problem. The right dimension of the cavity and additional weak interactions between the guest and the host (H-bonds, but also π - π stacking or van der Waals/London forces) constitute the most suitable conditions for a good association constant. The optimal binding of a guest inside a cavity is generally estimated using the *packing coefficient*, defined as the ratio between the sum (V_w) of the van der Waals volumes (v_w) of the n molecules in a given volume (V) and the volume (V).

$$PC = \frac{\sum_{i=1}^n v_w^i}{V} = \frac{V_w}{V}$$

For solvent molecules in the bulk, as well as for guests characterized by a good binding within a host in solution (one or more co-encapsulated guests), the PC is generally around $0,55 \pm 0,09$, as reported by Mecozzi and Rebek in 1998.¹⁴⁰ This restricted range of PC can be found in many natural systems, e.g. in biological receptors and provides a sort of guideline for developing synthetic receptors for a wide range of hosts.

With this general rule at hand non-covalent synthesis of several hosts was possible, in particular by Rebek's group, but the examples of supramolecular cavities enclosing organometallic catalytic centers mimicking metalloenzymes are still rare. The most successful systems were provided by Fujita and Raymond (§ 2.2.1) with metal-ligand based capsules, but very little has been done yet in the field of hydrogen-bonded capsules.

Glycourils units were used by Rebek's group to build the so-called *tennis-ball*, *baseball* and *softball*, exploiting the H-bonding capability of this particular building block, bearing in the same molecule both hydrogen bond donors (NH groups) and acceptors (C=O). The first synthesized capsule of this series was the *tennis-ball*, constituted simply of two glycouril molecules connected through an aromatic spacer (Figure 35A), that can dimerize in solution thanks to the formation of an array of eight hydrogen bonds.¹⁴¹ The so-formed dimer is able to encapsulate small guests such as methane, ethylene, argon or xenon. The substitution with hydroxyl groups at the central benzene ring allowed subsequently the tuning of the electronic properties of this same structure, while the variation of the spacer length influenced the bending of the structure, the shape and the inner volume. Moreover, enlarging the spacer and introducing an element of rigidity in the structure, namely a bridged anthracene, bigger homo and heterodimers can be formed.¹⁴² This concept serves as a basis for the synthesis of the *softballs*, that are larger semi-spherical capsules suitable for hosting bigger molecules, such as adamantanes, ferrocenes (1-adamantanecarboxylic acid - $K_d = 1.3$ mM - and 1-ferrocenecarboxylic acid - $K_d = 3.6$ mM) and camphor derivatives, as well as two benzene molecules.¹⁴³ Interestingly, the combination of two

achiral units results in the formation of two enantiomers of the capsule and the encapsulation of an asymmetric host inside this structure provides a population imbalance determined by the different affinity of each guest enantiomer in the surrounding chiral environment.¹⁴⁴ The high binding affinity of this capsule and the large cavity ($\sim 300 \text{ \AA}^3$) in which more than one molecule can be accommodated without breaking the “55% rule”, allowed its use as a nanoreactor for the Diels Alder reaction between *p*-quinone and cyclohexadiene, with a consequent significant rate acceleration.¹⁴⁵ The encapsulation of the two reagents in the dimer is fast and subsequently reaction occurs giving the endo Diels-Alder adduct. Unfortunately, the adduct presents higher affinity than the reagents for the host and this leads to an important drawback related to product inhibition. The system is non-catalytic, but size and shape selective and the concentration effect inside the *softball* provides a rate enhancement of about two orders of magnitude compared to the same reaction without the capsule in *p*-xylene. Considering the importance of substrate choice in synthetic enzyme mimetics, a true catalytic system was developed subsequently combining *p*-quinone with thiophene dioxide instead of cyclohexadiene. The reaction turned out to be positively influenced by the presence of the softball catalyst with 55% yield after two days at room temperature and 75% after 4 days. Under the same conditions, control experiments showed 10 and 17% yields, respectively (Figure 35C).¹⁴⁶ More importantly, the capsule provided true turnover because of the higher steric clashes of the product compared to the coencapsulation of two molecules of *p*-quinone, which was the resting state of the catalyst in the cycle.

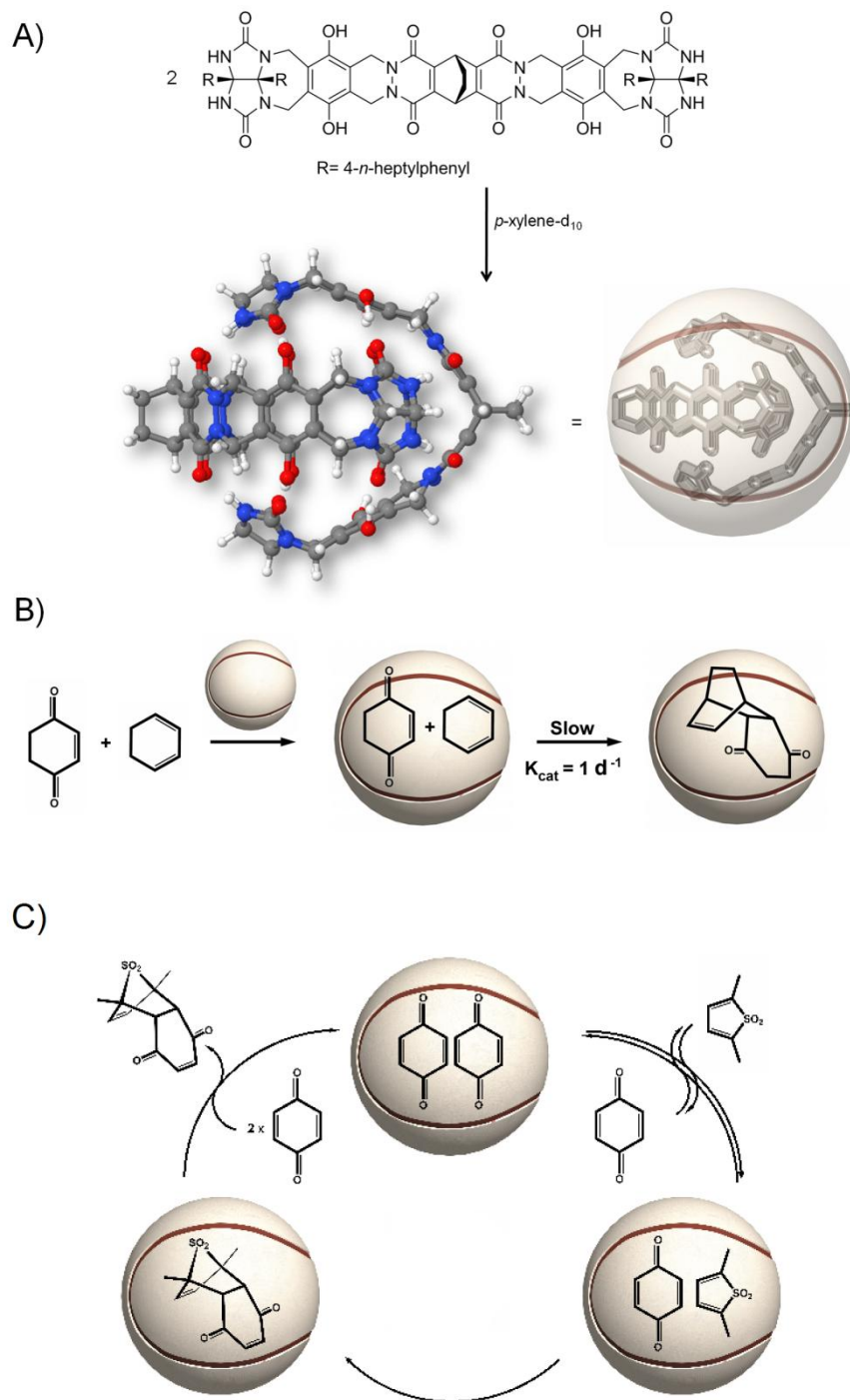


Figure 35 A) chemical structure and tridimensional model of Rebek's *softball* ; B) Diels Alder reaction between *p*-quinone and 1,3-cyclohexadiene as mediated by the dimeric self-assembled *softball* capsule. Hetero coencapsulation of the two reagents is not preferred over homo coencapsulation of quinone, but when it occurs the lifetime of the complex favors the reaction. The product is the best guest and no turnover is seen. C) Catalytic Diels-Alder reaction between *p*-quinone and thiophene dioxide mediated by hydrogen bonded *softball*. Changing the substrate combination the product is displaced by two molecules of *p*-quinone, having higher affinity for the capsule and catalytic turnover is ensured.

To facilitate the egress of the reaction product, a catalytic system based on an open-ended structure in place of a capsule was developed by the same research group several years after using a resorcin[4]arene derived octamide cavitand (Figure 36).¹⁴⁷ Cavitands are monomolecular hosts where the supramolecular feature is related to the particular folding that creates a cavity, as happens for cyclodextrins. In this particular case, the cavitand's vase-like shape is provided by intramolecular hydrogen bonds occurring between amide residues at the edges of the chemical structure. This assembly is characterized by a dynamic behavior that depends on the interconversion between the two rotational enantiomers of the concave form. The phenyl rings on the walls of the cavitand determine the preference for organic electron-poor guests, especially organic cations able to interact through cation- π noncovalent bonding. A suitable diene to perform Diels-Alder reactions catalyzed by this supramolecular pocket was found to be 9-anthracenemethanol that demonstrated good reactivity at room temperature for maleimides chosen because of their good affinity with the host, thanks to the formation of hydrogen bonds between their carbonyl groups and the imide seam of H-bonds of the cavitand. The selected maleimides "sit" inside the cavity with the alkylic part leaving the double reactive bond exposed to the bulk, where the adduct with the anthracene reactant is formed. The imide substrate (N-cyclooctylmaleimide proved to be the best guest) is then pre-oriented to react and this effect leads generally to a >20 fold acceleration. The adduct is readily released from the cavitand with the incoming of a new reactant molecule, having higher affinity than the product for the host (Figure 36B).

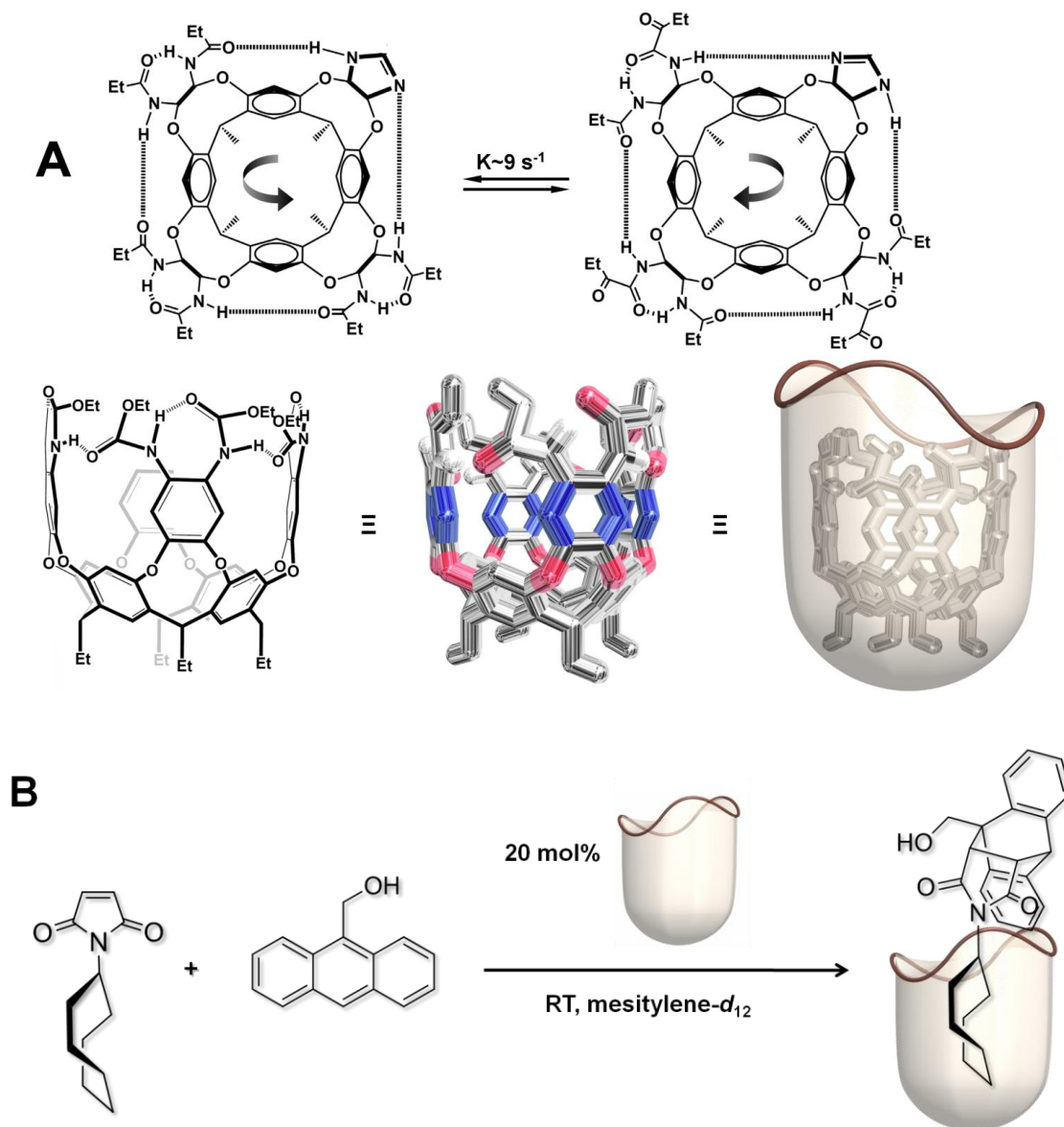


Figure 36 A) hydrogen bonded self folding cavitaand developed by Rebek and C) its use as a supramolecular catalyst for Diels-Alder reaction between N-cyclooctylmaleimide and 9-anthracenemethanol

The same cavitaand, functionalized with a salen-type ligand and metalated with Zn(II) was employed as a synthetic metallo-enzyme for the hydrolysis of *para*-nitrophenyl choline carbonate PNPCC, where the cavity contributes to the efficient pre-orientation of the substrate, while zinc metal center acts as the effective Lewis-acidic catalyst. This synergic effect led to an enhancement of the reaction rate of about twelve times.¹⁴⁸ The first example of organometallic catalysis within this supramolecular hydrogen-bonded receptor has been recently reported in a work by Ballester and coworkers (Figure 37),¹⁴⁹ where encapsulation and modified catalytic activity of a rhodium(I) complex was described. Previously, several cationic organometallic complexes

such as metallocenes proved to be suitable for inclusion in this type of hosts,¹⁵⁰ but no catalytic tests were reported for these species. In Ballester's work, $[\text{Rh}(\text{norbondadiene})_2]\text{BF}_4$ was encapsulated in Rebek's self-folding host by mixing the two species in CD_2Cl_2 solution, and partial dissociation of the complex was observed. The resulting inclusion complex appeared to have at least two solvent molecules coordinated to rhodium in place of one norbornadiene ligand. The exposition of this species, included in the cavitand, to 1 bar of H_2 gave no evidence of decomposition to Rh^0 , as expected for the free complex, and the subsequent addition of an excess of norbornadiene led to the hydrogenation of the latter with unusual product distribution. The reaction usually gives dimerization of norbornadiene as the only product, but if the complex is included in the cavitand, norbornene and norbornane are formed in addition to the dimer. Norbornene is the major product, most probably because the transition state leading to dimer formation is too big to fit easily into the cavity. Even if the mechanism is still unclear, this work proves a principle in supramolecular catalysis, demonstrating how an artificial receptor can modify activity and selectivity of an organometallic catalyst by encapsulation, acting as an organic ligand, but without the need of a defined metal-ligand bond between the metal center and the surrounding supramolecular structure.

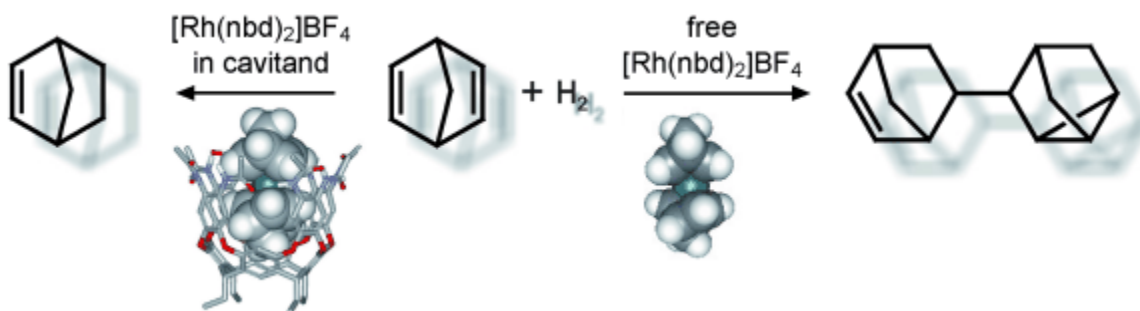


Figure 37 (from ref 149): The inclusion of $[\text{Rh}(\text{nbd})_2]\text{BF}_4$ (nbd=norbornadiene) in Rebek's cavitand produces a catalytically active species that promotes the hydrogenation of norbornadiene to norbornene and improves the stability of the Rh complex.

If this is true for unimolecular cavitands, no similar examples are known yet for self-assembling hydrogen bonded capsules. Capsules have a great potential in terms of modifying especially the selectivity of organometallic catalysts thanks to the creation of a complete environment in which reactions take place, experiencing dimension and shape constraints and alternative reaction pathways as well as different concentration, pH and/or pressure conditions compared to the bulk. The problems affecting this kind of system are *in primis* the need of a sufficient cavity volume in which catalyst and substrate could accommodate without exceeding the 55% rule, then the aggregation/disaggregation equilibrium of the capsule, that should be fast, but not faster than the reaction time; moreover the catalyst should be completely encapsulated into the nanoreactor at the concentration needed for the reaction, but still leaving enough space for the substrate. The problem of capsule dimension is probably the easiest to overcome thanks to the continuous development of

new artificial self-assembling systems with a wide range of properties. To the best of our knowledge the largest hydrogen bonded capsule is the calix[4]resorcinarene hexamer discovered by McGillivray and Atwood in 1997.¹⁵¹ The virus-like assembly exists in organic solvents like chloroform-*d* or benzene-*d*₆ even at concentrations as low as nanomolar,¹⁵²⁻¹⁵⁴ but a certain amount of water is required to keep the six units together (eight water molecules for each hexamer)¹⁵⁵ and this is usually accomplished by using water saturated solvents. The cavity volume is about 1375 Å³ and such space is normally filled by six to eight solvent molecules. The resorcin[4]arene scaffold provides an aromatic electron-rich internal surface that preferentially accommodates cationic species like tetraalkylammonium and phosphonium ions¹⁵⁶⁻¹⁵⁸ and these are, depending on their size, co-encapsulated with residual solvent molecules.¹⁵⁹ Despite its giant internal cavity and the easy synthesis, together with the possibility of including metal species such as cobaltocenium ions,¹⁶⁰ catalysis within this spherical “volleyball” is yet to be developed.

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4. RESULTS AND DISCUSSION

4.1 NITRILE HYDRATION

The results presented in this chapter were published in: Cavarzan, A.; Scarso, A.; Strukul, G. "Efficient Nitrile Hydration Mediated by Ru^{II} Catalysts in Micellar Media" Green Chemistry 2010, 12, 790-794.

4.1.1 AIM OF THE WORK

As previously discussed, water is highly desirable as a reaction solvent, but has been practically ignored for years from organic chemists, due to its non-innocent "personality" in many chemical transformation and towards commonly used organometallic complexes. But, if water tends to react so easily, why not using it as a reagent? This opens the discussion on the possibility to perform hydrolysis and hydration reactions directly in water, something obvious but at the same time tricky to achieve.

Nitrile hydration, for instance, represents a sustainable method for amide preparation, characterized by high atom economy and employed at the industrial level for the production of acrylamide. The conventional chemical synthesis of this commodity traditionally involved a copper salt as the catalyst of choice, but the significant amount of byproducts formed with this method and the main product tendency to polymerization induced industry to search for a new process. In the 90's enzymatic techniques substituted copper catalysis in order to improve the system selectivity, employing, in a fed-batch enzyme conversion process, nitrile hydratases from *Pseudomonas chlororaphis* B23, in which the amidase that usually degrades the product is almost inactive.^{161,162} This successful example (subsequently improved by testing other microorganisms) enhanced the research on nitrile hydratases and their application in organic syntheses, but, on the other hand, sustainable organometallic catalysis in this field remained poorly developed. Even if enzymatic catalysis ensures extremely high selectivities, it is often difficult to widen the scope of the reaction, being enzymes also highly substrate selective. Moreover, working with whole cells implies the existence of side/cascade reactions that should be suppressed (like amide hydrolysis in this case) and the obvious solution, enzyme isolation, is money and time consuming and bears the risk of compromising the catalyst robustness. Metal complexes that have been tested as catalysts in nitrile hydration are widespread in the literature,¹⁶³ namely Fe,¹⁶⁴ (nitrile hydratases are indeed metallo-enzymes containing Fe(III) or Co(III) centers¹⁶⁵), Ni¹⁶⁶⁻¹⁶⁸, Rh,¹⁶⁹ Au,^{170,171} Pd,¹⁷²

Mo,¹⁷³ rare earth metals,¹⁷⁴ Pt,¹⁷⁵⁻¹⁷⁷ the latter being the most investigated metal after Ru,¹⁷⁸⁻¹⁸⁵ for which ligand effect on catalytic activity was analyzed. Recently the Ru catalyzed hydration of nitriles was improved by using more environmentally friendly protocols, namely switching from organic solvents to water. In one case the application of this concept required the modification of the catalyst to render it water soluble,¹⁸³ while in a second work ruthenium homogeneous complexes were substituted by a heterogeneous system supported on nanoparticles.¹⁸⁵ The first system, developed by Gimeno's group and operating in pure water on a wide range of substrates employs $[\text{RuCl}_2(\eta^6\text{-arene})(\text{PTA})]$ complexes, PTA (phosphatriazaadamantane) being required to impart water solubility to the catalysts.

The present approach to the problem consisted in the use of traditional ruthenium complexes without the need of water soluble ligands but providing a homogeneous reaction medium in which the substrate can be solubilized too. The solubilization of the nitrile species allows the widening of the reaction scope to solid, bulky organic nitriles.

The approach to the problem reported in this thesis consists in the use of traditional ruthenium complexes without the need of water soluble ligands but providing an aqueous homogeneous reaction medium in which the catalyst as well as the substrate can be solubilized. The solubilization of the nitrile species allows the widening of the reaction scope to solid, bulky organic nitriles.

The ways to transfer catalytic reactions in water are mainly the three represented in Figure 38, namely (i) the use of intrinsically water soluble catalysts; (ii) the solubilization of intrinsically hydrophobic complexes *via* modification of the ligand with water soluble tags (see e.g. $[\text{HRh}(\text{CO})(\text{TPPTS})_3]$ in hydroformylation); (iii) the solubilization of hydrophobic complexes in water by means of supramolecular aggregates like micelles, without the need of any catalyst modification. The first represents Gimeno's approach. The third is the subject of this thesis. The supramolecular approach involves the addition of surfactants above the CMC to ensure the formation of molecular aggregates able to include the catalyst and the substrate in the hydrophobic core and solubilize both components in water.

