Covalent Cages with Inwardly Directed Reactive Centers as Confined Metal and Organocatalysts

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Jian Yang,[a] Bastien Chatelet,[a] Damien Hérault,[a] Jean-Pierre Dutasta,[b] and Alexandre Martinez*[a]

Abstract: Covalent cages with a well-defined cavity located close to a reactive center are of increasing interest because of their outstanding ability to mimic the catalytic properties of enzymatic systems. The size and shape of such synthetic nano-sized reactors strongly affect the behavior of the trapped reaction partners, which can adopt specific conformations and orientations. In particular, the use of molecular cages with confined reactive functions strongly modifies the outcome of catalytic transformations that are carried out therein. This review article describes covalent molecular cages presenting an endohedral functionalization of their inner space and reports on their catalytic activities compared with those of model systems that lack cavity.

1. Introduction

The complexity and remarkable tasks achieved by biological systems arouse an increasing interest. The non-covalent interactions and the resulting pre-organization account for the efficiency and selectivity of these systems. For instance, the folding of the protein chain in enzymes induce the formation of a well-defined cavity around the reactive center that can impose specific orientation and conformation of the incoming substrate, hence high catalytic activity and selectivity can be reached. Chemists have thus designed nano-reactors presenting a molecular cavity surrounding both the active site and the substrate, in order to mimic such efficient systems.[1–19] Nevertheless, endohedral functionalization is hard to achieve and has been rarely reported. Furthermore, such supramolecular catalysts often suffer from product inhibition: low turnover numbers are obtained when the product exhibits a high affinity for the cavity and remains in the confined space of the molecular cage, preventing any catalytic cycle.[20,21] Molecular receptors presenting a cavity just above a catalytic center, can fall into two main classes: covalent or self-assembled cages. These latter are obtained from smaller subcomponents, allowing the access to sophisticated structures in only few steps of synthesis. Following the pioneering work of M. Fujita, other remarkable examples of self-assembled cages have been reported by this group and those of K. N. Raymond, J. Rebek, Jr., P. Ballester, J. N. Reek, P. J. Stang, M. Hardie and J. N. Nitschke, to only cite a few.[22–28] Here, only covalent cages presenting both endohedral functionalization of their inner cavity and activity as metal- or organo-catalysts will be described in detail. The synthesis of such architectures and their use as catalysts are highly challenging and as a consequence only few examples have been reported to date. Recently, the groups of Ballester, Makita and Matt have described covalent cages bearing endohedral functionalization such as acidic pyrrole protons, cobalt or palladium ions encapsulated in calix-pyrrole based cages, hemicryptophanes or cyclodextrins, respectively. However, the catalytic activity associated with these promising structures were not investigated, hence these systems will not be described herein.[29–31] Moreover, we will only focus on examples where the catalytic activity of the cage complex has been compared with that of a model catalyst, which lacks cavity. Thus, we aim to limit the scope of this review to catalytic systems presenting a clear endohedral functionalization of their covalent cavity, i.e. a catalytic site fully encapsulated in a three-dimensional cage, with the reactive center pointing inward the cavity and for which the comparison with a relevant model compound has been performed. Therefore, artificial enzymes such as those reported by Matt, Bols, Breslow, Monflier and others, which have been reviewed recently, are out of the scope of this microreview.[32,33] Covalent molecular structures encaging a metallic active site will be firstly presented, then organo-catalysts confined in a molecular cavity will be described. Direct comparisons with the model catalysts, without cavity, will allow emphasizing the gains in activity and selectivity induced by the confinement of the catalytic center.

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2. Confined Metal-Catalysts

Supramolecular systems combining a well-defined cavity with a metallic center are mainly based on resorcinarenes, cylclodex-

trins (CD), or calixarenes scaffolds. In most of these structures, the metal ion is located at the rim of the molecular cavity, and their remarkable binding properties allow for an increase of the concentration of the guest substrate near the active site, and good catalytic activities can be observed. However, true endohedral functionalization of a host molecule, i.e. a metal trapped in the heart of the cavity, is hard to achieve. Moreover, once such challenging structures are obtained, no catalytic activity is usually observed because of ligand degradations, under the reaction conditions, or product inhibitions.[20,21,34] As a consequence, very few true endohedral functionalized covalent cages and their applications as catalysts have been reported.

The Fe^{II} porphyrin complex **1** sandwiched by two cyclodextrins was reported in 1990, by Kuroda et al. (Figure 1).[35] This compound mimics the catalytic activity of cytochrome P-450 and acts as an efficient catalyst in the epoxidation of cyclohexene, whereas its model parent, which lacks cavity, displays no catalytic activity for this reaction (55 % and less than 2 % yields for **1** and **2**, respectively).

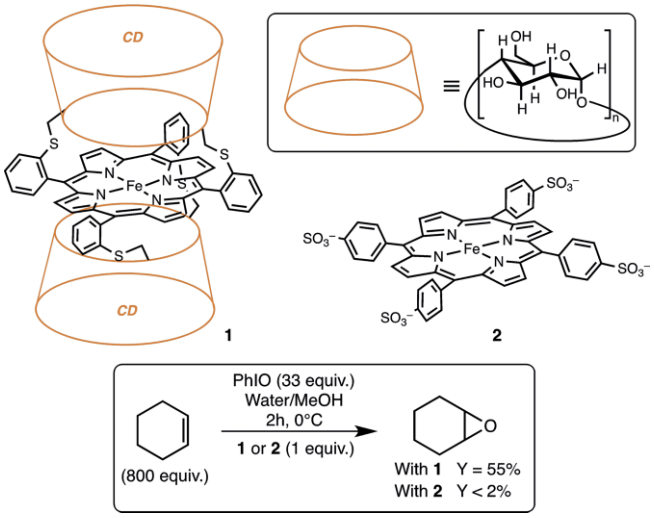

Figure 1. Cyclodextrin sandwiched Fe^{II} complex **1** and its model counterpart **2**. Their catalytic activities were compared using the epoxidation of cyclohexene as benchmark reaction.

Dr. Jian Yang studied chemistry at Huaibei Normal University from 2008. When obtained his B.Sc. degree in 2012, he started his graduate research in the field of metal organic framework (MOF) in South China Normal University, where he obtained his M.Sc. degree in 2015. Currently, he is sleeping.

Dr. Bastien Chatelet gained his PhD from the École Normale supéreure de Lyon in 2013 under the supervision of Dr. Véronique Dufaud. He studied the confinement of Verkade's superbases and their conjugate acids, the azaphosphatranes, in hemicryptophane structures. He then completed of postdoctoral work in the group of Pr. Guy Bertrand at the University of San Diego. He then got a position of lecturer at the École Centrale Marseille in the group of Pr. A. Martinez in 2