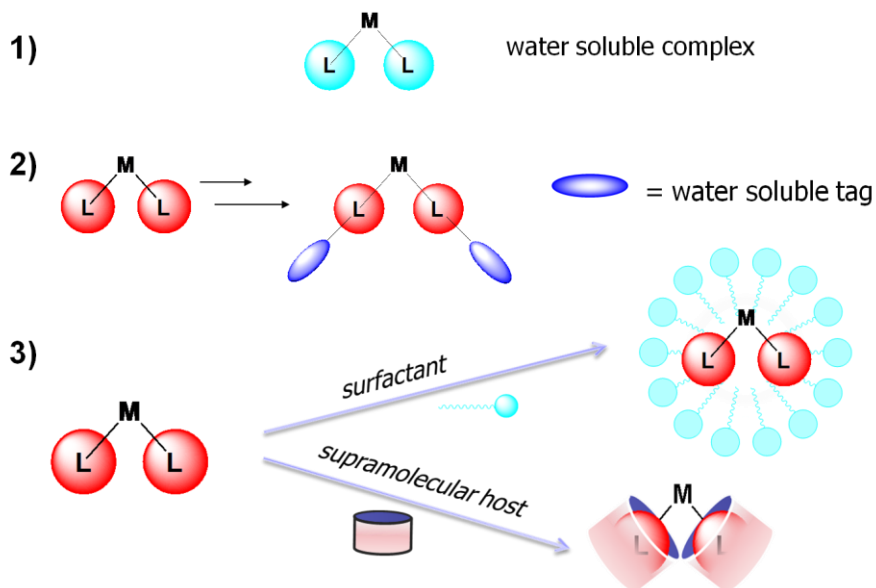
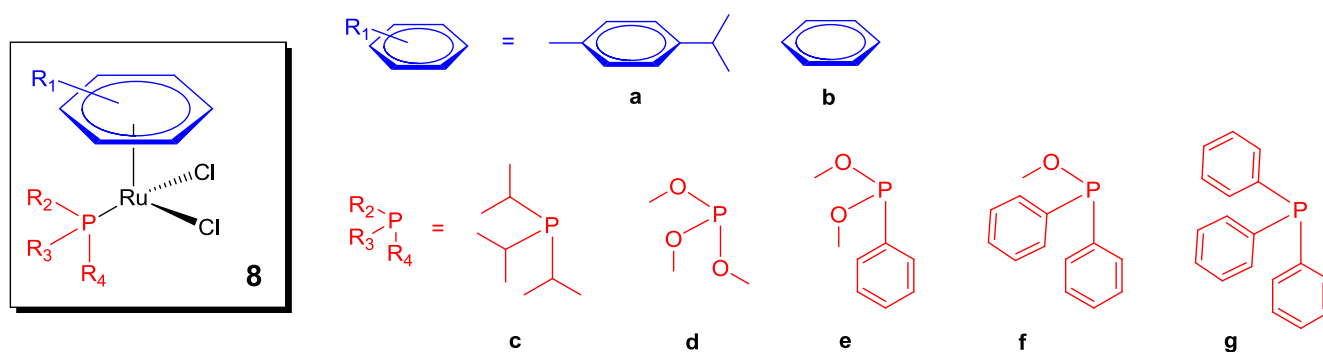


Figure 38: Three different approaches to perform organometallic catalysis in water. 1) employment of intrinsically water soluble metal complexes as catalysts; 2) solubilization of an intrinsically hydrophobic complex *via* modification of the ligand with water soluble tags; 3) solubilization of hydrophobic complexes in water by means of supramolecular aggregates like micelles, without the need of any catalyst modification.

4.1.2 CATALYST SCREENING

For the present work on nitrile hydration we employed Ru^{II} catalysts of general formula [RuCl₂(η^6 -arene)(PR₃)] **8** (Scheme 2) bearing a representative range of monophosphines.

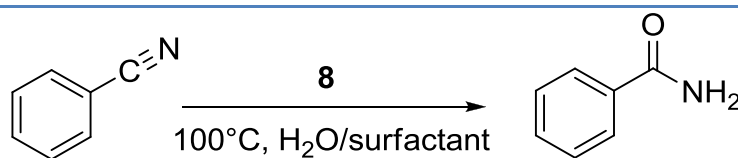


Scheme 2: Ru(II) complexes tested for nitrile hydration in micellar medium.

Initially catalyst screening was performed toward benzonitrile hydration using neutral non-coordinating surfactants like Triton X-100 and X-114 to avoid interfering with ligand substitution. Ru^{II} catalysts bearing

electron rich alkylphosphine **c** showed modest catalytic activity, and the same was observed with the electron-poor triethoxy phosphine ligand **d** (Table 5, entries 1 and 2). Substitution of one ethoxy residue with a phenyl group increased amide formation and with two aromatic units the highest catalytic activity was observed (Table 5, entries 3 and 5 respectively). Conversely, triphenylphosphine as ligand led to almost inactive Ru^{II} catalyst (Table 5, entry 6) demonstrating that a fine tuning of both steric and electronic properties is required for good catalytic performance. This catalyst screening can be easily accomplished thanks to the micellar medium that enables solubilization in water of neutral catalysts with different apolar ligands. It is worth noting that the complex of Os^{II} **8ae** turned out to be more active than the homologous Ru^{II} species (Table 5, entries 3 and 4). As already observed with intrinsically water soluble Ru^{II} species,¹⁹ the η^6 -arene residue showed a marked effect on catalytic activity, in fact substitution of the cymene residue **a** with benzene **b** caused a marked decrease of activity (Table 5, entry 7), probably because of a less labile Ru–arene bond.

Table 5: Catalyst screening of **1** in the hydration of benzonitrile in water.



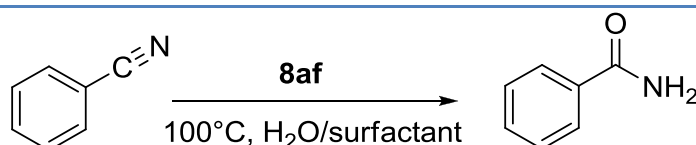
#	Catalyst	Medium	Time (h)	Yield (%)
1	8ac	H ₂ O/TritonX100 ^b	20	29
2	8ad	H ₂ O/TritonX100 ^b	20	27
3	8ae	H ₂ O/TritonX100 ^b	20	37
4	8ae-Os^a	H ₂ O/TritonX100 ^b	20	82
5	8af	H ₂ O/TritonX100 ^b	20	93
6	8ag	H ₂ O/TritonX114 ^c	20	30
7	8be	H ₂ O/TritonX114 ^c	20	5

Experimental conditions: [Sub]₀ = 0.15 M; **1**: 5 mol%, T = 100°C, water 0.5 mL. Yield determined by GC analysis. a) Analogous complex with Os [OsCl₂(η^6 -Cymene)(P(Ph)(OEt)₂)]. b) Polyoxyethylene(10)isooctylphenyl ether (150 mM); c) Polyoxyethylene(8)isooctyl cyclohexyl ether (150 mM).

4.1.3 OPTIMIZATION OF REACTION CONDITIONS

With complex **8af** as the best Ru^{II} catalyst at hand, we investigated the nature of the surfactant varying the charge, the length and the kind of functional groups of the tensides employed (Table 6).

Table 6: Surfactant screening in the hydrolysis of benzonitrile with catalyst **8af** in water.



entry	medium	time (h)	yield (%)
1	H ₂ O	2	11
		20	75
2	H ₂ O/SDBS ^a	2	36
		20	83
3	H ₂ O/CTAB ^b	2	44
		20	96
4	H ₂ O/zwitterionic ^c	2	16
		20	84
5	H ₂ O/PTS ^d	2	51
		8	90
6	H ₂ O/SPAN60 ^e	2	77
		8	89
7	H ₂ O/TritonX100 ^f	2	58
		8	95
8	H ₂ O/Triton X-114 ^g	2	81
		8	97
9	H ₂ O/Triton X-405 ^h	2	39
		8	73

Experimental conditions: [Sub]₀ = 0.15 M; **8af**: 5 mol%, T = 100°C, water 0.5 mL. Yield determined by GC analysis. a) Sodium dodecylbenzene sulfonate, (75 mM); b) hexadecyl trimethylammonium bromide (75 mM); c) N-dodecyl-N,N-dimethyl-3-ammonio-1-propanesulfonate (150 mM); d) polyoxyethanyl- α -tocopheryl sebacate (45 mM); e) Sorbitan monostearate (150 mM); f) Polyoxyethylene(10)isooctylphenyl ether (150 mM); g) Polyoxyethylene(8)isooctyl cyclohexyl ether (150 mM); h) Polyoxyethylene(40)isooctylphenyl ether (150 mM).

Charged anionic, cationic and zwitterionic surfactants (Table 6, entries 2-4) worked properly enabling good product formation after 20h reaction time. Better performance was possible using neutral surfactants, with amide formation that after 2h reaction time was >50% with PTS²¹ and SPAN 60. Even better catalytic activity was achieved with Triton surfactants, and among all, X-114 (Table 6, entry 8) allowed to observe almost quantitative amide formation in 8h. Experimental conditions were investigated in detail (Table 7), observing that the best catalyst loading was 2-5 mol% while surfactant concentration screening showed that values above 150 mM influenced negatively the outcome of the reaction.

Table 7: Effect of different catalyst loading and surfactant concentration in the hydrolysis of benzonitrile with catalyst 8af in water.^a



entry	catalyst (mol%)	surfactant (mm)	time (h)	yield (%) ^b
1	1	150	2	39
			20	96
2	2	150	2	83
			20	96
3	5	150	2	81
			20	97
4	10	150	2	69
			20	93
5	5	75	2	81
			20	93
6	5	300	2	68
			20	95
7	5	600	2	42
			20	92

a)Experimental conditions: [Sub]₀= 0.15 M, T= 100°C, water 0.5 mL. b)Yield determined by GC analysis.

4.1.4 SUBSTRATE SCOPE AND RECYCLE TESTS

Once optimized the catalyst, the kind and amount of surfactant and temperature, the substrate scope of the reaction was investigated (Table 8). Aromatic nitriles reacted readily with catalyst **8af** except electron-poor ones such as 2-cyanopyridine (Table 8, entry 4). Alkyl nitriles turned out to be suitable substrates, with yields up to 80% depending on the hydrophobic part of the reagent. More hydrophilic substrates bearing alcoholic moieties reacted more slowly, probably because of their higher hydrophilicity that hampered their interaction with the apolar core of the micelles where the catalyst is likely dissolved. In the last column of Table 8 we report also the yields obtained in the absence of surfactant. As can be seen, in most cases either low or no conversions are observed, providing evidence for the fundamental role of the surfactant in bringing catalyst and reactants into contact. However, when the nitrile becomes more hydrophilic (entries 8–10) its solubility in water at 100 °C is likely to be high, helping the dissolution of an appreciable amount of poorly water-soluble catalyst. This is why for hydrophilic nitriles some activity is observed, in some cases comparable to the micellar system. An important issue with these systems is the possibility to separate and recycle the catalyst. A preliminary experiment was carried out by adding a further 1 mmol of benzonitrile at the end of the experiment reported in Table 6, entry 8, to check whether the catalyst was still active. A further 30% conversion of benzonitrile in benzamide was observed after 30 h. This lower conversion can be due to both a dilution effect and to competition between benzonitrile and benzamide for coordination to the metal. Using the experimental conditions reported in Table 6 (substrate 1 mmol), we then attempted to optimize catalyst recycling using neutral Triton X-114 surfactant. Under these conditions phase separation is virtually impossible because of emulsion formation when the organic solvent (necessary for separating the catalyst from the organic products) is added. CTAB was then checked as a charged surfactant in order to minimize its solubilization in organic media. Chloroform was used for extraction and dissolution of the Ru^{II} species in the organic phase was observed (as confirmed by green color transfer from the micellar phase to the chlorinated phase) while the surfactant and the benzamide remained dispersed in water. Amide product could be precipitated by diluting the aqueous solution (20 times) and cooling the system to 5 °C. The catalyst was thus isolated by organic solvent evaporation, and to this, water, CTAB and nitrile substrate were added for the recycling experiments. The reaction led to 95% yield in benzamide in the first cycle, 81% in the second followed by a decrease of catalytic activity in the third cycle, where the yield was 54%. This loss of activity is probably due to incomplete recovery of the catalyst during work-up. GC-MS analysis on the first extracted organic phase

showed the presence of p-cymene, suggesting that the active catalytic species lacks this aromatic ligand, which is probably displaced by the incoming nitrile moiety.

Table 8: . Substrate scope of the nitrile hydration reaction with catalyst **8af**

$\text{R}-\text{C}\equiv\text{N} \xrightarrow[100^\circ\text{C, H}_2\text{O/TritonX114}]{\mathbf{8af}} \text{R}-\text{C}(=\text{O})\text{NH}_2$					
entry	substrate	time (h)	yield in micelle(%)	yield in H ₂ O(%)	
1		12	95	0	
2		24	89	0	
3		24	90	5	
4		24	10	0	
5		24	80 ^a	11	
6		7	77	11	
7	 56% 44%	24	72 ^b	21 ^b	
8	 45% 55%	24	41 ^b	79 ^b	
9		24	50	45 ^c	
10		24	14	10	

Experimental conditions: [Sub]₀ = 0.15 M, 5 mol% **8af**, 100 °C, [TritonX114] = 150 mM, 0.5 mL water. Yield determined by GC analysis. a) 6% acid formation. b) Sum of isomers. c) 10% acid formation.

4.1.5 CONCLUSIONS

Summarizing the results reported in this part, complex **8af** (5 mol%) associated with Triton X-114 provides good yields for nitrile hydration from a representative range of substrates at 100°C, demonstrating comparable catalytic activity to intrinsically water-soluble Ru(II) catalysts bearing hydrophilic ligands.¹⁸³ In conclusion, we have demonstrated that micelles represent suitable media for reactions involving water as a reagent, such as nitrile hydration catalyzed by Ru^{II} species **8**. Neutral surfactants showed the best catalytic activity, probably because they do not interfere (as charged species do) with ligand exchange on the catalyst, enabling almost quantitative hydration on benzonitrile. With respect to the use of intrinsically water-soluble catalysts, micellar media represent an alternative approach to solubilize hydrophobic complexes in water and allow the facile screening of different catalysts without the need for elaborate ligand modification, but with a less straightforward separation and recycling. Specifically, this reaction medium enabled the screening of common monophosphine ligands, observing that a proper balance of steric and electronic features are required.

4.1.6 EXPERIMENTAL

General. ¹H NMR, ¹³C{¹H} and ³¹P{¹H} NMR spectra were recorded at 298 K, unless otherwise stated, on a Bruker AVANCE 300 spectrometer operating at 300.15, 75.5, 121.50 MHz, respectively. δ values in ppm are relative to SiMe₄ for ¹H and ¹³C and 85% H₃PO₄ for ³¹P. All reactions were monitored by GC analysis. GLC measurement were taken on a Hewlett-Packard 6890A gas chromatograph equipped with a FID detector (carrier gas He) and 25 m HP-5 column T_{inj} 280°C, T_{det} 300°C, 100°C X 5 min, 10 °C/min to 200°C. GC-MS analysis were performed on a quadrupole Trace GC 2000 ThermoFinnigan instrument equipped with a 30 m HP-5MS column (carrier gas He). Ru^{II} complexes were prepared according to a general method reported in the literature²⁴ and were a generous gift of Professors G. Albertin and S. Antoniutti of this University. Nitriles and surfactants are all commercially available products and were used as received. The identities of the amide products were assessed by comparison of their ¹H, ¹³C and GC/MS spectra.

General procedure for the catalytic reactions: The Ru^{II} catalysts **8** (7.5 mM, 5 mol% of Ru), water (0.5 mL), the proper amount of surfactant and the corresponding nitrile (0.15 M, 75 μmol) were introduced in a vial

equipped with a screw capped septum. The reaction mixture was stirred at 100°C for the time requested. The course of the reaction was monitored by regular sampling of aliquots of the solution, followed by dilution with MeOH and analysis by GC. Quenching of the reaction was found to be not necessary. Catalyst recycle experiments were performed on 1 mmol amount of benzonitrile using CTABr as surfactant following experimental conditions reported in Table 2.

4.1.7 ACKNOWLEDGEMENTS

Thanks are expressed to Profs. G. Albertin and S. Antoniutti for providing Ru^{II} complexes and to Dr. L. Sperti for GC-MS analysis.

4.2. BAEYER-VILLIGER OXIDATION IN MICELLAR MEDIA

The results presented in this chapter were published in:

- ♦ Cavarzan, A.; Bianchini, G.; Sgarbossa, P.; Lefort, L.; Gladiali, S.; Scarso, A.; Strukul, G. "Catalytic Asymmetric Baeyer–Villiger Oxidation in Water by Using Pt^{II} Catalysts and Hydrogen Peroxide: Supramolecular Control of Enantioselectivity" *Chemistry-a European Journal* **2009**, 15, 7930-7939;
- ♦ Cavarzan, A.; Scarso, A.; Sgarbossa, P.; Michelin, R. A.; Strukul, G. "Green Catalytic Baeyer–Villiger Oxidation with Hydrogen Peroxide in Water Mediated by Pt^{II} Catalysts" *ChemCatChem* **2010**, 2, 1296-1302.

4.2.1 PLATINUM CATALYZED BAEYER-VILLIGER (BV) OXIDATION: AN OVERVIEW

As discussed in Chapter 3.2.1.6, metal-catalyzed Baeyer–Villiger oxidation in water, especially in the asymmetric version, represents a relatively new research topic that offers several opportunities for improvement. The story of transition metal catalysis in this reaction started with a report by Mares et al. in 1978 using Mo(IV) peroxo complexes and concentrated (90%) hydrogen peroxide for the oxidation of cyclic ketones.¹⁸⁶ Yields and turnover numbers were low (maximum 25%), reflecting the difficulty to bring together two putative electrophiles i.e. the peroxy oxygen and the carbonyl carbon. As was later demonstrated by Di Furia the work by Mares was most likely an example of acid instead of transition metal catalysis.¹⁸⁷ The need of performing nucleophilic peroxide activation had been known for some time, as the platinum complex $[(PPh_3)_2Pt(O_2)]$ was able to effectively interact with ketones to form stable peroxometallacycles.¹⁸⁸ This feature intrigued Strukul and coworkers, who started in 1979 to deepen the knowledge on platinum catalysis,^{22,188} using initially square-planar *cis* complexes of general formula $[(P-P)Pt(CF_3)X]$ (where P-P stands for a general bidentate phosphine ligand and X is either a solvent molecule or an OH group) and subsequently varying the substituents but maintaining the same structure, as showed by the catalysts employed also in this thesis. As was demonstrated in the epoxidation of alkenes,¹⁸⁹ the metal center has the double function of increasing the electrophilicity of the substrate and of activating the oxidant H_2O_2 towards nucleophilic attack accomplished through a quasi-cyclic intermediate. Moreover, platinum coordinates the otherwise poor leaving group OH^- facilitating the release of the product. Changing the phosphine backbone and the counterion the catalytic system can be adapted to different substrates and reaction conditions. The first genuine example of transition metal catalysis in the Baeyer–Villiger oxidation of a variety of cyclic ketones was observed with $[(dppe)Pt(CF_3)(CH_2Cl_2)]BF_4$ (*dppe* = 1,2-diphenylphosphinoethane)^{190,191} (Figure 39) that proved to be effective at room temperature with high turnovers and high regioselectivities when using substituted cyclic ketones such as camphor or menthone.

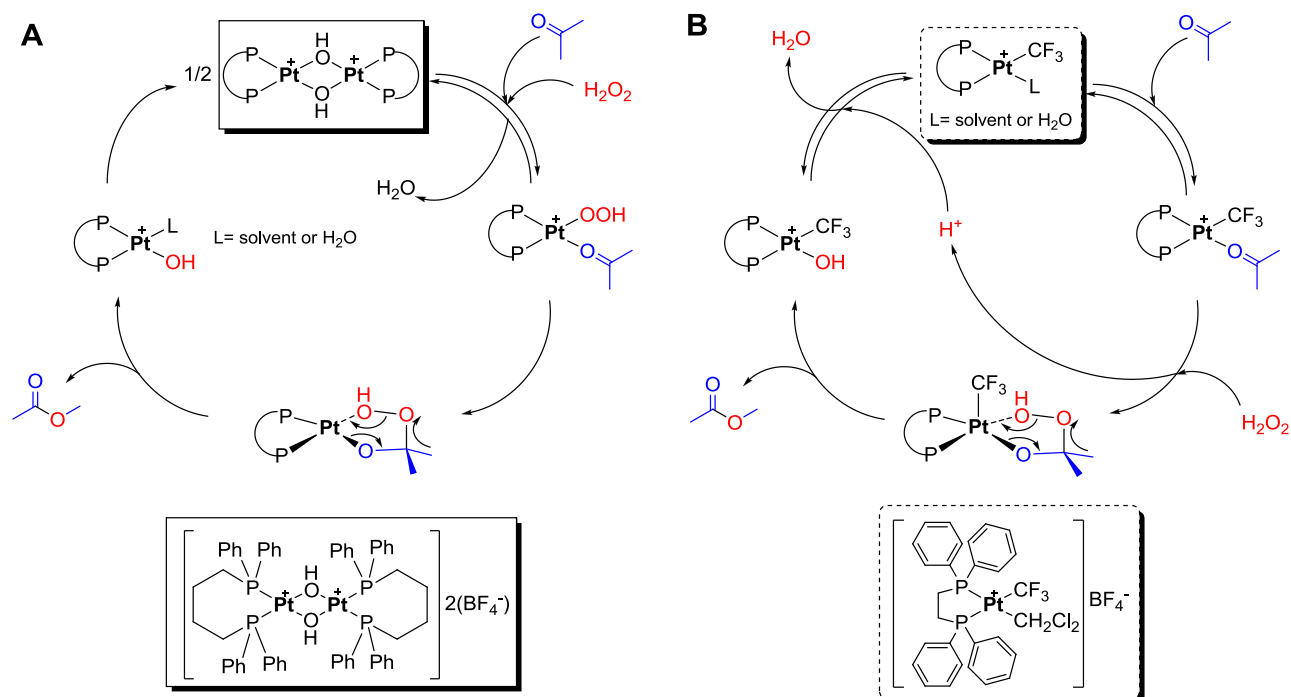


Figure 39: Comparison between two mechanisms for the Baeyer Villiger oxidation of ketones mediated by A) dimeric Pt(II) complexes bearing bidentate phosphine ligands. The pathway includes the dissociation of the dimer to generate the active catalytic species; B) monomeric Pt(II) complexes representing the first generation of catalysts developed in the group of Strukul. The peroxometalicyclic species at the bottom of both cycles are analogous to the Criegee intermediate but with Pt in place of H^+ .

Investigating the effect of CF_3 substitution, a new class of catalytic dimeric complexes was developed, characterized by the general formula $[(P-P)Pt(\mu-OH)]_2^{2+}$ that have been known since 1975, but underestimated for years because of their low reactivity. These dimeric species were used to perform BV oxidations on cyclic and acyclic ketones (the first example of transition metal catalysis on this substrates in the literature) and disclosed the influence of the phosphine bite angle on the reactivity in the oxidation 2-methylcyclohexanone. Spanning the alkyl chain length connecting the two P donors from one to four carbon atoms, a direct dependence of the yield on the natural bite angle was observed, 1,4-diphenylphosphinobutane (*dppb*) providing the best turnover (110).¹⁰⁰ The half-order dependence of the reaction rate on catalyst concentration suggests that the catalytic mechanism includes the opening up of the dimer to generate the catalytic species as depicted in Figure 39. Another systematic screening on the oxidation of the same substrate was performed by testing a series of homologous complexes of increasing electrophilicity obtained by increasing the degree of fluorine substitution on the phenyl rings of *dppe*.¹⁹² As deduced from the previous mechanistic observations, the higher the Lewis acidity of the metal center, the better the activity of the catalyst. The pentafluorophenyl substituted phosphine *dfppe* proved to be the best ligand in terms of conversion of 2-methylcyclohexanone to

the corresponding lactone and the same $[(dfppe)Pt(\mu-OH)]_2(BF_4)_2$ catalyst is effective also for other cyclohexanones always maintaining high selectivities towards the “normal” lactone.^{***}

The enantioselective version of the BV oxidation of cyclic ketones was developed on *meso* 4-substituted cyclohexanones with hydrogen peroxide employing chiral dimeric Pt(II) complexes bearing a series of commercial chiral enantiopure diphosphines (binap, diop, pyrphos, norphos, Me-duphos, bppm). Figure 40 shows some representative results obtained using the (*R*)-binap chiral auxiliary, that demonstrated to be the best choice in terms of turnovers and ee's of the dissymmetrization for all the substrates tested.¹⁰³

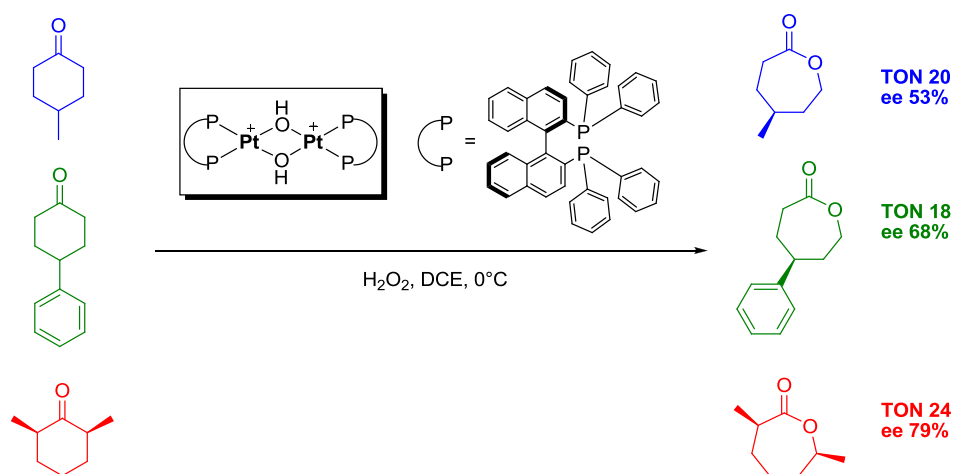


Figure 40: enantioselective oxidation of *meso*-cyclohexanones using a Pt(II) dimeric catalyst bearing (*R*)-binap as chiral ligand. In all cases “normal” lactone is preferentially formed with generally high ee values.

The relative inertness of platinum complexes makes these catalysts stable in presence of water, although in all the cited examples the use of an organic solvent is necessary to solubilize the catalyst and the presence of water, coming from diluted hydrogen peroxide, determines the formation of a biphasic system in which water droplets are dispersed in the organic phase. Performing this transformation directly in water would be recommended in order to avoid chlorinated solvents and possibly to improve the recyclability of the catalytic phase, even if homogeneous oxidation catalysts suffer from a short lifetime, especially if bearing phosphine ligands that can be oxidized.

^{***} For non-symmetric cyclic ketones, two lactones can be obtained as products of the Baeyer-Villiger oxidation, depending on the migrating alkyl group. For 2-methylcyclohexanone for instance, the two possible products are 7-methyloxepan-2-one and 3-methyloxepan-2-one, the first called the “normal” one because migration of the more substituted carbon is preferred.

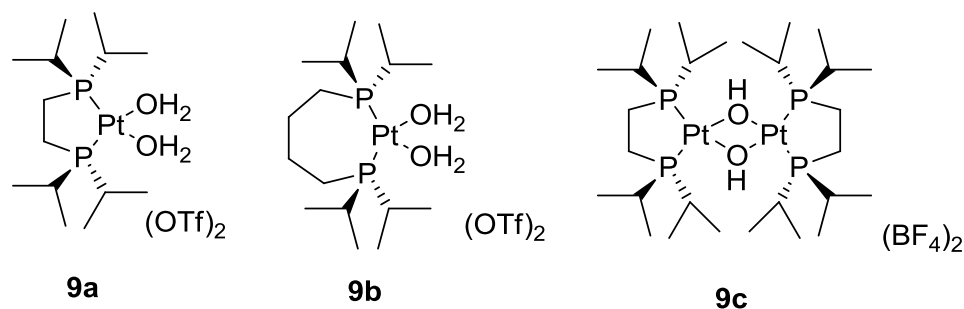
4.2.2 AIM OF THE WORK

Spurred by the good results observed in the asymmetric BV oxidation reaction with H_2O_2 performed with Pt(II) catalysts in organic media, we decided to explore the possibility to perform BV in aqueous medium starting from intrinsically water soluble *bis*-cationic Pt(II) catalysts bearing small diphosphine ligands. Reactions are carried out in water using micelles to enhance solubilization of the substrates, consequently emphasizing the unique solvent effect played by water in BV oxidation reaction.¹⁹³ The scope was subsequently widened to enantioselective BV dissymetrization of cyclic ketones, wherein micelles served the scope of solubilizing not only the substrates, but also the catalysts, since chiral water-insoluble catalysts bearing bulky chiral phosphines were employed. This approach allowed to avoid chemical tagging of the chiral ligand with hydrophilic substituents and led to an enhancement of the enantioselectivity of the reaction due to tighter catalyst-substrate interactions favored by the micellar supramolecular aggregate.

4.2.3 BV OXIDATIONS MEDIATED BY WATER-SOLUBLE CATALYSTS

4.2.3.1 Catalyst Positioning in the Micellar Medium

The catalysts employed for this work are platinum monomeric and dimeric complexes with small alkyl diphosphine ligands, as depicted in Scheme 3. The monomeric species bear two vacant sites that are normally filled by two water molecules, as determined by X-ray diffraction analysis.^{194,195}



Scheme 3: water-soluble bis-aquo (9a, 1b) and μ -OH (1c) complexes used as catalysts for Baeyer-Villiger oxidations of cyclic ketones with H_2O_2 in micellar medium.

Catalysts **9a-c** were tested in 2008 by Strukul and Scarso in the BV oxidation with H_2O_2 in chlorinated organic solvents¹⁹⁶ observing the higher activity of monomeric catalysts compared to dimeric ones. The choice of these three complexes depends on their small size and double positive charge of that allows dissolution also in pure water leading to clear solutions, as confirmed by ^1H and ^{31}P NMR spectra in D_2O (Figure 41). Conversely, cyclic ketones are only sparingly soluble in water and surfactant addition is necessary to form homogeneous solutions. To detect the type of interactions occurring between the micelle and the organometallic complex in solution, 2D NMR experiments like NOESY and DOSY were performed. NOESY (Nuclear Overhauser Effect Spectroscopy) experiments allow the visualization of proton-proton coupling determined by spatial proximity between the two species, even if they are not chemically bound. Diffusion-ordered spectroscopy (DOSY) NMR, on the other hand, is based on a pulse-field gradient spin-echo NMR experiment, in which the components in solution experience diffusion phenomena. Consequently, the signal of each component decays with different diffusion rates as the gradient strength increases, constructing a bidimensional NMR data set of a mixture. . In the output of this analysis the logarithm of diffusion coefficient D is plotted against the monodimensional ^1H spectrum of the mixture and this corresponds in a sort of “chromatographic” separation between the species on the basis of their diffusion rate. This is extremely useful for supramolecular structures and in particular for large symmetric assemblies like micelles or the resorcin[4]arene capsule in Chapter 6, for which information on shape and dimension can be easily obtained in a non-invasive way; therefore host-guest systems are often characterized using this method.

These experiments were carried out for **9a** in D_2O in the presence of SDS (sodium dodecylsulfate). The DOSY experiment (Figure 41D) clearly shows that the catalyst has similar diffusion coefficient compared to the micelles, much larger than for the free catalyst in solution (Figure 41C), even though no cross peaks were present in the NOESY spectrum between **9a** and SDS resonances. ^{31}P NMR spectrum of **9a** with SDS in D_2O (Figure 41B) shows a slight shift to higher field for the main complex maintaining the $J_{\text{P-Pt}}$ almost unaffected. This means that the catalyst, probably because of charge pairing, interacts on the surface of the anionic micelles without being buried in the hydrophobic core, acting as counter cation for the sulphate anions of the surfactant. Minor secondary species are also present but not assigned to specific complexes.

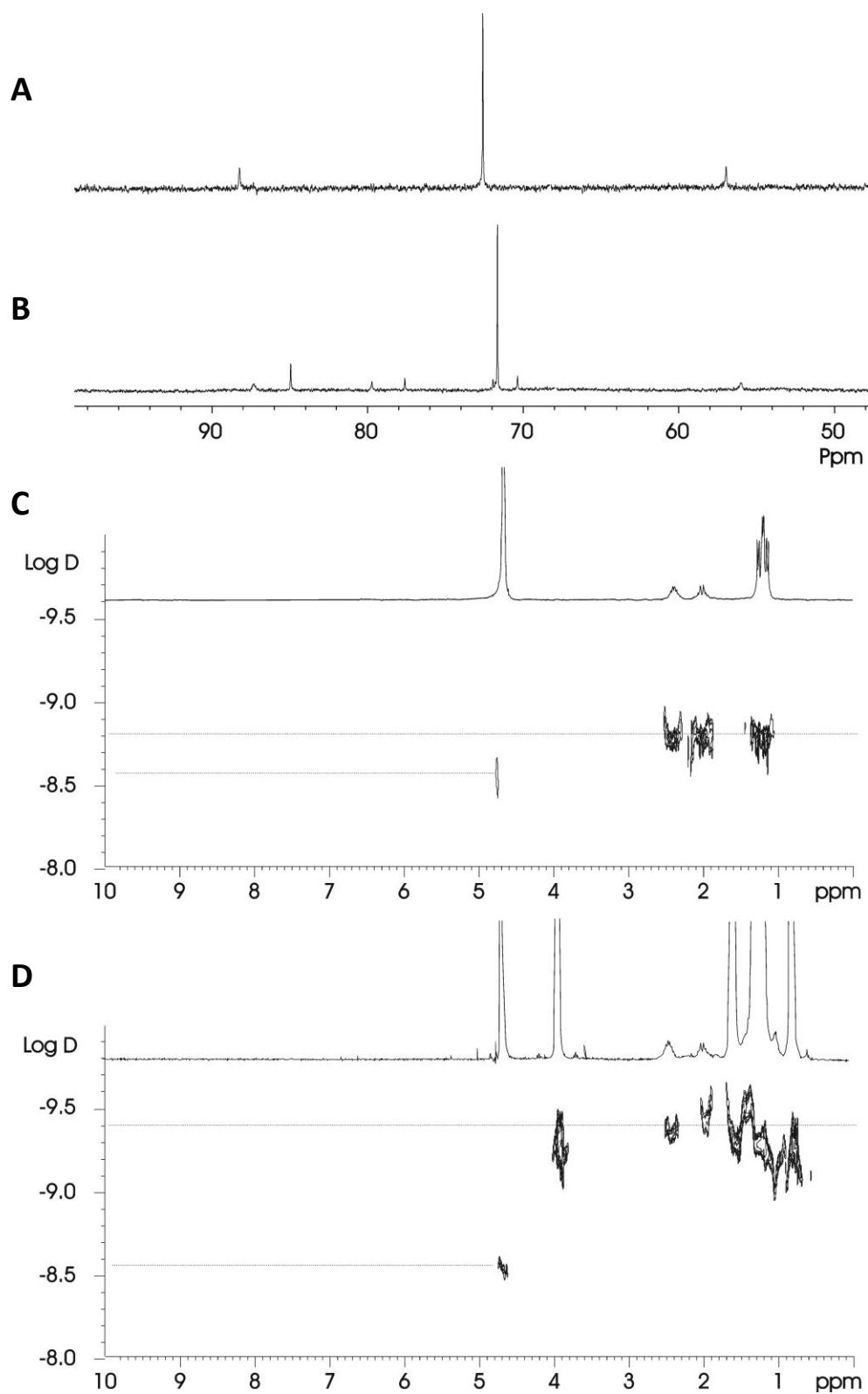


Figure 41: ^{31}P NMR spectra of catalyst 9a in A) D_2O , B) D_2O with SDS (75 mM). DOSY spectra of catalyst 9a in C) D_2O , D) D_2O with SDS (75 mM).

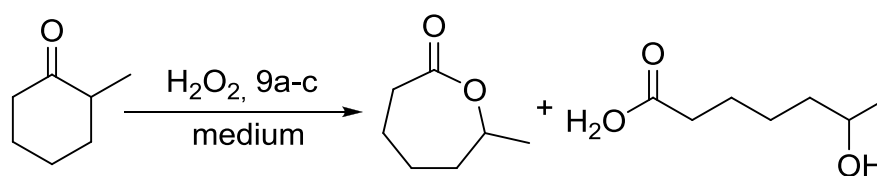
4.2.3.2 Optimization of Reaction Conditions

The cyclic ketone 2-methylcyclohexanone was employed as a test substrate for the BV oxidation mediated by the three different catalysts and various surfactants or additives, as reported in Table 9. While in organic solvent the only oxidation product detected was the lactone (entry 1), a significant increase in the yield on oxidation products up to 63% (entry 3) was observed in water without surfactant with concomitant formation of ϵ -hydroxy-heptanoic acid. The latter is produced by a side consecutive hydrolysis reaction of the lactone with consequent ring opening and carboxylic acid formation. The large increase in conversion observed switching from organic solvent to water is ascribed to the use of the latter as solvent. This observation is unexpected if compared to what recently demonstrated by theoretical calculations¹⁹³ and experimentally observed in organic media,¹⁹⁷ where the rate constant of the reaction decreases as the solvent polarity increases. A control experiment with triflic acid in solution excluded acid catalysts to justify the activity observed in water (Table 9, entry 2).

This discrepancy finds an explanation considering that some unique properties of water as solvent, such as the hydrophobic effect or the acid-base character, are not easily modeled by calculations. The increase of the reaction temperature to 60°C led to an increase of the yield to 88% (Table 9, entry 4) while at the same time the ratio between lactone and the open hydroxy-acid decreased to 11:89. In order to further increase the conversion, surfactants were added to favor substrate solubilization and different classes were tested, ranging from neutral, zwitterionic and anionic, while cationic surfactants were not employed as they usually contain halogenated counter-anions which completely stop the catalytic activity of Pt(II) catalysts leading to the corresponding inactive [(P-P)PtX₂] ((P-P)=diphosphine, X=halogen) complexes. Zwitterionic surfactants did not improve lactone formation (Table 9, entry 12) while neutral surfactants like Triton-X100 and SPAN60 increased product formation. Even better results were observed with anionic surfactants, in particular SDS showed almost quantitative conversion of the ketone with selective formation of the opened ϵ -hydroxy-heptanoic acid (Table 9, entries 5-7) regardless the concentration of SDS employed. Other well defined supramolecular water soluble hosts like α -cyclodextrin and tetrasulfonatomethylcalix[4]resorcinarene were tested (entries 17 and 18), observing that while the former decreased catalytic activity compared to pure water probably sequestering the substrate and preventing interaction with the catalyst in solution, the latter showed tetra-anionic cavitand catalytic promotion similar to SDS, further confirming the synergic effect between solubilization of the substrate and solvent effect on catalytic steps.

Water affects in different ways also the ligand effect on catalytic activity. In fact it is worth noting that while Pt(II) catalysts bearing larger bite angles were usually more active in the BV reaction in organic media,¹⁰⁰ this is not the case in water since catalyst **9b** (Table 9, entry 10) showed lower activity compared to **9a**. Moreover, the formally monomeric bis-cationic character of the catalyst seems essential for good activity as confirmed observing the reduced activity of the dimeric μ -OH complex **9c** (Table 9, entry 11), this time in agreement with the behavior in organic media.¹⁹⁶

Table 9: Surfactant screening in the BV oxidation of 2-methyl cyclohexanone with catalysts **9a-c** in water.^a



entry	catalyst	medium/additive ^b	T (°C)	time (h)	conversion%	lactone/acid ^c
1	9a	DCE ^d	RT	24	46	100:0
2	HOTf	H ₂ O/SDS (75 mM)	60	24	0	-
3	9a	H ₂ O	RT	24	63	30:70
4	9a	H ₂ O	60	24	88	11:89
5	9a	H ₂ O/SDS (38 mM)	60	24	94	0:100
6	9a	H ₂ O/SDS (57 mM)	60	24	97	0:100
7	9a	H ₂ O/SDS (94 mM)	60	24	95	0:100

entry	catalyst	medium/additive ^b	T (°C)	time (h)	conversion%	lactone/acid ^c
8	9a	H ₂ O/SDS (75 mM)	60	24	99	0:100
9	9a (0,2 mol%)	H ₂ O/SDS ^c (75 mM)	60	24	85	0:100
10	9b	H ₂ O/SDS (75 mM)	60	24	82	9:91
11	9c	H ₂ O/SDS (75 mM)	60	24	81	9:91
12	9a	H ₂ O/SB3-12 (150 mM)	60	24	39	0:100
13	9a	H ₂ O/TRITON X-100 (33 mM)	60	24	79	30:70
14	9a	H ₂ O/TRITON X-114 (150 mM)	60	24	45	15:85
15	9a	H ₂ O/SDSU (25 mM)	60	24	89	0:100
16	9a	H ₂ O/SPAN 60 (150 mM)	60	24	82	12:88
17	9a	H ₂ O/ β -CD (5% mol)	60	24	65	8:92
18	9a	H ₂ O/ tetrasulfonatomethylcalix[4] resorcinarene (5% mol)	60	24	97	0:100

a) Experimental conditions: Catalyst (1 mol%), [sub]=5.7, [H₂O₂]=57, t=24 h; b) values in parentheses refer to concentration of additive; c) yield and lactone/acid ratio determined by integration of ¹H NMR spectra; d) data from ref. ¹⁹⁶; DCE=1,2-dichloroethane.

4.2.3.3 Origin Of Hydrolysis

To shed light onto the formation of the hydrolyzed product we performed a series of catalytic tests on the lactone derivative under different experimental conditions (Table 10). A solution of SDS in water yielded a weakly basic medium (pH 7.5), while additional H₂O₂ lowered the pH to 5 and further addition of **9a**, at 1mM concentration as in the catalytic experiments, lowered the pH to 3. The Pt^{II} catalyst in aqueous solution thus acts like a monoprotic Brønsted acid.

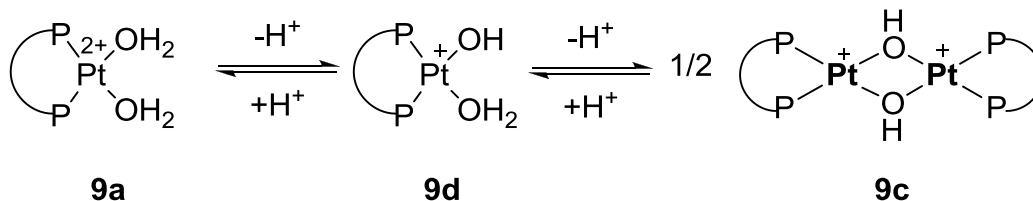
Lactone 7-methyloxepan-2-one in SDS solution with H₂O₂ under the experimental conditions outlined in Table 2 led to 44% hydrolysis in 20 h (Table 10, entry 1). In the presence of catalyst **9a**, the hydrolysis was complete within 20 h (Table 2, entry 3), whereas the same system buffered at pH 7.4 led to the lowest amount of hydrolyzed products (Table 10, entry 5). On the contrary complex **9c**, which in water does not lower the pH of the solution, led to carboxylic acid formation comparable to the SDS solution (Table 10, entry 2). Hydrolysis in SDS with H₂O₂ using 1 mM triflic acid showed hydrolysis rates comparable to the reaction in the presence of **9a** (Table 10, entry 4). Data are consistent with a Brønsted acid-catalyzed lactone hydrolysis caused by the intrinsic Brønsted acidity released by **9a** in aqueous solution. Moreover, lactone 7-methyloxepan-2-one is rather sensitive to such catalysis, whereas other more robust lactones in the same experimental conditions remained unaffected during the reaction.

Table 10: Hydrolysis tests on the lactone 7-methyloxepan-2-one catalyzed by Pt^{II} complexes or H⁺.^a

entry	catalyst	time (h)	yield%
1	-	1.5	1
		20	44
2	9c	1.5	7
		20	48
3	9a	1.5	28
		20	97
4	HOTf	1.5	16
		20	97
5	9a + phosphate buffer (pH 7.4)	1.5	0
		20	27

a) Experimental conditions: Catalyst (1 mol%), [sub]=5.7x10⁻¹M, [H₂O₂]=5.7x10⁻¹M, [SDS]=75 mM; b) yield determined by integration of ¹H NMR spectra.

These experiments raise the question of the nature of the catalytically active species in the system. Complexes **9a** and **9c** are linked together by the stepwise equilibrium shown in Scheme 4. In organic solvents and with more labile counter anions, such as BF₄⁻, the equilibrium is normally shifted towards the formation of the bridging hydroxy species.¹⁹⁸

**Scheme 4:** proton exchange equilibrium involving monomeric and dimeric cationic Pt^{II} complexes in water.

The mechanism of the BV oxidation with the latter catalysts **9c**, has been interpreted in terms of formation of a [(P-P)Pt(ketone)(OOH)] intermediate bearing a hydroperoxo moiety, although this species has never been experimentally detected.¹⁹¹ In water, the situation seems to be different. The aforementioned pH experiments

indicated that even if the starting complex is **9a**, full hydrolysis of one water molecule to yield **9d** occurs immediately and the ^{31}P NMR spectra (Figure 41A, B) very likely refer to the latter species. The single peak in the ^{31}P NMR spectrum could be easily explained on the basis of a rapid proton $\text{HO}\cdots\text{HOH}$ exchange, favored by the aqueous medium. **1d** can produce the $[(\text{P-P})\text{Pt}(\text{ketone})(\text{OOH})]$ intermediate very quickly by simple exchange reactions, thus avoiding the bridge-splitting process necessary to form the same intermediate from **9c**. This mechanism would explain the superior catalytic activity of **9a** with respect to **9c** (Table 9), even if the previously mentioned release of 1 equivalent of H^+ leads to hydrolysis of the BV lactone product, at least in the case of 2-methyl cyclohexanone. The existence of the equilibrium shown in Scheme 4 has also been proven by approaching the system from the right hand side. Addition of 1 equivalent of triflic acid (with respect to platinum) to a solution of **9c** in D_2O (^{31}P NMR: $\delta=68.3$ ppm, $^1\text{J}(\text{P,Pt})=3506$ Hz) led to immediate complete formation of **9d** (^{31}P NMR: $\delta=72.6$ ppm, $^1\text{J}(\text{P,Pt})=3799$ Hz).

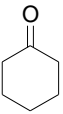
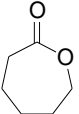
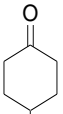
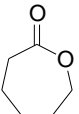
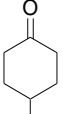
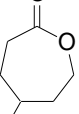
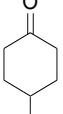
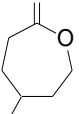
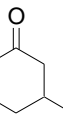
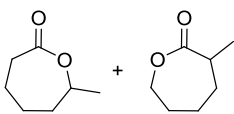
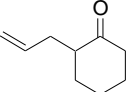
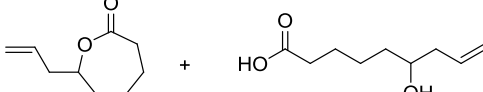
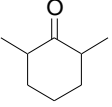
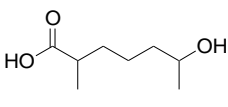
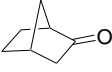
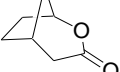
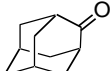
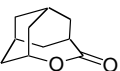
4.2.3.4 Scope of the Reaction

Having optimized the experimental conditions, we investigated the scope of the reaction with a series of cyclic and bicyclic ketones (Table 11). Productivity and product distribution were highly dependent on the nature of the substrate employed. Ring-strained four membered ring ketones reacted readily leading to the corresponding lactones in high yields within a few hours, even at 5°C (Table 11, entries 1–5). It should be emphasized that under these experimental conditions the spontaneous reaction in the absence of catalyst never exceeded 15% yield. Cyclopentanone led to only 16% yield of lactone but, if substituted in the α position the yield increased up to 56 %, with partial hydrolysis of the lactone to the corresponding open δ -hydroxy hexanoic acid (Table 11, entries 6 and 7). Even larger six-membered ring ketones led to lactones in low yields if substituted in the β or γ position, whereas for α -substituted reagents, lactone formation was favored but partial hydrolysis to the corresponding carboxylic acids occurred (Table 11, entries 13 and 14). Even bicyclic systems such as 2-norbornanone and 2-adamantanone reacted readily, affording the lactone in moderate to good yields (Table 11, entries 15 and 16). However, no products derived from hydrolysis were observed, probably because the rigidity of the bicyclic scaffolds disfavors the hydrolytic step. In principle, compounds of different polarity may show a different distribution between the different domains within the micellar solutions with possible influence on the reactivity. However these phenomena are very difficult to prove. Attempts have been made to separate the catalyst from the products in the case of the oxidation of methylcyclohexanone by extracting it with ethyl acetate, but ketones, lactones, and (in this particular case)

hydroxyacids are moderately to fully soluble in water, leading to the formation of emulsions for which phase separation is practically impossible to accomplish.

Table 11: Scope of the BV oxidation reaction with H₂O₂ mediated by Pt^{II} catalyst **9a** in water/SDS medium.

Entry ^a	Substrate	Product	Time(h)	Yield% ^b
1 ^c			1 8	71 99
2 ^c			8	99
3 ^c			8	99
4 ^c			8	85
5 ^c			3	100 (92:8)
6			20	16
7			20	56 (79:21)

Entry ^a	Substrate	Product	Time(h)	Yield% ^b
8			20	48
9			20	21
10			20	13
11			20	26
12			20	11 (57:43)
13			20	55 (25:55)
14			20	57
15			20	52
16			20	80

a) Experimental conditions: 60°C, [sub]= 5.7·10⁻¹ M, [10a]= 5.7·10⁻³ M, [H₂O₂]= 5.7·10⁻¹ M, [SDS]= 75 mM. b) Yield determined by ¹H-NMR integration; c) T=5°C

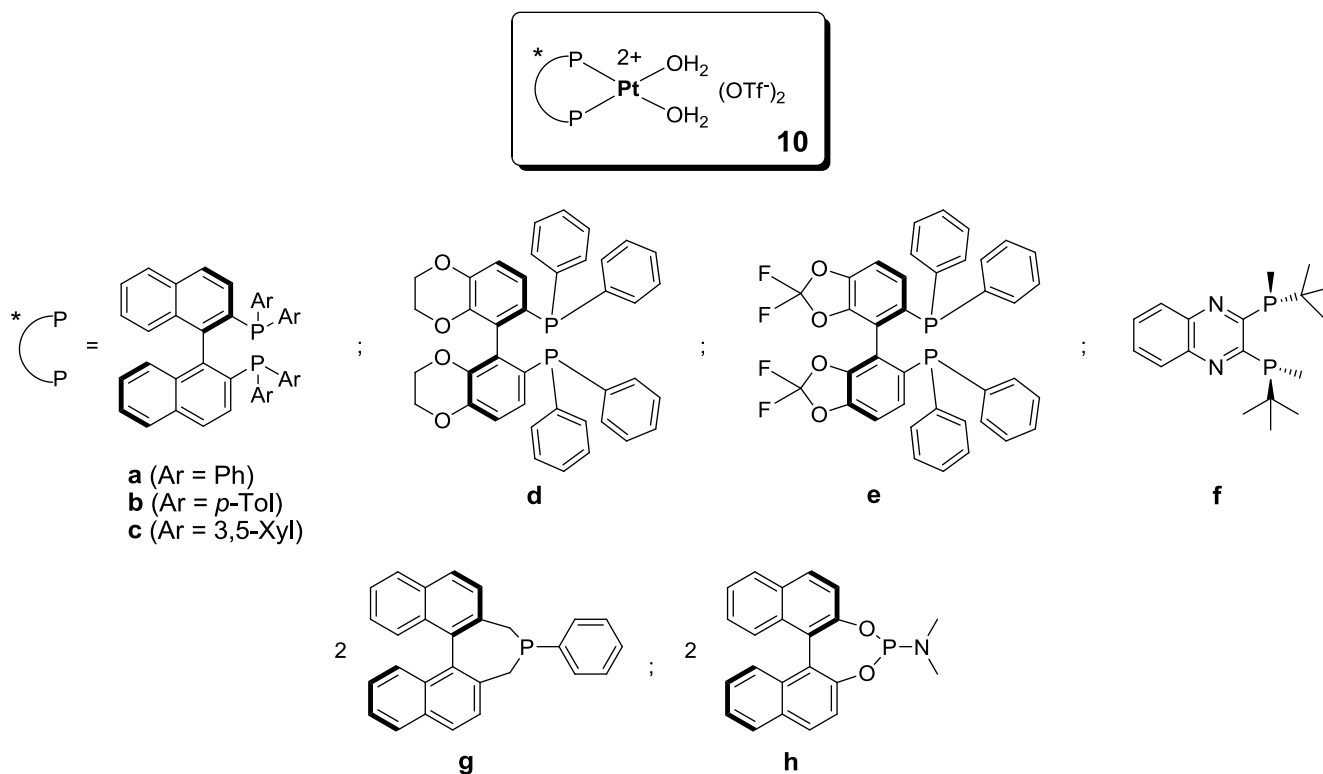
4.2.3.5 Conclusions

The catalytic system reported herein, based on intrinsically water-soluble Pt^{II} complex **9a**, showed good catalytic activity within hours in the BV oxidation of cyclic ketones in water with H₂O₂ as terminal oxidant. Exchanging organic solvents for water greatly favored oxidation reactions, leading to higher lactone formation when SDS as anionic surfactant is employed. Furthermore, the solubility of the catalyst in water led to hydrolysis with release of one equivalent of H⁺ and the likely formation of a long-sought but never experimentally identified hydroxy platinum species that is the crucial intermediate in the BV oxidation with this class of Pt^{II} catalysts. For more acid-sensitive substrates, higher productivity is paralleled by formation of the corresponding ω -hydroxy acids because of H⁺-catalyzed hydrolysis of the intermediate lactone in water. Mild experimental conditions, such as moderate temperature and low catalyst loading (≤ 2 mol %), enabled moderate to good yields.

4.2.4 ASYMMETRIC BV OXIDATION MEDIATED BY WATER-INSOLUBLE CATALYSTS

4.2.4.1 Catalyst Positioning In Micellar Medium

For the asymmetric version of the BV oxidation of cyclic ketones, monomeric chiral enantiopure Pt^{II} complexes in Scheme 5 were employed, where Pt coordinates bidentate phosphine ligands with different electronic properties. Besides the bidentate species, two monodentate ligands were also tested, namely the monophosphine **g** and the phosphoramidite **h**. In all cases, the surfactant plays the role of solubilizing both catalysts and substrates, as all complexes are water-insoluble.



Scheme 5: Chiral Pt^{II} catalysts (**10a–h**) employed in the asymmetric BV oxidation of cyclic ketones with 35% H₂O₂.

The characterization of the catalytic system in aqueous solution was carried out on complex **10a** and reported in the figures below. In Figure 42A and B, the ¹H and ³¹P NMR spectra of catalyst **10a** in D₂O in the presence of sodium dodecylsulfate (SDS) as surfactant are shown. Both spectra demonstrate catalyst solubilization by means of interaction with the micellar system because no signals were detected in the absence of SDS. The ¹H NMR spectrum clearly shows the presence of the aromatic resonances of the 2,2'-bis(diphenylphosphino)-1-1'-

binaphthyl (binap) chiral ligand and the ^{31}P NMR spectrum shows the presence of two equivalent phosphorus atoms with P–Pt coupling constants typical of **10a**. In Figure 42C the 2D DOSY spectrum shows the resonances of the catalyst characterized by the same diffusion coefficient of the micelles, proving the reciprocal interaction between the two. Moreover, to better investigate the catalyst position in the micelles, the NOESY spectrum is also reported (Figure 42D), which shows positive cross peaks between the aromatic resonances of **10a** and the signal of the methylene groups of SDS, whereas negative cross peaks are observed between different aromatic resonances belonging to the BINAP ligand. . This clearly indicates that the catalyst resides in the apolar core of the micelle, neither deeply buried (no cross peaks were observed between **10a** and the terminal methyl group of SDS) nor on the external surface of the micelles (no cross peaks were observed with the methylene close to the sulfate moiety). This behavior is different from that observed in asymmetric sulfoxidation using the same dimeric Pt^{II} complex $[\text{Pt}((R)\text{binap})(\mu\text{-OH})]^{2-}(\text{BF}_4)_2$ with SDS, in which the catalyst, because of its larger size, did not dissolve into the hydrophobic core of the micelle but simply interacted as a counteranion with the negative outer shell of the supramolecular aggregate.¹⁹⁹

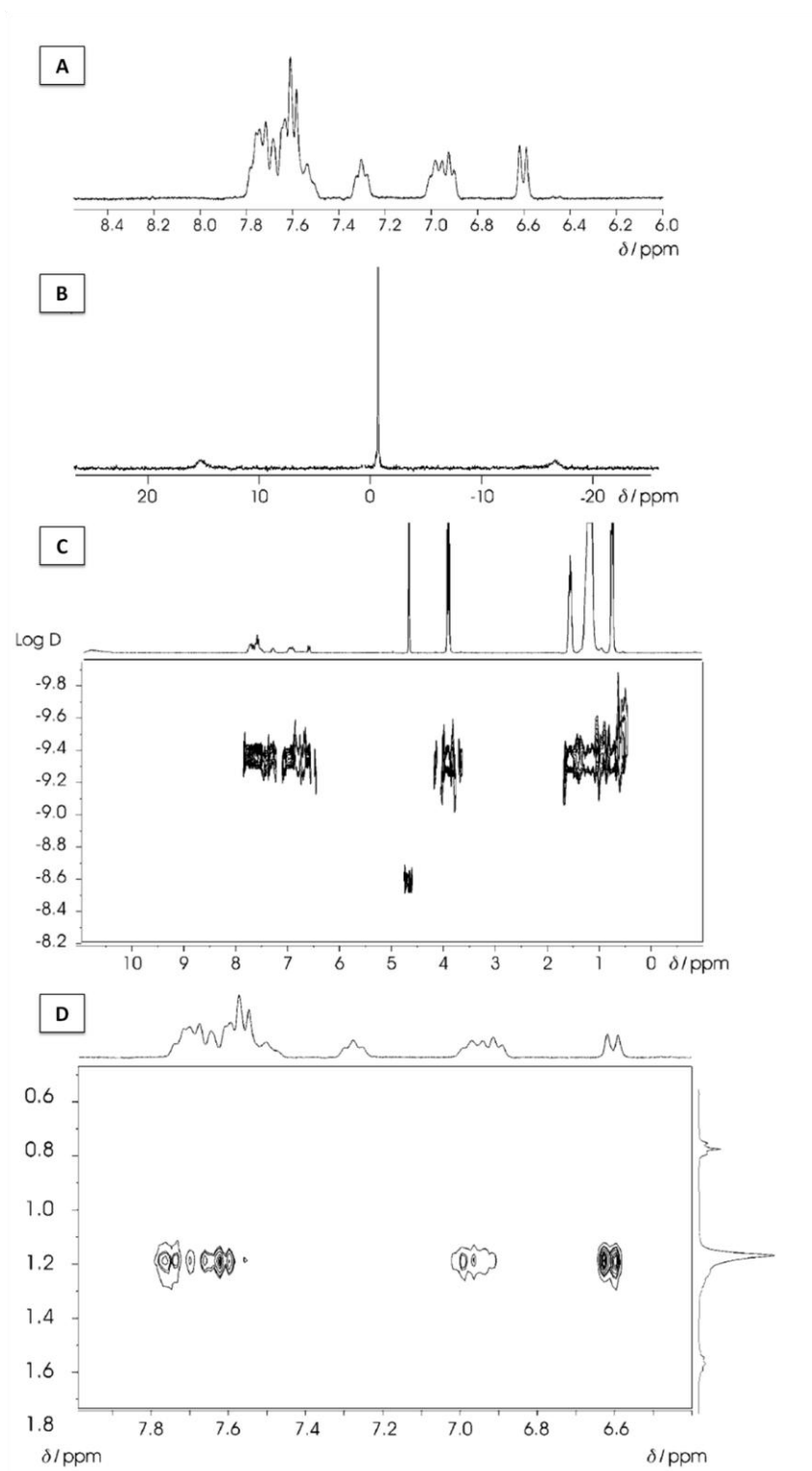
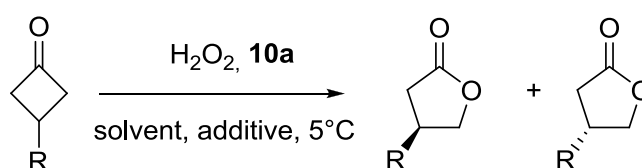


Figure 42: NMR spectra of catalyst 9a in D₂O in the absence and presence of SDS as surfactant. a) ¹H; b) ³¹P{¹H}; c) DOSY spectrum with evidence of same diffusion coefficient for micelles and catalyst and d) NOESY spectrum with evidence the cross peaks between catalyst and the methylene residues of the surfactant

4.2.4.2 Optimization Of Reaction Conditions

Initially, the catalytic activity of catalyst **10a** in water was tested on 3-phenylcyclobutanone as a model substrate, with commercial 35% H₂O₂ as the terminal oxidant. A wide series of surfactants was employed to enhance both catalyst and substrate solubility and steer selectivity (Table 12).

Table 12: Asymmetric BV oxidation of meso-3-substituted-cyclobutanones in water with H₂O₂ catalyzed by chiral Pt^{II} complex **10a** in the presence of different surfactants.^a

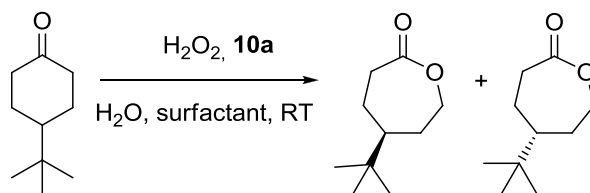


Entry	R	medium	time(h)	yield% ^b	ee% ^c
1	Ph	CH ₂ Cl ₂	5	86	37
2	Ph	H ₂ O/SDS ^d	5	80	10
3	Ph	H ₂ O/SDBS ^e	5	76	15
4	Ph	H ₂ O/Triton X-100 ^f	5	71	31
5	Ph	H ₂ O/Triton X-114 ^g	22	95	28
6	Ph	H ₂ O/Triton X-405 ^h	22	81	27
7	Ph	H ₂ O/POA ⁱ	24	94	22
8	Ph	H ₂ O/PTS ^j	24	99	56
9	Cy	CH ₂ Cl ₂	5	98	31
10	Cy	H ₂ O/SDS	5	80	26
11	Cy	H ₂ O/SDBS	24	96	19
12	Cy	H ₂ O/PTS	24	98	32

a) Experimental conditions: [Sub]₀=0.5M; [H₂O₂]=0.5M; [10a]=1 mol%, solvent: water or CH₂Cl₂ 0.5 mL. b) Yield determined by GC analysis on HP-5 column. c) ee determined on chiral GC column Lipodex B, absolute configuration not assigned. d) Sodium dodecylsulfate (75 mM). e) Sodium dodecylbenzene sulfonate, (75 mM). f) Polyoxyethylene(10)isooctylphenyl ether (150 mM). g) Polyoxyethylene(8)-isooctyl cyclohexyl ether (150 mM). h) Polyoxyethylene (40)isooctylphenylether (150 mM). i) Polyoxyethylene alcohol (C₁₂H₂₅-C₁₈H₃₇)-(OCH₂CH₂)₅ (150 mM). j) Polyoxyethanyl- α -tocopheryl sebacate (45 mM).

As expected, the ring strain of the cyclobutanone allows the catalyst to afford good yields of lactone in an ordinary organic medium, albeit with moderate ee values. When switching to a water–surfactant medium, catalytic activity decreases and longer reaction times are required to ensure almost quantitative conversions. When using anionic surfactants, the enantioselectivity of the reaction in water is markedly lowered compared with the same reaction in dichloromethane, whereas with neutral surfactants a higher ee value (56%) was achieved by employing the recently developed tenside polyoxyethanyl- α -tocopheryl sebacate (PTS) (Table 12, entry 8).²¹ Changing the *R* substituent in the substrate to cyclohexyl did not change the overall behavior, again the use of anionic surfactants resulted in lower ee values and the use of PTS ensured comparable enantioselectivity and yield compared to chlorinated solvents, but after longer reaction times. The same desymmetrization approach was applied to *meso*-cyclohexanones. These substrates are more challenging because of their intrinsically lower reactivity, which results from lack of ring strain. The catalytic activity of catalyst **10a** was tested in the oxidation of 4-*tert*-butylcyclohexanone as a model substrate in water, with a variety of surfactants as dispersing agents (Table 13).

Table 13: Enantioselective BV oxidation of 4-tert-butyl-cyclohexanone using 35% hydrogen peroxide and catalyst **10a** in micellar medium provided by different surfactants. ^a



entry	medium	time(h)	yield% ^b	ee% ^c
1	DCE	4	21	62
		24	37	66
2	H ₂ O/SDS	3	6	83
		24	8	89
3	H ₂ O/SDBS	3	10	73
		24	15	79
4	H ₂ O/SDSU ^d	3	2	56
		24	6	76
5	H ₂ O/SPAN 60 ^e	3	5	57
		24	10	63
6	H ₂ O/Triton X-100	3	3	64
		24	10	77
7	H ₂ O/PTS	3	5	54
		24	7	52

a) Experimental conditions: [Sub]₀=0.05M, [H₂O₂]₀=0.07M, [10a]= 5 mol%, water 0.5 mL, T=RT. [ionic surfactants]=75 mM, [neutral surfactants]=150 mM, [PTS]=45 mM. b) Yield determined by GC analysis on HP-5 column. c) ee determined on chiral GC column Lipodex B, (S)-lactone as major enantiomer. d) Sodium dodecansulfonic acid (75 mM).

e) Sorbitan monostearate (150 mM).

As expected, the observed catalytic activity is lower than that observed for cyclobutanones even though a higher catalyst loading was employed (in some cases the system is not catalytic because the yield is lower than the catalyst loading). As observed in Table 13, the use of different micellar media slows down the reactivity compared with a common organic solvent such as dichloroethane (DCE). On the other hand, enantioselectivity was improved in the micellar medium, increasing from 66% in DCE to 89% in water/SDS. Such enhancement in stereocontrol is better understood if expressed in terms of enantiomeric ratio $[R]/[S]$ ²⁰⁰ (chlorinated solvent

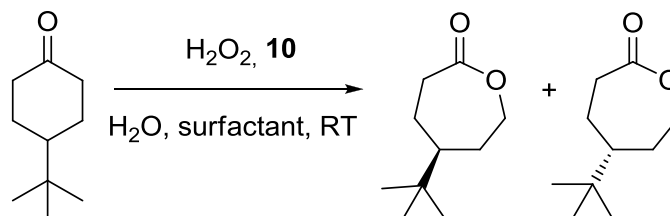
83:17, water–SDS 96:6) which is directly correlated to the $\Delta\Delta G^\ddagger$ between the two diastereomeric transition states leading to enantiomeric lactones, as expressed by the equation:

$$\frac{[R]}{[S]} = \frac{k_1}{k_2} = e^{-\Delta\Delta G^\ddagger/RT}$$

Moving from chlorinated solvent to water/SDS medium almost doubles the ΔG^\ddagger : an increase of about 3.1 kJ mol⁻¹ is observed, which is a rather impressive result if one considers that only the reaction medium has changed. Such a high degree of control in the catalytic reaction arises from supramolecular attractive and repulsive interactions caused by the more ordered nano-environment provided by the micelle. In fact, the catalyst is surrounded by the highly oriented alkyl chains of the surfactant compared with the same catalyst in a bulk apolar solvent. To reach the catalyst, the substrate has to pass through the alkyl chains of the surfactant and this turns out in a more controlled interaction between the catalyst and the substrate. Analogously, in the rate-determining step of the reaction, the solvation of the transition states leading to the two enantiomeric products are also more controlled. A comparison with asymmetric reactions in chiral liquid crystals is therefore viable, in which the reaction occurs in a highly enantioselective fashion due to the high degree of order imparted by the alignment of the molecules of the medium.²⁰¹⁻²⁰³ In the latter system as well as in micelles, the orientation of the molecules is a consequence of supramolecular interactions, but whereas for liquid crystals these interactions arise by enthalpic contributions of intermolecular interaction, for micelles they are caused by entropic contribution deriving from the hydrophobic effect imparted by water. Different anionic surfactants, such as sodium dodecylbenzene sulfonate (SDBS) and dodecansulfonic acid sodium salt (characterized by either a larger hydrophobic portion or a less polar head, respectively), performed better in terms of activity but were less selective in enantiodiscrimination compared with SDS. Even neutral surfactants like Triton-X100 or SPAN 60 provided the enantioenriched lactone with up to 77% ee. The cationic surfactant cetyltrimethyl ammonium bromide (CTABr) was unsuccessful; catalytic conversion was suppressed most likely because of the bromide counteranion binding to the catalyst, leading to [Pt((*R*)-binap)Br₂] as an inactive complex. A catalyst screening was performed using both monomeric and dimeric Pt^{II} complexes with chiral C₂-symmetric diphosphines, as well as monomeric catalysts endowed with chiral monophosphines (Table 14). It is worth noting that the same chiral ligand BINAP behaved differently when present in the monomeric, more selective catalyst compared with a dimeric catalyst (Table 14, entries 1 and 2). In addition to the different steric requirements of the catalysts, this difference might also be attributed to their different positioning in the micelles because the monomeric catalyst prefers to reside in the apolar core of the micelle, whereas the dimeric catalyst remains on the external surface of the anionic SDS micelles.¹⁹⁹ Other chiral ligands based on the binaphthyl backbone showed good enantioselectivities, higher than in the organic solvent, but lower yields than catalyst **10a**. P-

chiral catalyst **10f** showed lower enantioselectivity, whereas catalysts with hindered monophosphines, such as **10g**, were poorly enantioselective with meso-cyclohexanones. Catalyst **10h** was completely inactive, probably due to high steric hindrance around the Pt^{II} metal center.

Table 14: BV reaction of 4-tert-butylcyclohexanone with H₂O₂ catalyzed by different catalysts **2** in water/SDS medium.^a

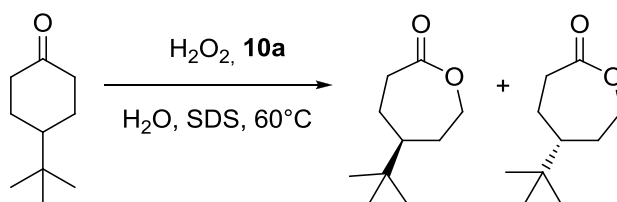


entry	catalyst	yield% ^b	ee% ^c	abs. config.
1	10a	8	89	S
2	[Pt((<i>R</i>)-binap)(μ-OH)] ₂	3	78	S
3	10b	5	82	S
4	10e	5	82	S
5	10f	7	66	S
6	10g	7	16	R

a) Experimental conditions: [Sub]₀=0.05M, [H₂O₂]₀=0.07M, [cat]= 5 mol%, water 0.5 mL, T=RT, reaction time 24h, [SDS]=75 mM. b) Yield determined by GC analysis on HP-5 column c) ee determined on chiral GC column Lipodex B, (*S*)-lactone as major enantiomer.

Using the combination of catalyst **10a** and SDS as the best catalytic system, the catalytic performance was improved by varying catalyst loading, temperature and other experimental parameters (Table 15). Lactone yields were improved either by using a larger amount of oxidant or catalyst, or by performing the reaction at higher temperature. No detrimental effect on the enantioselectivity was observed at higher temperatures. At 60 °C the lactone can be obtained in 23% yield and 89% ee. Surfactant concentration was another crucial parameter that strongly affected both yields and enantioselectivities. Increasing surfactant concentration above the critical micellar concentration (8 mM for SDS) caused an increase in activity as well as selectivity, due principally to a better solubilization of the catalyst. Larger concentrations of surfactant mean larger micelles and possible variation from the usual spherical version of the micelle to more elongated shapes, causing a different reciprocal positioning of catalyst and substrate, which may affect both catalytic activity and enantioselectivity. Overall, an intermediate SDS concentration of 75 mM was the best compromise between activity and selectivity.

Table 15: BV reaction of 4-tert-butylcyclohexanone with H₂O₂ catalyzed by **10a** in SDS micellar medium under different experimental conditions.^a



entry	T	cat. loading (%mol)	H ₂ O ₂ (equiv.)	[SDS] (mM)	time(h)%	yield% ^b	ee% ^c
1	RT	5	1.3	75	3	6	83
					24	8	89
2	RT	5	3	75	3	5	81
					24	11	89
3	RT	10	1.3	75	3	5	81
					24	13	89
4	60°C	5	1.3	75	3	13	87
					24	23	89
5	RT	5	1.3	37.5	3	2	64
					24	5	74
6	RT	5	1.3	150	3	4	81
					24	6	84
7	RT	5	1.3	300	3	4	75
					24	8	92

a) General experimental conditions: [Sub]₀=0.05M, water 0.5 mL. b) Yield determined by GC analysis on HP-5 column c) ee determined on chiral GC column Lipodex B, (S)-lactone as major enantiomer.

After optimizing these parameters, the scope of the reaction was investigated, operating at 60 °C with 5 mol% catalyst, 1.3 equivalents of hydrogen peroxide and [SDS]=75 mM. For meso-cyclohexanones, a decrease in yield was observed compared with the reaction in organic chlorinated solvent, but much higher enantioselectivities were observed for all substrates, as reported in Table 16.

Table 16: BV oxidation of prochiral cyclohexanones with H₂O₂ catalyzed by **10a** with SDS in water.^a

entry	R	yield% in DCE ^b	ee _{DCE} %	Yield% in H ₂ O/SDS ^b	ee _{mic} %
1	Ph	3	53 ^c	7	79 ^c
2	Me	12	40 ^c	5	66 ^c
3	Et	31	34 ^d	9	69 ^d
4	Pr	28	35 ^d	8	74 ^d

a) Experimental conditions: [Sub]₀=0.05M, [H₂O₂]₀=0.07M, [10a]= 5 mol%, water 0.5 mL, [SDS]=75 mM, T=60°C, reaction time 24h. b) Yield determined by GC analysis on HP-5 column c) ee determined on chiral GC column Lipodex B, (S)-lactone as major enantiomer. d) ee determined on chiral GC column CHIRALDEX γ-TA.

Although the difference in behavior between meso-cyclobutanones and meso-cyclohexanones is clear as far as reactivity is concerned, the differences in enantioselectivity between the two substrate classes deserve further discussion. In fact, in both chlorinated and aqueous media all catalysts tested showed moderate asymmetric induction with the cyclobutanone substrates and much better results with the cyclohexanones. The preference for one enantiomer over the other of the lactone is a direct consequence of which migration of the methylene residue adjacent to the carbonyl occurs in the rate-determining step. In both types of substrates, the *R* substituent is remote from the carbonyl coordinated to the metal site. It is therefore likely that with cyclobutanones, such migration is less sensitive to the steric constraint imparted by the chiral ligand because of the smaller -CH₂-CO-CH₂- angle typical for an *sp*² carbon (close to 90° in cyclobutanones but close to 120° in cyclohexanones). This implies that methylene migration is much better controlled by the catalyst steric properties in a more rigidly held six-membered ring compared with a “loose” four-membered ring. Also noteworthy is the effect of surfactant type on the enantioselectivity of the BV reaction. Higher ee values were obtained by using neutral surfactants compared with anionic surfactants for *meso*-cyclobutanones, whereas exactly the opposite was true for *meso*-cyclohexanones. No clear explanation is possible because several parameters affect the stereochemical outcome of the reaction, but at first glance a relationship between the reciprocal solubility and the positioning of the substrates in the micelles seems plausible. Smaller *meso*-cyclobutanones are less hydrophobic and hence more deeply solubilized in the apolar core of the micelle by

using neutral surfactants, whereas better enantioselectivity was obtained with the more hydrophobic *meso*-cyclohexanones, which reside in the smaller hydrophobic core of anionic surfactants.

4.2.4.3 Conclusions

The catalytic systems reported showed good activity within hours in the catalytic asymmetric BV oxidation of cyclic ketones in water with the aid of surfactants. In particular, the results observed for *meso*-cyclohexanones are, to the best of our knowledge, among the best reported in terms of enantioselectivity and second only to enzymatic catalysis,^{23,204} when the unusual aqueous medium is used. Mild experimental conditions, such as low temperature and low catalyst loading (<5 mol%) enabled moderate to good yields as well as good enantioselectivities in several examples. Whereas for *meso*-cyclobutanones enhancement of enantioselectivity was observed with the neutral PTS surfactant, with *meso*-cyclohexanones anionic micelles ensured a remarkable increase in ee value compared with organic chlorinated solvents. Overall, the use of surfactants in water for the BV reactions studied implies the partition of all reaction components (substrate, oxidant and catalyst) between the micelle, bulk water, and the interphase between the two. As a consequence, the lipophilicity of all species is crucial to rationalize their positioning in the micellar system, and as a general observation, more hydrophilic substrates gave better results in neutral surfactants whereas anionic micelles were preferred for more lipophilic substrates. Analogously, a general increase in enantioselectivity was observed for more apolar substrates in water–surfactant medium compared with reaction in chlorinated solvent, with remarkable examples such as those reported in Table 13. This demonstrates that water/surfactant mixtures are viable media for Pt^{II}-mediated BV oxidation reactions of cyclic ketones, as well as for other oxidation reactions studied recently.^{8,14} The general observation that the larger ee enhancements moving from CH₂Cl₂ to the water–surfactant medium were observed with SDS as the surfactant, especially for more apolar substrates, could be interpreted in terms of tighter binding of substrate and catalyst in the palisade created by the alkyl chains of the surfactant. The entropic driving force for this is the hydrophobic effect that tends to squeeze apolar surfaces together to minimize their interaction with water. Compared with other surfactants SDS contains relatively shorter alkyl chains and, at the same time, relatively polar head groups. Both of these properties favor close contact between the catalyst and substrate, which are both hosted in the core of the micelle. Such supramolecular control is not possible in common organic solvents, in which there is a lower general order of the molecules around the catalyst by means of simple solvation. A similar

principle is observed in several enzymes, in which the binding of substrates and their juxtaposition in the hydrophobic active site is driven by the hydrophobic effect.

4.2.5 EXPERIMENTAL

General: ^1H and $^{31}\text{P}\{^1\text{H}\}$ NMR spectra were recorded at 298 K, unless otherwise stated, on a Bruker AVANCE 300 spectrometer operating at 300.15 and 121.50 MHz, respectively. δ values in ppm are relative to SiMe_4 and 85% H_3PO_4 . $^{19}\text{F}\{^1\text{H}\}$ NMR spectra were recorded at 298 K on a Bruker AC200 spectrometer operating at 188.25 MHz. δ values in ppm are relative to CFCl_3 . All reactions were monitored by ^1H NMR spectroscopy.

GLC data were measured on a Hewlett–Packard 5890 A gas chromatograph equipped with a FID detector (carrier gas He). All reactions were monitored either by GC or by ^1H NMR spectroscopy. Enantiomeric excesses were determined by extraction of the reaction mixture with ethyl acetate, drying, and dissolving the residue in hexane. The ee of the solution was then analyzed as reported below. Elemental analyses were performed by the Department of Analytical, Inorganic and Organometallic Chemistry of the Università di Padova.

Substrates: All ketones used as substrates as well as hydrogen peroxide (35%) were commercial products (Aldrich) and were used as received without further purification. *meso*-cyclobutanones were prepared following procedures reported in the literature.^{205,206} Lactone and hydroxy acid products of the BV oxidation reactions were assigned by comparison with NMR data. All the surfactants and water soluble additives were commercial products and were used without purification: SDS (Sodium dodecylsulfate), SB3-12 (zwitterionic N-dodecyl-N,N-dimethyl-3-ammonio-1-propanesulfonate), SPAN60 (sorbitan monostearate), Triton-X100 (polyoxyethylene(10)isooctyl phenyl ether), Triton X-114 (polyoxyethylene(8)isooctylcyclohexyl ether), SDSU (sodium dodecylsulfonate), β -cyclodextrin (β -CD). Tetrasulfonatomethyl calix[4]resorcinarene was prepared following a procedure reported in the literature.²⁰⁷

Absolute configurations of lactone products were confirmed by ^1H NMR spectroscopic analysis in comparison with reported assignments.¹⁰⁵ Ligand **g** was prepared as reported in the literature.²⁰⁸ All the surfactants employed are commercial products and were used as received.

NMR spectroscopy experiments: The 2D-NOESY experiments were acquired with a spectrum width of 10 ppm, a relaxation delay d_1 of 1 s, using 2000 data points in the t_2 dimension and 512 data points in the t_1 dimension, with subsequent weighting with the sine-bell function using 160 scans for each t_1 increment. The mixing time

d8 employed was 600 ms. The 2D-DOSY spectra were recorded with a Bruker AMX 300 spectrometer (^1H =300.15 MHz) equipped with a PABBO BB- ^1H Z GRD probe head. The pulse sequence used was ledbpgp2s 2D sequence for diffusion measurements using stimulated echo and LED using bipolar gradient pulses with two spoil gradients. The duration of the magnetic field pulse gradients (d) and diffusion time (D) were 1 and 75 ms, respectively. The pulsed field gradients were incremented from 1 to 32 Gcm^{-1} . A series of 32 spectra on 16000 data points were collected with 32 transients; the total measuring time was approximately 1 h. After Fourier transformation and baseline correction, the diffusion dimension was processed with the Bruker Xwin-NMR software package. In the experiments, gradients were calibrated against the HOD diffusion constant at 258C (D_2O (99.9% D) $19.0 \times 10^{-10} \text{ m}^2 \text{ s}^{-1}$). Spectra were measured at 25°C with a 90° pulse duration of 8.3 ms and a relaxation delay of 5 s.

Synthesis of the complexes: All work was carried out with the exclusion of atmospheric oxygen under a dinitrogen atmosphere by using standard Schlenk techniques. Solvents were dried and purified according to standard methods. The catalysts **10f**, **10g**, and **10h** are new complexes and were synthesized through chlorine abstraction from the corresponding (**f–h**) PtCl_2 complexes **11f**, **11g**, and **11h**, which were prepared by the treatment of [$\text{PtCl}_2(\text{cod})$] (cod =1,5-cyclooctadiene) with the corresponding phosphine **f**, **g** or **h**.

11f: Ligand **f** (1 equiv) was added to a solution of [$\text{PtCl}_2(\text{cod})$]²⁰⁹ (100 mg, 0.25 mmol) in dichloromethane (20 mL) at room temperature. The reaction mixture was stirred for 2 h and then, after concentration, the product was precipitated as a white solid using pentane. The product was then filtered and dried under vacuum (138 mg, 93%). ^1H NMR (CDCl_3 , 25°C, TMS): δ =8.30 (dd, J =3.57 Hz, 2H; Ar), 8.02 (dd, J = 3.57 Hz, 2H; Ar), 2.38–2.16 (m, 6H; CH3), 1.19 (d, J =15.9 Hz, 18H; tBu); $^{31}\text{P}\{^1\text{H}\}$ NMR (CDCl_3 , 25°C, TMS): δ =29.6 (s, $1J(\text{Pt},\text{P})$ =3448 Hz).

elemental analysis calcd (%) for $\text{C}_{18}\text{H}_{28}\text{Cl}_2\text{N}_2\text{P}_2\text{Pt}$: C 36.01, H 4.70; found: C 36.11, H 4.66.

10f: A 0.35M solution of AgOTf (2.05 equiv) in acetone was added to a solution of **3 f** (100 mg, 0.17 mmol) in acetone (20 mL) at room temperature. The reaction mixture was stirred for 2 h, then the AgCl formed was filtered off. After concentration, the solution was treated with pentane to give a white solid, which was filtered off and dried under vacuum (89 mg, 62%). ^1H NMR (CDCl_3 , 258C, TMS): δ =8.35 (dd, J =3.57 Hz, 2H; Ar), 8.13 (dd, J =3.57 Hz, 2H; Ar), 2.27 (d, J =12.4 Hz, 6H; CH3), 1.28 (d, J =17.6 Hz, 18H; tBu); $^{31}\text{P}\{^1\text{H}\}$ NMR (CDCl_3 , 258C, TMS): δ =26.4 (s, $1J(\text{Pt},\text{P})$ =3764 Hz); elemental analysis calcd (%) for $\text{C}_{20}\text{H}_{28}\text{F}_6\text{N}_2\text{O}_6\text{P}_2\text{PtS}_2$: C 29.03, H 3.41; found: C 29.09, H 3.36.

11g: Yield: 124 mg, 71%; ^1H NMR (CDCl_3 , 25°C, TMS): δ =8.29 (d, J = 8.10 Hz, 1H; Ar), 8.10–7.95 (m, 2H; Ar), 7.79 (d, J =7.97 Hz, 1H; Ar), 7.63–7.34 (m, 8H; Ar), 7.33–7.17 (m, 3H; Ar), 7.12 (d, J =8.10 Hz, 1H; Ar), 6.57 (d, 8.51 Hz,

1H; Ar), 3.5–2.5 (m, 4H; CH₂); ³¹P{¹H} NMR (CDCl₃, 25°C, TMS): δ=25.01 (s, 1J (Pt,P)=3571 Hz); elemental analysis calcd (%) for C₅₆H₄₂Cl₂P₂Pt: C 64.50, H 4.06; found: C 64.55, H 4.03.

10g: Yield: 45.7 mg, 73%; ¹H NMR (CDCl₃, 25°C, TMS): δ=8.32 (d, J= 8.37 Hz, 1H; Ar), 8.10–7.95 (m, 2H; Ar), 7.80 (d, J=7.97 Hz, 1H; Ar), 7.63–7.35 (m, 8H; Ar), 7.31–7.18 (m, 3H; Ar), 7.12 (d, J=8.60 Hz, 1H; Ar), 6.58 (d, J=8.60 Hz, 1H; Ar), 3.8–2.5 (m, 4H; CH₂); ³¹P{¹H} NMR (CDCl₃, 25°C, TMS): δ=15.97 (s, 1J (Pt,P)=3871 Hz); elemental analysis calcd (%) for C₅₈H₄₂F₆O₆P₂PtS₂ : C 54.85, H 3.33; found: C 54.78, H 3.40.

11h: Yield: 105 mg, 71%; ¹H NMR (CDCl₃, 25°C, TMS): δ=8.30–7.28 (m, 12H; Ar), 2.30 (br s, 6H; CH₃); ³¹P{¹H} NMR (CDCl₃, 25°C, TMS): δ=93.91 (s, 1J(Pt,P)=5605 Hz); elemental analysis calcd (%) for C₄₄H₃₆Cl₂N₂O₄P₂Pt: C 53.67, H 3.68; found: C 53.62, H 3.71.

10h: Yield: 110 mg, 88%; ¹H NMR (CD₂Cl₂, 25°C, TMS): δ=8.11–7.33 (m, 12H; Ar), 2.35 (br s, 6H; CH₃); ³¹P{¹H} NMR (CDCl₃, 25°C, TMS): δ=63.11 (s, 1J (Pt,P)=6269 Hz); elemental analysis calcd (%) for C₄₆H₃₆F₆N₂O₁₀P₂PtS₂: C 45.59, H 2.99; found: C 45.55, H 3.04.

Catalytic Studies: General procedure for non-asymmetric BV oxidation reaction with **9a–c** in water with H₂O₂: In a vial equipped with a screw capped septum the cyclic ketone (0.3 mmol) was dissolved in water (0.5 mL) with the aid of the proper amount of SDS (75 mM). Complex **9a–c** was added (1% mol) to this solution and the vial was thermostatted at the desired temperature. 35% H₂O₂ (0.4 mmol) was then added in one portion and the resulting mixture was vigorously stirred. The reaction progress was monitored by sampling through the septum. Quenching of the reaction was performed by addition of NaCl to the sample. Conversion was determined by integration of ¹H NMR spectra. Typically in the case of cyclohexanone, the signals monitored were as follows. Ketone: δ=0.84 ppm (d, J=6.5 Hz); acid: δ=1.03 ppm (d, J= 6.0 Hz); lactone: δ=1.19 ppm (d, J=6.5 Hz).

General procedure for asymmetric BV oxidation with chiral complexes **10a–h**: In a vial equipped with a screw-capped septum, the cyclic ketones (0.25 mmol) were dissolved in water (0.5 mL) with the aid of the proper amount of surfactant (1 mM in micelles). Complex **10a–h** was added (1–5 mol%) and the vial was heated at the desired temperature. 35% H₂O₂ (1 equiv) was then added in one portion and the resulting mixture was vigorously stirred. The reaction progress was monitored by sampling through the septum. Quenching of the reaction was performed by addition of solid NaCl to the sample.

In both procedures the absence of diffusional problems was determined by the independence of conversion vs. time plots on the stirring rate and the concentration of commercial 35% H₂O₂ solution was checked iodometrically prior to use.

Enantiomeric excess determination: Enantiomeric excesses of five-membered ring lactones derived from *meso*-cyclobutanones were analyzed by GC: 4-phenyldihydrofuran-2(3*H*)-one: chiral GC column Lipodex B, He 1 mLmin⁻¹, 170 °C isothermal analysis, carrier He 1.0 mLmin⁻¹, t_R = 24.8 min, 25.5 min; 4-cyclohexyldihydrofuran-2(3*H*)-one: chiral GC column Lipodex B, 170 °C isotherm analysis, carrier He 1.0 mLmin⁻¹, t_R =25.6 min, 26.6 min. Enantiomeric excesses of seven-membered ring lactones derived from *meso*-cyclohexanones were analyzed as follows: 5-tert-butyloxepan-2-one: GC column Lipodex B, He 1 mLmin⁻¹, 180 °C isothermal analysis, t_R = 7.35 min, 7.85 min; 5-phenyloxepan-2-one: GC column Lipodex B, He 1 mLmin⁻¹, 190 °C isothermal analysis, t_R =25.5 min, 27.2 min 5-methyloxepan-2-one: GC column Lipodex B, He 1 mLmin⁻¹, 150 °C isothermal analysis, t_R =7.78 min, 8.47 min; 5-ethyloxepan-2-one: Chiral GC column ASTEC γ -TA, He 1 mLmin⁻¹, 120 °C X 5 min, 5°Cmin⁻¹ up to 200 °C, t_R =28.1 min, 28.6 min; 5-propyloxepan-2-one: chiral GC column ASTEC γ -TA, He 1 mLmin⁻¹, 120 °C X 5 min, 5 °Cmin⁻¹ up to 200 °C, t_R =32.4 min, 32.8 min.

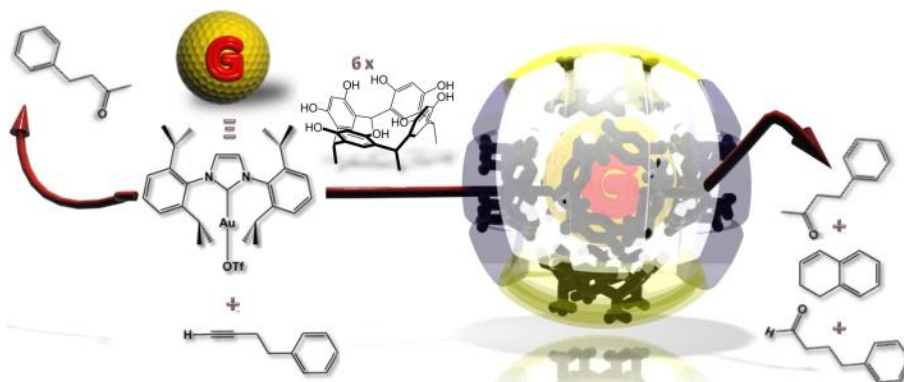
4.2.6 ACKNOWLEDGEMENTS

Thanks are expressed to Dr. P. Sgarbossa for the synthesis of [(P-P)PtCl₂] complexes and for elemental analyses. G. Bianchini is acknowledged for meso-cyclobutanones synthesis. Dr. L. Sperti and Dr. M. Bertoldini are gratefully acknowledged for GC-MS analysis and for chiral GC analysis respectively.

4.3. ALKYNES HYDRATION WITHIN A HEXAMERIC HOST

The work concerning the encapsulation of the complex was carried out during a six months stage at the "Van't Hoff Institute of Molecular Sciences" (University of Amsterdam).

The results presented in this chapter are going to be published in: Cavarzan A., Scarso A., Sgarbossa P., Strukul G., Reek J.N.H. "Supramolecular Control on Chemo and Regioselectivity via Encapsulation of (NHC)-Au Catalyst within a Hexameric Self-Assembled Host", *J. Am. Chem. Soc.*, **2011**, accepted.



4.3.1 SHALL WE PLAY VOLLEYBALL?

"In life science and virus science, in particular, the concepts are chemistry, symmetry, and mathematics. With very advanced methods, nature builds capsids with chemical structures that we say are synonymous with symmetry and mathematics."

Andersson, S. *Zeitschrift fur Anorganische und Allgemeine Chemie* **2009**, 635, 717-724.

It's probably easy to forget the dramatic consequences brought by viruses for living organisms when you observe them using a microscope. Viruses' structures are amazing architectures in which nothing is casual, starting from the shape. Two main structural types of viruses are known: the rod-shaped ones and the spherical ones. The latter class shows an incredible regularity of the capsid (the part in which viral DNA is enclosed), composed of smaller subunits arranged in a highly symmetric way resembling either Platonic or Archimedean solids (Figure 43).^{†††} This constitutes one of the clearest and most efficient self-assembly examples in biology, fulfilling the need of a fast building process, governed by limited genetic information,

^{†††} "In geometry an Archimedean solid is a highly symmetric, semi-regular convex polyhedron composed of two or more types of regular polygons meeting in identical vertices. They are distinct from the Platonic solids, which are composed of only one type of polygon meeting in identical vertices." From <http://en.wikipedia.org>

allowing virus to rapidly produce a large number of copies of itself. The virus particle has a well-defined size arising from the combination of protein subunits and nucleic acid chains,²¹⁰ that come together to lower the global free energy of the system by means of thermodynamic and entropic favorable contributions given by the assembled form against the disassembled one. The subunits are connected by supramolecular interactions favored by a complete surface complementarity between the single parts, similar to what happens for an enzyme with its specific substrate.

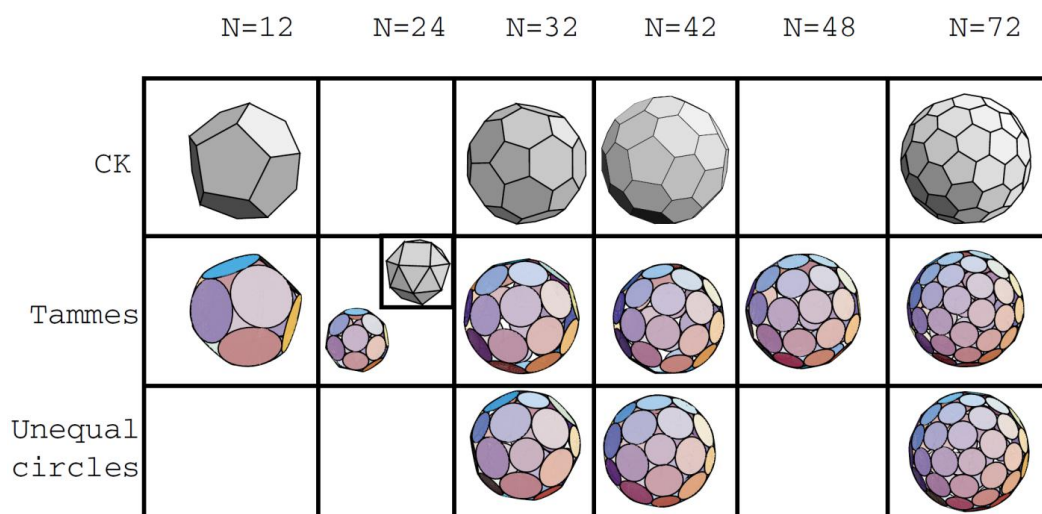


Figure 43:²¹¹ Possible conformations of viral capsids (both natural and *in-vitro*). The first row shows the Platonic polyhedra theorized by Caspar and Klug.²¹⁰ The other rows show other possible geometrical forms deriving from the optimal packing arrangements of N circular disks to cover a sphere, known in the mathematical literature as the Tammes Problem. The structure reported in the second column ($N=24$) is an Archimedean solid known as the *snub cube*.

These elegant objects were built by nature to transport the viral DNA in a protected environment until the injection in the attacked cell (some viruses, like the T-even bacteriophages are real “molecular syringes”²). However besides the understanding of their natural function, increasing attention is gaining the potential use of suitably modified viruses as nanocontainers for medicinal applications or innovative materials development.²¹² The recent advances in supramolecular chemistry are pushing chemists towards the construction of supramolecular virus-like structures with the desired features instead of modifying natural viruses. To mimic such a refined system, an efficient self-assembly process is required, together with a reversible hosting capability, in order to release the guest in certain conditions. These properties have suggested hydrogen bonded capsules as good candidates for this task and particularly promising is the large hexamer called *volleyball* formed by C-alkylresorcin[4]arenes subunits (*vide* §3.1.1) that reminds viral capsids assemblies.²¹³ The global structure of the hexameric form conforms to the snub-cube (one of the 13 Archimedean solids) as depicted in Figure 44 and represents a viable way to build spheroidal cages with octahedral symmetry by means of copies of the same subunit, analogously to viruses self-assembly of the

capsids using identical protein building blocks. This approach, based on the combination of regular polygons, can be outlined as a general strategy to build spherical hosts.²¹⁴

The 60 hydrogen bonds holding the pieces together like a seam provide an extraordinary example of cooperativity,²¹⁵ imparting stability to this structure in the solid state as well as in solution of suitable apolar solvents. J. Rebek Jr., whose group studied extensively this hexamer in solution and used for the first time the term *volleyball*,¹⁵³ defines this structure “an example of a system on the verge of assembly”²¹⁶.

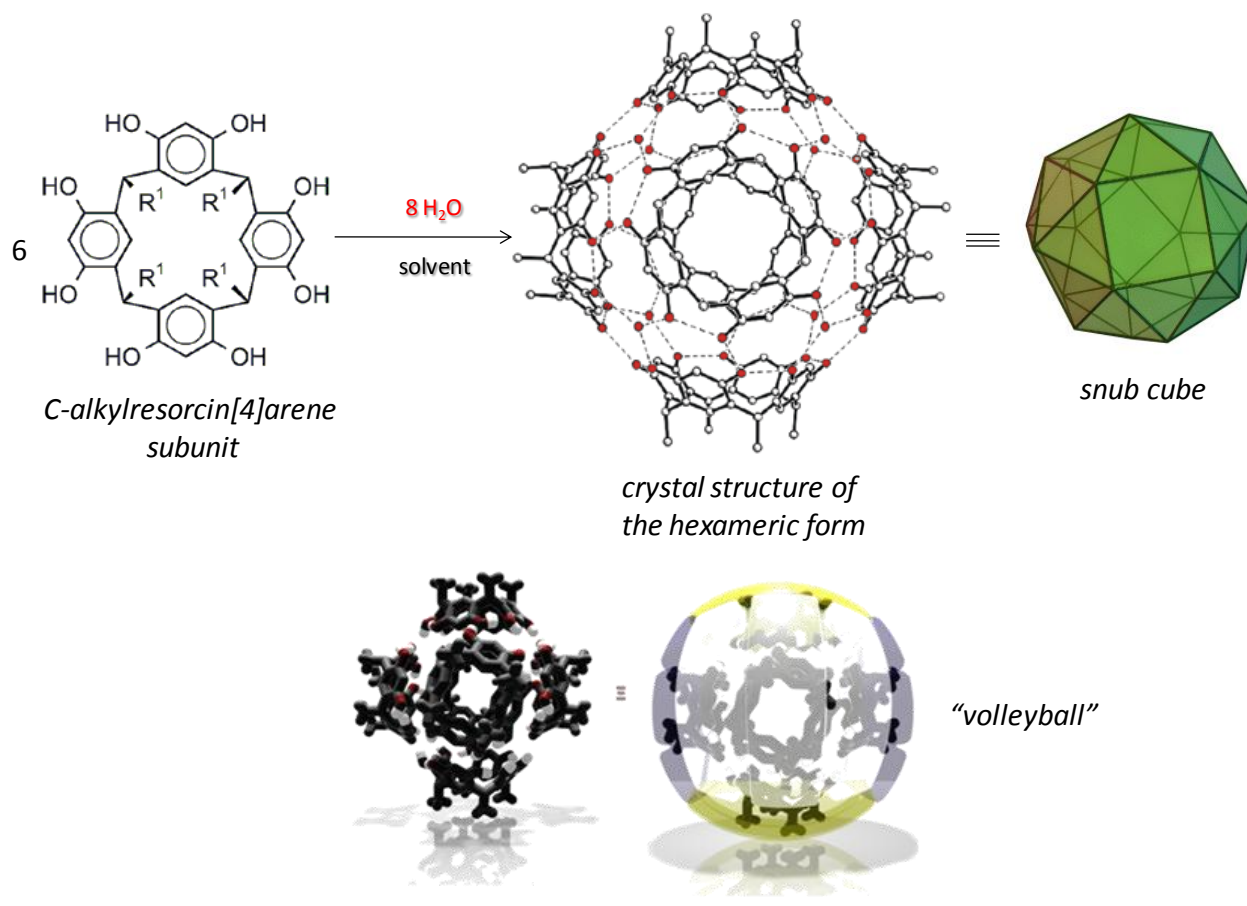


Figure 44: the hexameric assembly of C-alkylresorcin[4]arene subunits conforms to a snub cube, one of the 13 Archimedean solids, in which the vertices of the square faces correspond to the corners of the calixarenes and the centroids of the eight triangles that adjoin three squares correspond to the eight water molecules¹⁵¹ (the red dots in the crystal structure represent oxygen atoms participating to the H-bonds). The spheroidal aggregate was defined by Rebek “the volleyball”.

The hexamer self assembles spontaneously in wet chloroform and benzene, including eight water molecules to form the complete snub cube that is globally chiral. The aggregate hosts preferentially cationic species, but neutral ones can also be included in the electron-rich internal cavity if they demonstrate a high surface complementarity. Chirality at the supramolecular level, a distinctive characteristic of biological assemblies, opens the possibility of guest discrimination using the *volleyball* by means of diastereomers formation, similar

to what happens for Rebek's "softball".¹⁴⁴ In 1997,¹⁵¹ when the C-methylcalix[4]resorcinarene hexamer was described for the first time, a plethora of possible future applications were suggested for this nanocapsule, including chiral catalysis, drug delivery and separation media. The first one in particular was supported by the fact that the internal cavity was large enough to include organometallic complexes, a very uncommon property among organic supramolecular hosts. The large surface interaction between a hosted organometallic catalyst, the capsule and the substrates, together with additional supramolecular interactions, would provide something similar to an enzymatic catalyst (*vide* §1.1).

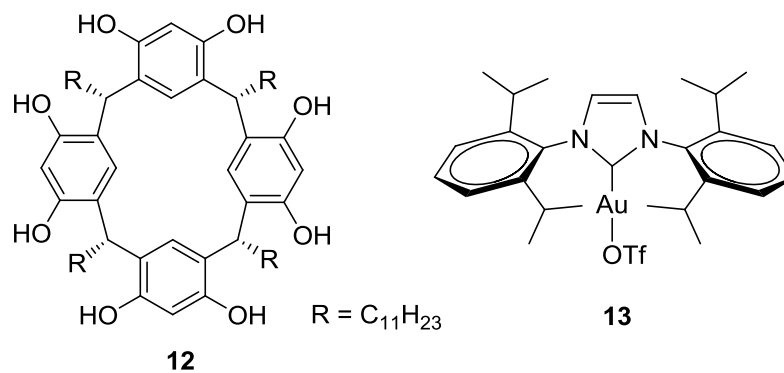
In more than 10 years, this idea never turned into reality.

4.3.2 AIM OF THE WORK

Herein we report the first example of a transition metal catalyst encapsulated in the hexameric capsule formed by C-undecylcalix[4]resorcinarene subunits. Furthermore we demonstrate that, in the hydration reaction of terminal alkynes, an (NHC)-Au carbene complex yields chemo- and regio-selectivities that are strongly different from the same catalyst operating free in solution. The same supramolecular catalytic system underwent further substrate selectivity trials with a mixture of three alkyl alkynes.

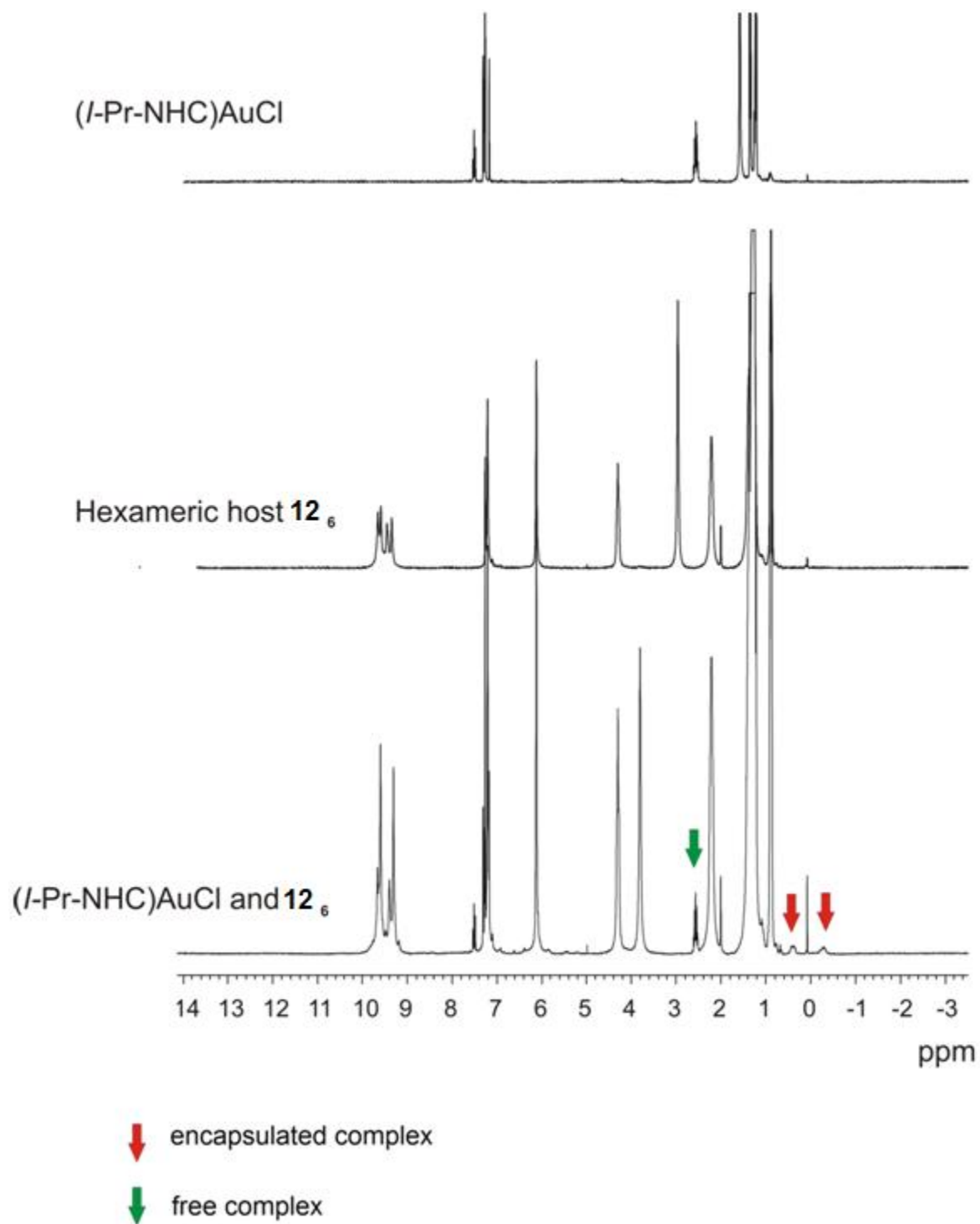
4.3.3 COMPLEX ENCAPSULATION

As mentioned before, both cationic and neutral guests of appropriate shape can be enclosed in this capsule, with a preference for the first species. We found initially that the neutral (*i*-Pr-NHC)AuCl complex [Chloro[1,3-*bis*(2,6-diisopropylphenyl)imidazol-2-ylidene]gold(I)] can be encapsulated within the hexameric host by just mixing this complex and the resorcin[4]arene in a 1:7 ratio. Encapsulation of the complex is evidenced by the appearance of a new set of signals in the ¹H NMR for the *i*-Pr residue of the Au complex that is significantly up-field shifted compared to the free complex ($\Delta\delta = -0.95$ ppm, Figure 45). A ¹H NMR spectrum of the mixture using a different stoichiometry shows the co-existence of signals for the free and bound complex, indicative of a low exchange rate between encapsulated and free species on the NMR timescale. As the active species in catalysis is generally cationic in nature,²¹⁷ we prepared (*i*-Pr-NHC)Au(OTf) **13** (Scheme 6) and studied its binding properties.



Scheme 6: C-undecylcalix[4]resorcinarene (**12**) and [trifluoromethanesulfonyl[1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene]gold(I)] (**13**).

As shown by the ^1H NMR spectra reported in Figure 46, such complex showed quantitative coordination in the capsule when working with the same 1:7 stoichiometry reported above. The ^1H -NMR spectrum clearly shows the up-field shifted resonances of the *i*-Pr residues of the ligand at -0.26 and 0.37 ppm ($\Delta\delta = -0.99$ ppm) as broad signals. Analogously, the vinyl resonances of the encapsulated complex appeared between 5 and 7 ppm while the resonances for the free complex in solution completely disappeared.

Figure 45: Encapsulation Spectra for (*I*-Pr-NHC)AuCl @ 12_6 .

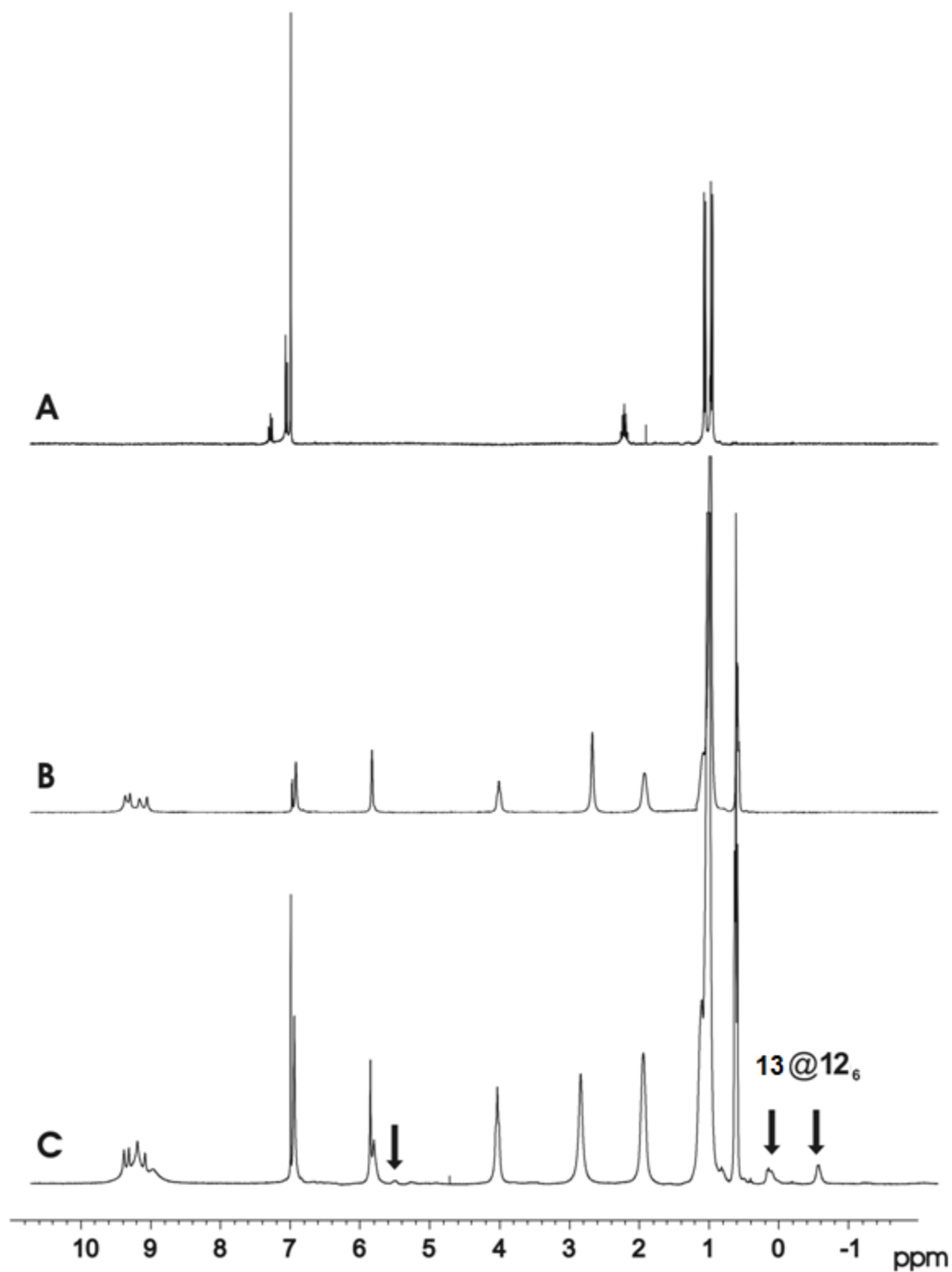


Figure 46: ^1H NMR spectra in CDCl_3 at 298K. A) 13 (3.3mM); B) 12 (24 mM); C) 12 (24 mM) and catalyst 13 (3.3 mM).

The encapsulated and free complex **13** showed very different diffusion coefficients ($7.9 \times 10^{-10} \text{ m}^2\text{s}^{-1}$ vs. $1.4 \times 10^{-9} \text{ m}^2\text{s}^{-1}$ respectively) as evidenced by DOSY experiments. On the other hand, the similar diffusion coefficients observed for encapsulated **13** and the hexameric host indicate that complex **13** resides indeed inside the capsule (Figure 47). The ^{19}F NMR signal of the triflate anion of the complex did not change upon encapsulation which means that it probably remains excluded by the encapsulation process.

Further evidence for the encapsulation was provided by the ^1H NOESY spectra; besides the expected intramolecular contacts between different resonances of **13**, the NOESY spectrum of the encapsulated complex showed clear cross peaks between the *i*-Pr residues of the Au complex and both the hydroxyl residues of the capsule and the aryl proton between the OH groups of the aromatic moieties, confirming the presence of the Au complex within the self-assembled capsule (Figure 48). Similar spectra, that are indicative for binding and evidence close contacts, were obtained when the experiments were performed in benzene- d_6 instead of CDCl_3 as solvent.

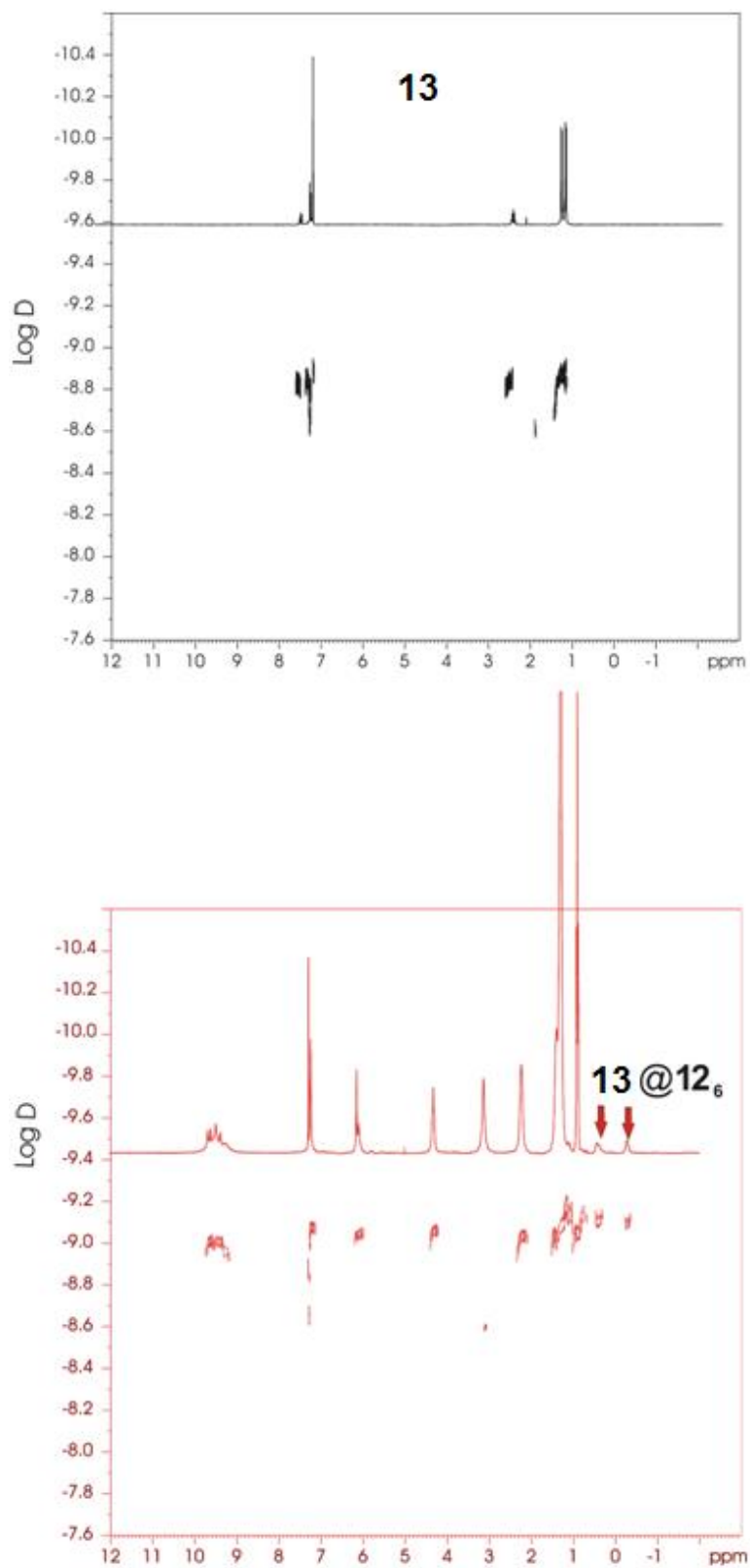


Figure 47: DOSY spectra for free catalyst 13 in solution (black) and encapsulated catalyst 13 in the hexamer 12₆ (red).

- Cross-peaks between **13** and the hexameric assembly **12₆**
- Cross-peaks between **13** and water molecules
- Intramolecular cross-peaks of encapsulated **13**

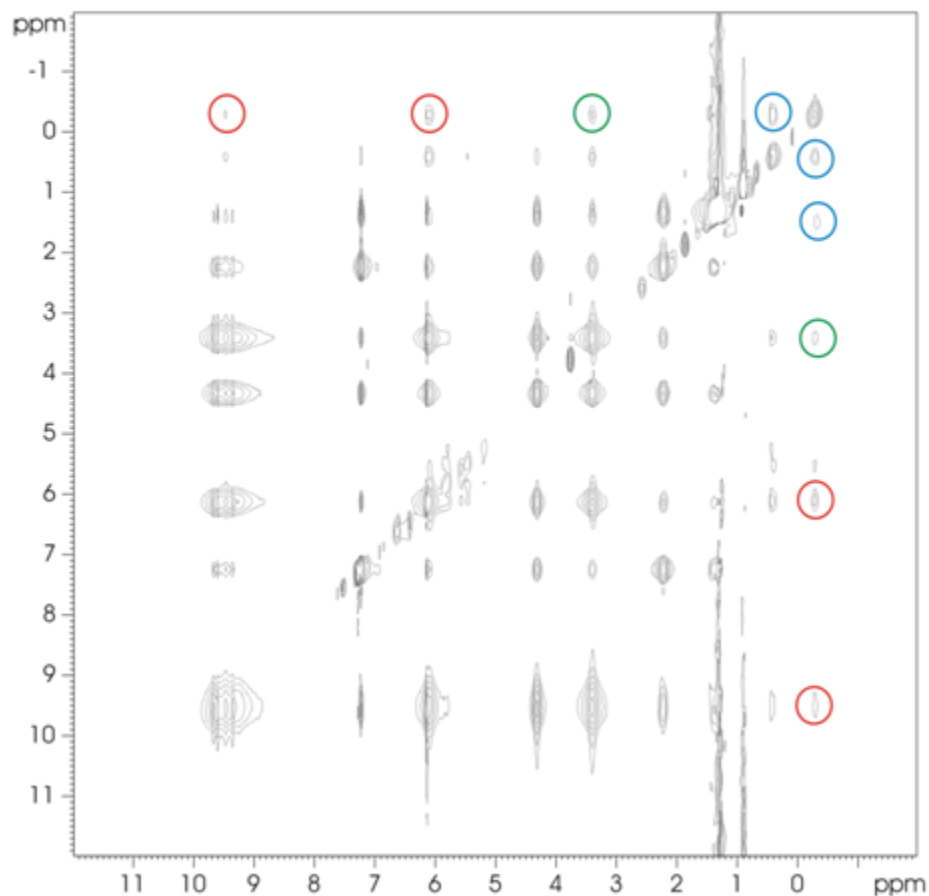


Figure 48: NOESY spectrum for **13@12₆**, in CDCl₃.

The process can be reversed as the encapsulated catalyst can be displaced by a guest with a better binding, such as cationic tetraethyl ammonium tetrafluoroborate (**14**). In fact, addition of 10 equivalents of **14** to a solution of the encapsulated **13** led to complete displacement of the latter and encapsulation of the organic cation (Figure 49).

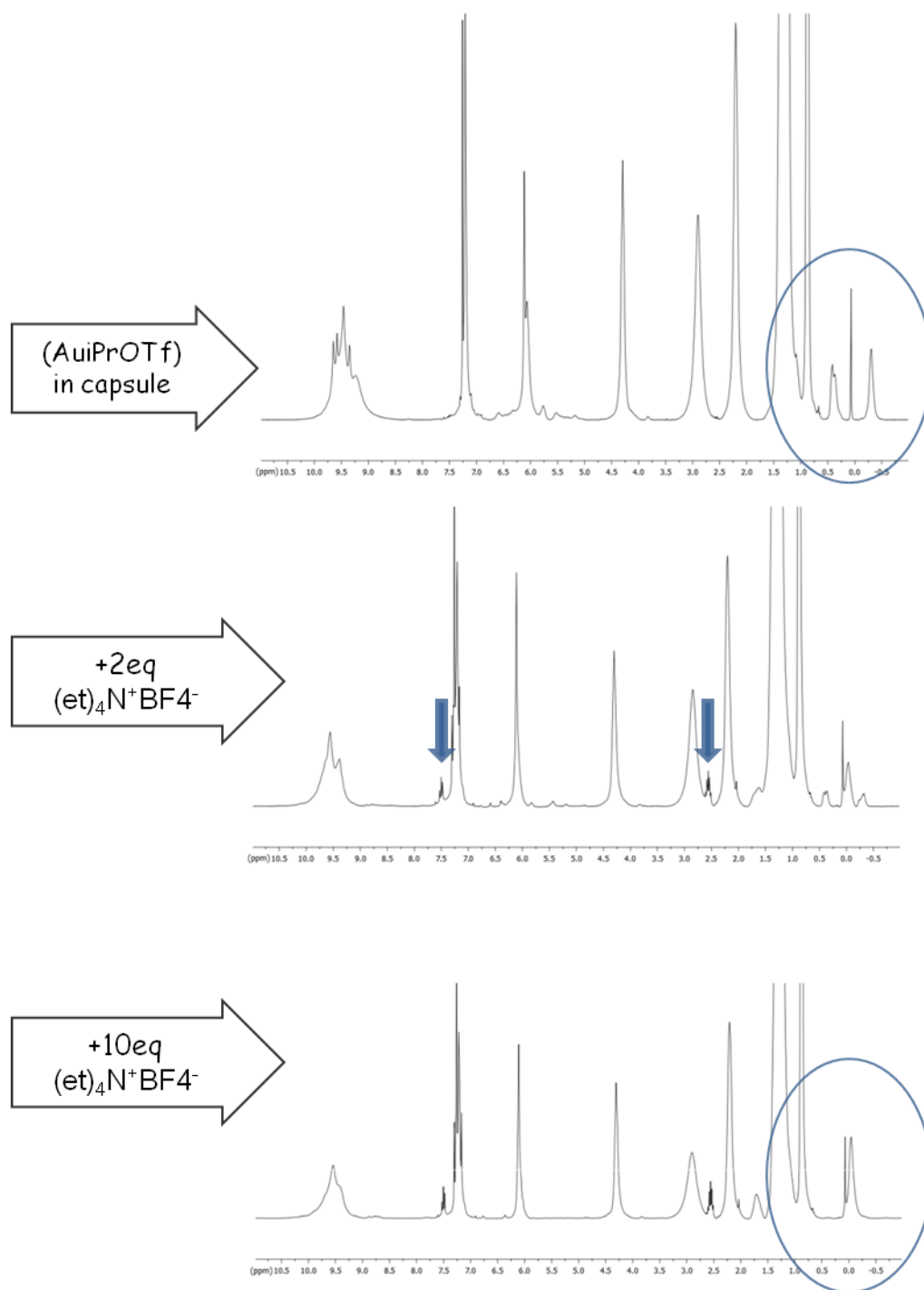


Figure 49 Guest exchange for (Et)₄N⁺ to (*i*-Pr-NHC)AuOTf @ 12_c.

Complex **13** has a molecular volume of about 400 Å³ and consequently occupies about 30% of the volume of the cavity. This means that two to four extra solvent molecules are co-encapsulated to ensure stable complexation, in agreement with the general 55% occupancy rule proposed by Rebek.¹⁴⁰ Such solvent

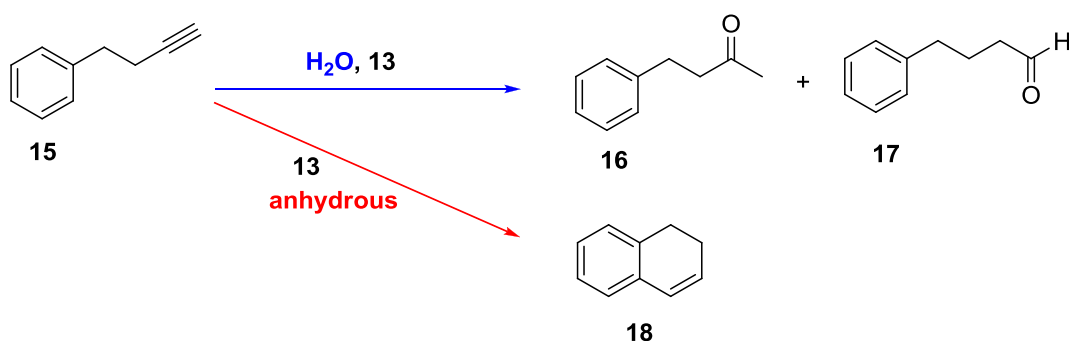
molecules can be easily exchanged with substrate molecules of comparable size and shape, suggesting the possibility that the encapsulated complex is able to convert substrates while in the cavity.

4.3.4 ALKYNE HYDRATION

4.3.4.1 4-Phenyl-1-Butyne Hydration

(NHC)-Au complexes are known to efficiently catalyze a variety of organic transformations,^{218,219} in particular the ones involving multiple bonds, such as enyne cycloisomerization,^{220,221} propargylic esters rearrangement,²²² hydroamination of alkenes²²³ and alkyne hydration.²²⁴

For these initial experiments, we selected the latter as a test reaction to investigate the supramolecular effect of the capsule on the activity and selectivity of the catalyst, also because the presence of water is required for capsule formation. 4-phenyl-1-butyne **15** was chosen as a substrate yielding two possible hydration products, 4-phenyl-2-butanone **16** and 4-phenyl-butanal **17**. Recent literature demonstrated that Au catalysts usually give Markovnikov addition of water to terminal alkynes leading to the almost exclusive formation of methyl ketones.^{224,225} Under anhydrous conditions the same catalyst transforms such substrate into 1,2-dihydronaphthalene **18** via an intramolecular rearrangement.²²⁶ Therefore, Au catalyst **13** was evaluated, both in its free and encapsulated form, in the hydration of 4-phenyl-butyne in benzene-d₆ under identical experimental conditions (Scheme 7).



Scheme 7: 4-phenyl-butyne **15** provides two possible hydration products **16** and **17** and one cyclization product **18** under anhydrous conditions.

As expected the reaction carried out with free **13** in water saturated benzene- d_6 at 70°C led to the almost exclusive and quantitative formation of **16** as hydration product within 30 minutes, with only traces of **17** and **18** (Figure 50).

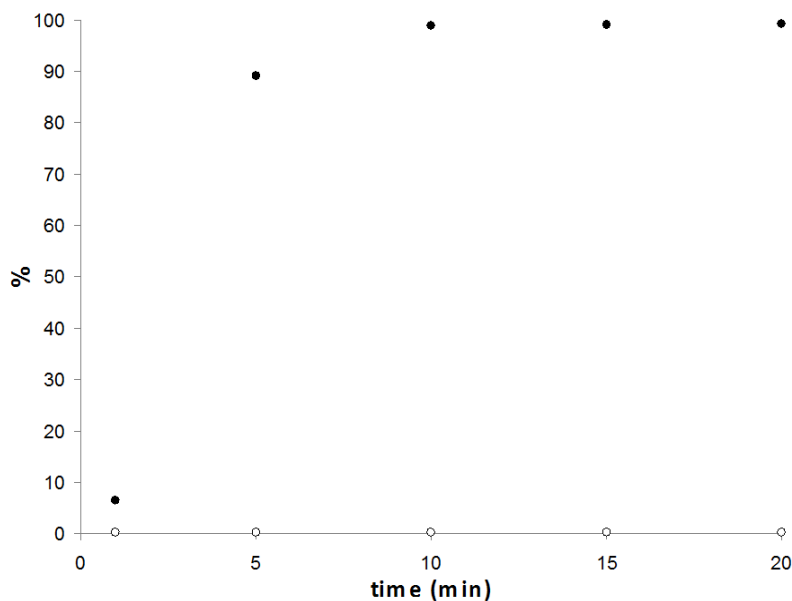


Figure 50: Reaction profiles for **15** (66 mM) with catalyst **2** (3.3mM) in water saturated benzene- d_6 at 70°C. ● **16**, ○ **17** and **18**.

Predictably, once encapsulated in the self-assembled capsule **12₆**, the catalyst was much slower and only 5% conversion was observed after 30 min, indicating that the reaction rate is controlled by the barrier provided by the capsule to the approach of the substrate to the catalyst. The catalyst was, however, sufficiently stable and continued to convert the substrate and after 400 min 28% of the substrate was converted (Figure 51). Interestingly, the encapsulated catalyst gives rise to a different product distribution than the free catalyst. In addition to product **16** (12%), also significant amounts of linear aldehyde **17** (4%) was formed as hydration product, which is unprecedented for Au catalysts.²²⁴ This clearly demonstrates that the regio-selectivity can be steered to the opposite direction with respect to the natural catalyst selectivity by putting it in a sterically constrained environment. Furthermore, we observed also the formation of 1,2-dihydronaphthalene **18** (12%), a product that is formed after intramolecular rearrangement usually found only in the absence of water. Apparently, the intramolecular reaction is favoured when taking place within the cavity due to unusual folding of the substrate. Alternatively, the capsule may impose a barrier for the entrance of water, making the intermolecular reaction relatively slow compared to the intramolecular one.

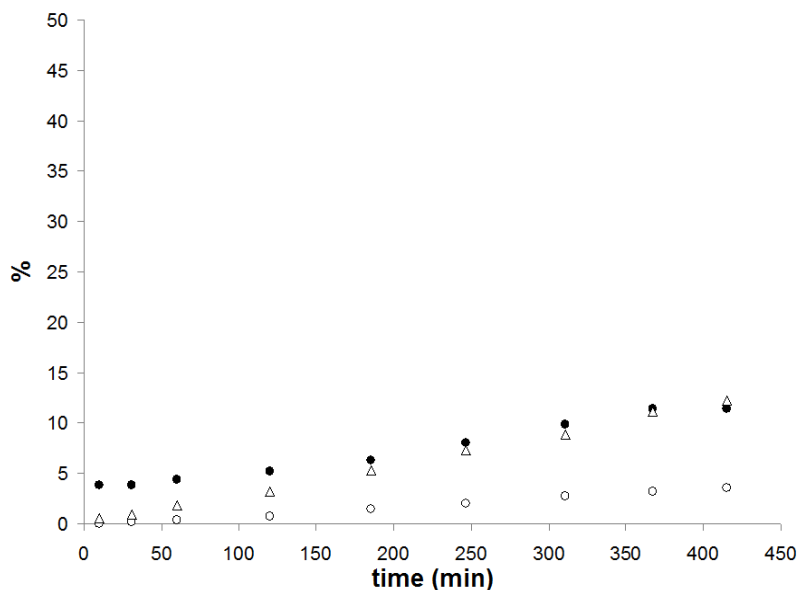


Figure 51: Reaction profiles for **15** (66 mM) with catalyst **2** (3.3mM) in water saturated benzene- d_6 at 70°C in the presence of **12** (33mM). • **16**, ○ **17** and Δ **18**.

The ammonium salt **14** binds better than the complex, providing a mean to control the reactivity of the encapsulated catalyst and evidence for the reaction taking place inside the capsule. In a typical experiment 10 equivalents of **14** were added after the reaction had progressed for 400 min. As displayed in Figure 52, a rapid increase of the yield in **16** was observed, while the amount of **17** and **18** remained almost unchanged, providing clear experimental evidence for the complete displacement of **13** from the capsule. Once released to the bulk solvent, the catalyst produces exclusively **16** as the hydration product.

To confirm these experimental results, further NMR studies were performed in order to prove the co-encapsulation of the substrate and the catalyst inside the hexameric capsule. Unfortunately, no evidence of the encapsulated substrate was found and this could probably be imputed to a fast exchange of the alkyne between the hexameric cavity and the bulk. This should be related to the energy barrier provided by the calyx[4]resorcinarene scaffold that is reasonably harder to overcome for the bulky cationic catalyst than for the substrate, being the alkyne neutral and smaller than the complex. However these predictions are still very hypothetical and need more accurate studies to be validated.

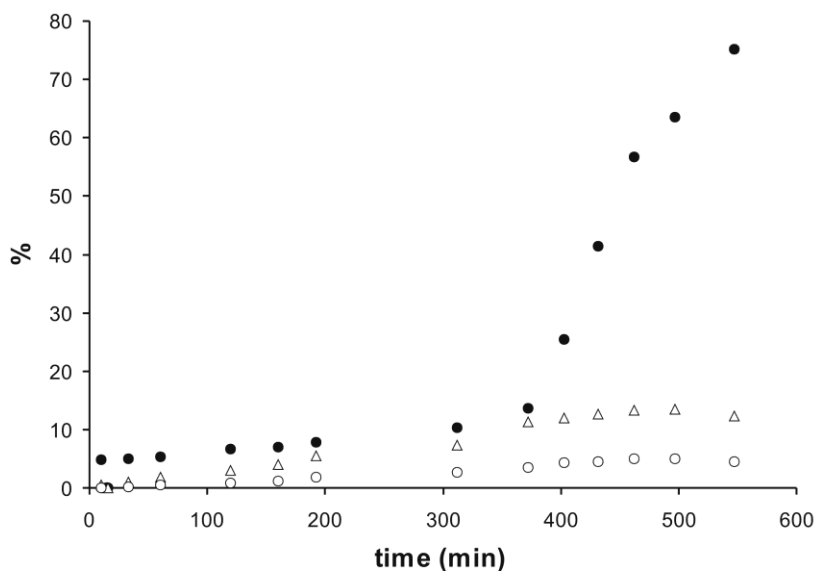
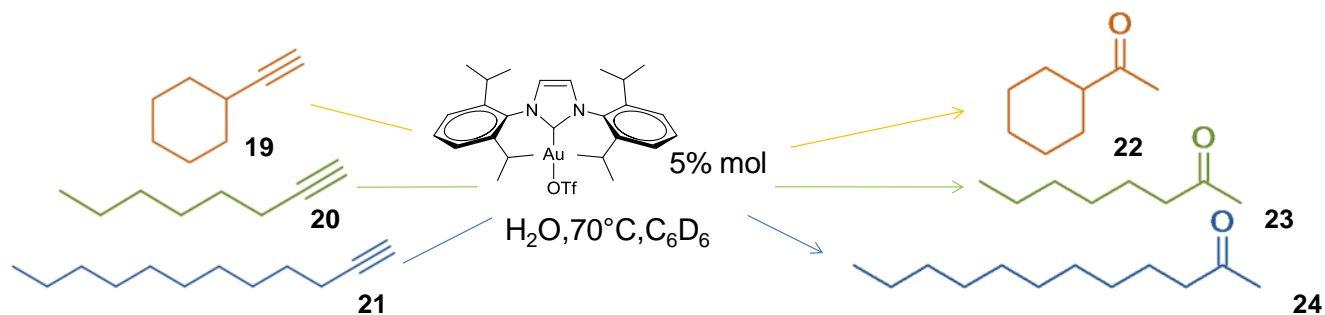


Figure 52: Reaction profiles for **15** (66 mM) with catalyst **13** (3.3mM) in water saturated benzene- d_6 at 70°C in the presence of **12** (33mM) with addition after 400min of **14** (33mM). • **16**, ○ **17** and Δ **18**.

4.3.4.2 Substrate Selectivity



Scheme 8: substrate selectivity test for alkyne hydration mediated by [(iPr)Au](OTf).

The similarity of this particular system with enzymatic catalysts was further tested in terms of substrate selectivity. Three alkyl alkynes (**19**, **20**, **21**) were added in one pot to the preformed supramolecular catalyst (*i*-Pr-NHC)AuOTf @ **12**₆ and the reaction profiles of the hydration to the correspondent ketones **22**, **23**, **24** were compared with the ones in absence of the capsule. In this competitive experiment, the free complex converts quantitatively the three substrates within 250 minutes without any significant preference among them. (Figure

53). As expected the reaction becomes slower when the gold species is encapsulated in **12**₆ and the maximum yield in ketone achieved after 4 hours is generally below 50%, but notably, the reaction profiles show a visible preference of the supramolecular catalyst for the cyclic alkyne. This preference was quantified calculating the initial rate from each curve and comparing the values between the free and the encapsulated gold(I) complex. In the case of the cyclic alkyne, the initial rate with the supramolecular catalyst is about three times higher than that obtained for other two substrates (**22:23:24** = 3.4:1.3:1), while the free complex provides almost the same slope for all the alkynes (**22:23:24** = 1.5:1.0:1, Figure 54).

A possible explanation for this phenomenon probably relies in the markedly different shape of the cyclic substrate compared to the linear ones that probably allows a better fit in the space left by the gold complex within the hexamer cavity. Further studies to go deeper in selectivity aspects for encapsulated complexes in the self-assembled hexamer are currently ongoing in our laboratories.

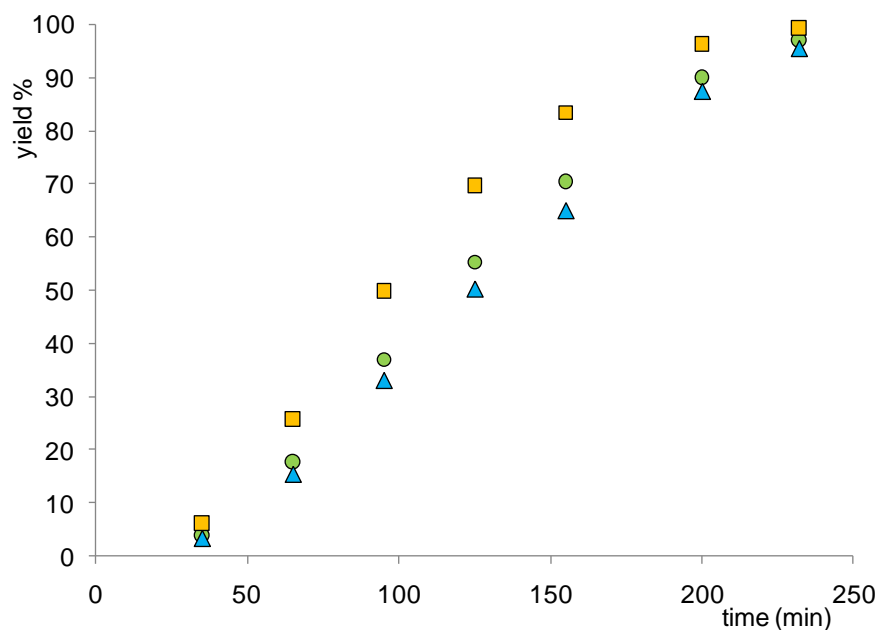


Figure 53: Reaction profiles for 19, 20, 21 (65 mM) with catalyst 13 (3.3 mM) in water saturated benzene-d₆ at 70°C. ■ = 22; ● = 23 and ▲ = 24.

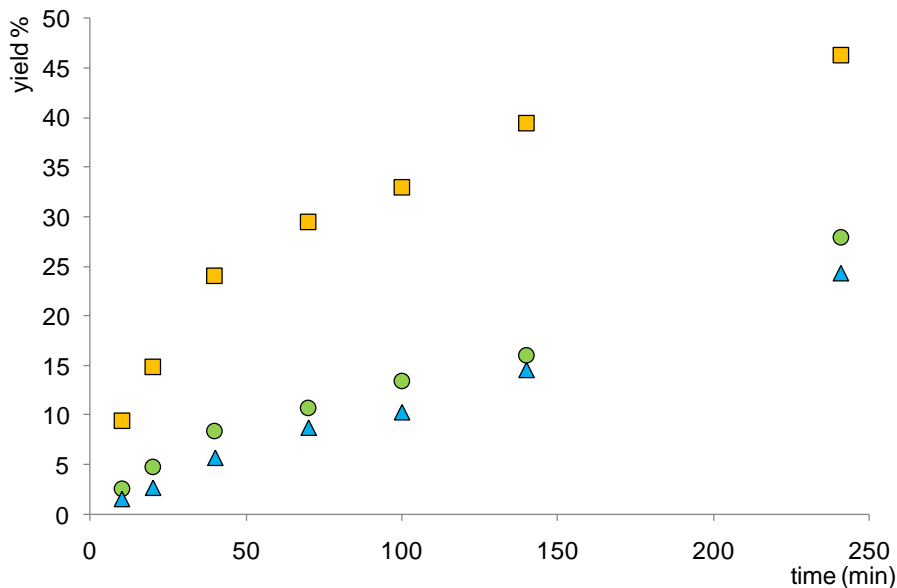


Figure 54: Reaction profiles for 19, 20, 21 (65 mM) with catalyst 13 (3.3 mM) in water saturated benzene-d₆ at 70°C in presence of 1 (33 mM).

■ = 22; ● = 23 and ▲ = 24.

4.3.5 CONCLUSIONS

In conclusion, here the first example of an organometallic catalyst encapsulated in the supramolecular hexameric assembly of C-undecylcalix[4]resorcinarene has been presented. Interestingly, the encapsulation occurs in organic solvents, and the cavity size is sufficiently large to co-encapsulate substrates that subsequently can be converted by the active site. The catalytic activity and selectivity of an NHC-Au catalyst is controlled by the nano-environment provided by the self-assembled capsule as host, leading to unusual regioselectivity in the hydration of 4-phenyl-butyne. In addition, a cyclization product is formed only if the catalyst is encapsulated. The preliminary substrate selectivity tests demonstrate that an organometallic complex can achieve substrate selectivity, which is a peculiar feature of enzymes, simply via encapsulation.

4.3.6 EXPERIMENTAL

General: ^1H NMR, and $^{31}\text{P}\{^1\text{H}\}$ NMR spectra were recorded at 298 K, unless otherwise stated, on a Bruker AVANCE 300 spectrometer operating at 300.15, 121.50 MHz, respectively. δ values in ppm are relative to SiMe_4 and 85% H_3PO_4 . $^{19}\text{F}\{^1\text{H}\}$ NMR spectra were recorded at 298 K on a Bruker AC200 spectrometer operating at 188.25 MHz. δ values in ppm are relative to CFCl_3 .

Substrates and catalyst precursor. 4-phenyl-1-butyne, cyclohexylacetylene, 1-octyne, 1-dodecyne and (*i*-Pr-NHC)-Au-Cl chloro[1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene]gold(I) are commercially available products (Aldrich) and were used as received without any further purification. Resorcin[4]arene was prepared following reported procedure.²²⁷ All the products of the hydration and intramolecular cyclization of 4-phenyl-1-butyne were identified by GC-MS and ^1H -NMR analysis.

Synthesis of catalyst (*i*-Pr-NHC)-Au-OTf (13**):** Complex **13** was synthesized by a modified procedure than that reported by Tsui.²²⁸ The reaction was performed under nitrogen using the standard Schlenk technique. Starting complex NHC-Au-Cl was purchased from Sigma-Aldrich and used without further purification. To a solution of NHC-Au-Cl (0.10 g, 0.16 mmol) in acetone (20 ml) at -10°C were added 0.046 g (0.18 mmol) of silver trifluoromethanesulfonate. The suspension was stirred for 1 hour in the dark then let warm to RT. After filtration of the solid AgCl, the solution was concentrated and treated with *n*-hexane to give **2** as a white solid. Yield 0.10 g, 84.5%. ^1H NMR (δ , acetone- d_6): 7.58 (t, $J = 8.0$ Hz, 4H, $p\text{-CH}_{\text{Ar}}$), 7.35 (d, $J = 8.0$ Hz, 4H, $m\text{-CH}_{\text{Ar}}$), 7.31 (s, 2H, CH_{im}), 2.49 (sept., $J = 7.0$ Hz, 2H, $\text{CH}_{i\text{-Pr}}$), 1.27 (dd, $J = 7.0$ Hz, $J = 20.0$ Hz, 24H, $\text{CH}_{3i\text{-Pr}}$); ^{19}F $\{^1\text{H}\}$ NMR (δ , acetone- d_6): -81.03 (s, CF_3).

Catalytic Studies: Water saturated solvent was prepared by shaking benzene- d_6 with bidistilled water at a room temperature in a separation funnel and subsequent phase separation. Catalyst **2** ($2 \cdot 10^{-3}$ mmol, 5% mol) was placed in a screw-capped vial equipped with silicone septum and dissolved in the water saturated benzene- d_6 (0.6 mL). Resorcin[4]arene **12** (10 equivalents) was then added to the solution. After stirring for 2h at room temperature, 4-phenyl-1-butyne **15** or the three alkyl alkynes **19**, **20**, **21** (0.04 mmol each) and bidistilled water (2 μL , 4 mmol) were added. The reaction was then thermostatted at 70°C . Reaction progress was monitored by ^1H -NMR and GC analysis by periodically sampling directly from the reaction mixtures.

Conversion, product assignment and distribution were determined by direct GC analysis of the reaction mixture. In the case of substrate **15** conversions reported are based on the average of three experiments.

4.3.7 ACKNOWLEDGEMENTS

Special thanks go to Prof. J.N.H. Reek and to all HomKat group (University of Amsterdam) for hosting me from the 1st of May until the 1st of November 2009 and for fruitful discussions. Thanks are also expressed to Dr. P. Sgarbossa for the synthesis of (i-Pr-NHC)-Au-OTf, to Dott.ssa L. Sperti for GC-MS analysis and to Dr. G. Borsato for graphical help.

5.CONCLUDING REMARKS

This three-year journey across supramolecular catalysis started with an overview on enzymes and their extraordinary features, presenting them as an example to imitate. The active site of an enzyme is build by nature to include both the effective catalytic moieties and additional functional groups providing extra supramolecular interactions that stabilize the transition state of the reaction with consequent enhancement of the reaction rate. The focus on the supramolecular interactions that take place within the enzyme structure inspired the idea to develop catalytic systems enclosed in self-assembled hosts to mimic an enzyme-like environment and compare their activity and selectivity behavior in reactions with traditional organometallic systems in solution. We have demonstrated that when transition metal complexes are enclosed in micelles, these hosts, similarly to the bulky protein backbone of an enzyme, create a hydrophobic pocket in water were lipophilic catalyts and substrates can be accommodated by virtue of hydrophobic effect. This situation strongly impacts on the activity and selectivity observed.

In Chapter 4, a supramolecular catalyst was obtained by encapsulating a Ru(II) complex within micelles formed by the non-ionic surfactant Triton X-114 (Figure 55). The micelles allowed the solubilization in water of otherwise insoluble $[\text{RuCl}_2(\eta_6\text{-arene})(\text{PR}_3)]$ catalysts without the need of any synthetic expedient and the encapsulation of the catalyst resulted in high activities for the hydration of nitriles in water switching on the reaction (in hydration tests of a bulky hydrophobic nitrile, such as 4'-pentyl-4-biphenylcarbonitrile, the yield went up from 0% in pure water to 89% in micelle). An important feature making this micellar system suitable for practical applications is the possibility to recycle the catalytic species by using a cationic surfactant (CTAB) that simplifies phase-separation. A negligible activity loss for benzonitrile hydration (from 97% to 95% yield) was observed choosing CTAB instead of Triton X-114 and, after extraction with chloroform, the catalytic aqueous phase containing the cationic surfactant could be recycled three times.

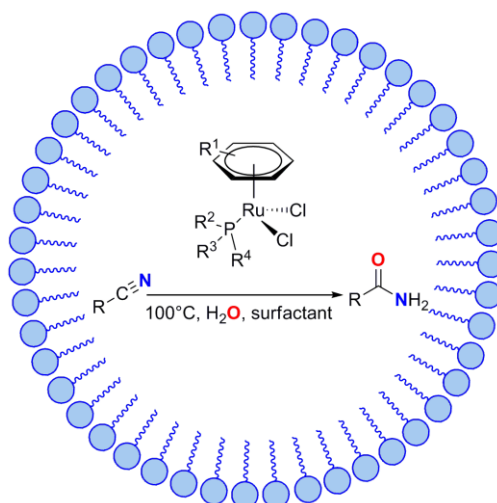


Figure 55: Ru^{II} catalyzed nitriles hydration in micellar medium (Chapter 4)

In the case of water soluble (P-P)Pt^{II} monomeric and dimeric complexes the cationic catalyst was anchored on the anionic micellar surface and the role of the micelle was to increase the solubilization of the organic substrates in aqueous medium. The substrate was then concentrated inside the micellar core, dynamically interacting with the catalyst while diffusing through the micellar surface. Experimentally, this system provided high yields especially for poorly reactive cyclohexanones (the yield of 2-methylcyclohexanone oxidation went up to 99%), assessing a new competitive methodology for oxidation of cyclic ketones in water. Hydrolysis of the formed lactone was observed in some cases, allowing the production of the correspondent ω-hydroxy acid in one pot (Figure 56).

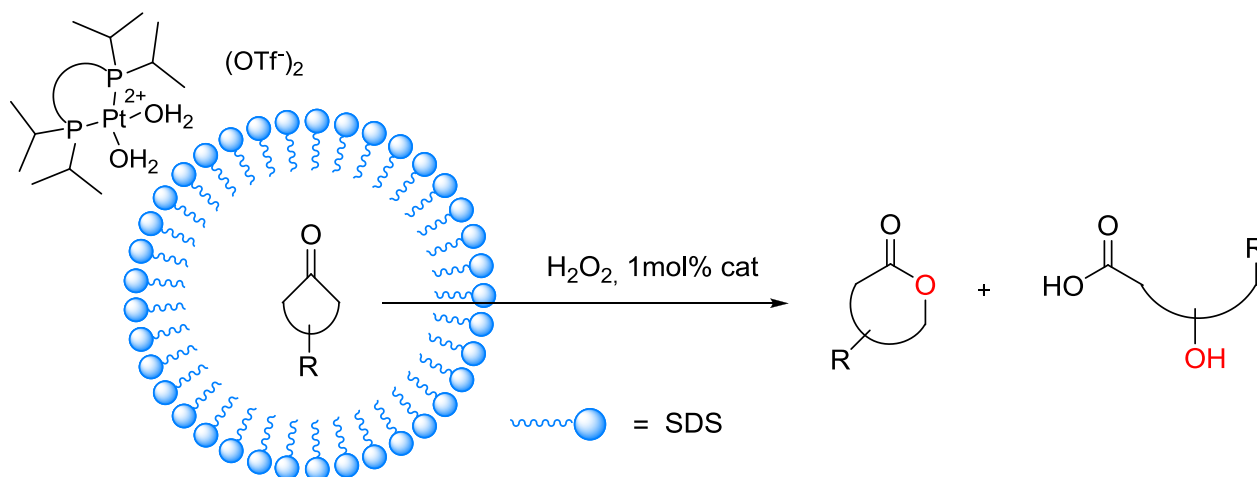


Figure 56: BV oxidation of cyclic ketones in micellar media mediated by Pt^{II} water-soluble complexes. The catalyst, bearing small alkyl bidentate phosphines, is located on the micellar surface.

The selectivity of the reactions, stereoselectivity in particular, is directly correlated to the compartmentalization of catalysts and reagents within the host cavity that has a defined shape and emphasizes steric effects between the substrates and the metal center. This resulted in tighter reciprocal interactions and a preferential orientation of the substrate before the reaction with consequent enhancement of selectivity. In the Baeyer Villiger oxidation of prochiral cyclic ketones (Figure 57), the inclusion of chiral Pt(II) catalyst within the micelles imparted an enantiomeric excess on the resulting lactones (especially for *meso*-cyclohexanones) generally higher than the same catalyst dissolved in organic medium. In this case the catalyst was positioned inside the hydrophobic core of the aggregate, being the micelle a sort of second-sphere ligand of the metal. Such a system presents similarities with some metallo-enzymes like myoglobin, where the heme group containing the metal (Fe^{II}) is embedded in the protein exclusively by means of non-covalent interactions, namely the hydrophobic effect provided by the protein backbone and an additional amino group (belonging to an aminoacid of the peptide chain) coordination on the iron atom. The supramolecular catalysts based on surfactant micelles and platinum complexes exploits the same “pocket effect”, but in addition to that it is much easier to handle and more flexible (in terms of substrate scope and operating conditions) than enzymes: this makes such systems particularly appropriate for practical purposes.

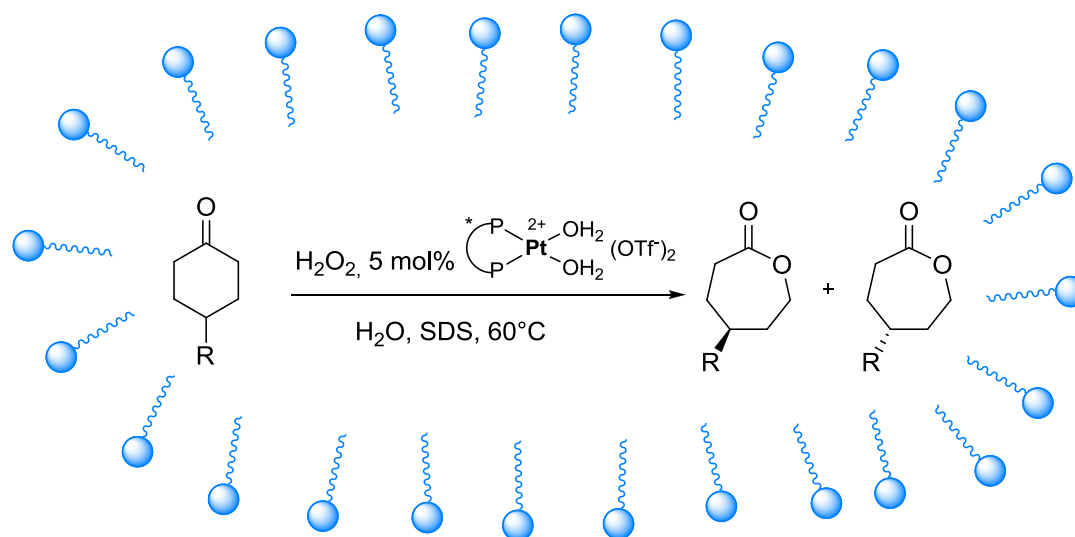


Figure 57: dissymmetrization of cyclic *meso*-ketones through BV oxidation in water mediated by chiral Pt^{II} complexes (Chapter 5).

The experimental effect of the steric constrain experienced by a catalyst inside a supramolecular host is either a higher enantioselectivity by the encapsulated complex compared to the free one, as described before or a different product distribution, as showed for alkynes hydration mediated by a (NHC)-gold complex within the

resorcin[4]arene hexameric assembly (Chapter 6). In the latter case the production of the cyclic moiety instead of the open ketone is probably directed by a pre-folding of the substrate, due to the limited free space inside the cavity, and by the poor water content in the internal cavity.

The impressive enzymatic structures existing in nature require thousand of aminoacid residues and have been shaping for ages by evolution, therefore reproducing such structures artificially is extremely challenging. One of the problems affecting supramolecular artificial structures was indeed the tedious synthesis of hosts embedding catalytic species, but exploiting self-assembling of simple molecules large assemblies can be obtained spontaneously by simply mixing the components in the appropriate conditions. Enzyme complexity is still far to achieve, especially considering their structural adaptability towards the substrates and the high level of molecular recognition imparted by the effective combination of all the factors cited before. However analyzing the experimental results reported for different substrates in BV oxidations or nitrile hydrations or the product distribution provided by the gold catalyst inside the resorcin[4]arene capsule (Figure 58) a certain substrate selection due to the hosts could be observed, poorly specific but sufficient to prove the principle.

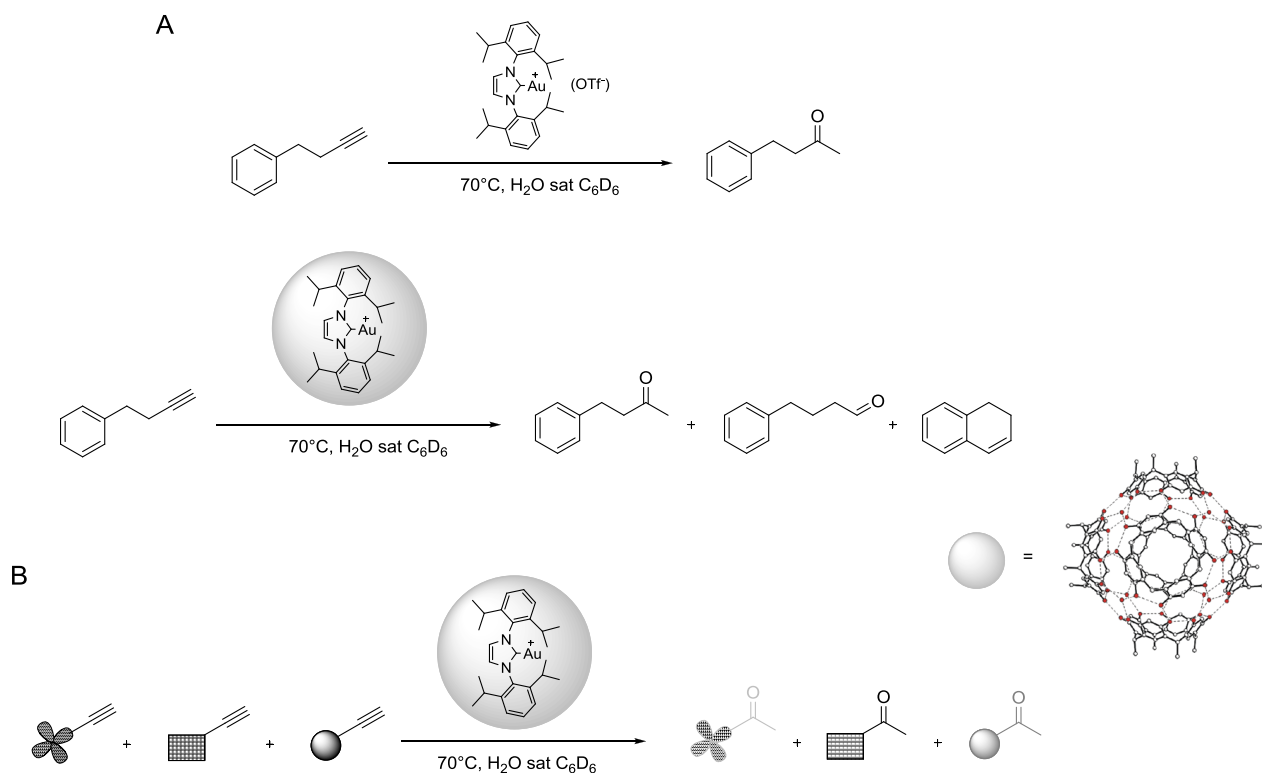


Figure 58: (NHC)-Au catalyst encapsulated in resorcinarene hexameric capsule. A) different product selectivity between free and encapsulated complex. B) substrate selectivity upon encapsulation of the gold complex among three similar substrates. The three different shades of grey of the products indicates the diverse reaction rate of every single alkyne.

A short step toward the selectivity challenge is represented by the substrate selectivity tests reported in Chapter 6 for Au catalyzed alkynes hydrations. The differences in the relative initial reaction rates for the hydration of three aliphatic alkynes are significant especially because related to small differences in size and shape, far away from the reactive portion of the molecule. Clearly the specificity of certain enzymes is such that just one precise molecule expresses the maximum enzyme activity and only other two or three, closely related to this one, can be converted.² This implies that the way to develop a real artificial enzyme is a long one and substantial improvements are needed.

Nowadays industry require the manufacture of molecular complexity from simple starting materials with a minimum number of synthetic steps, avoiding protection–deprotection loops employing selective catalysts. Considering these issues, as showed in this thesis, the reversible encapsulation of organometallic catalysts is a desirable approach, because the activity and selectivity of traditional highly active catalysts can be modified, without time and money consuming synthetic alterations, and adapted to different solvents and substrates. For surfactant based micelles, for instance, the choice of the surfactant is directly correlated to the yield and selectivity of the catalytic system and every reaction tested could be optimized by finding the right surfactant-catalyst-substrate combination, without any particular synthetic procedures.

The answer to this need of high efficient chemical processes is often identified in biocatalysis, but the key to success most probably resides in a fruitful interaction between biocatalysis and organometallic homogeneous catalysis. This will help seeking for true artificial enzymes, conjugating tradition and novelty.

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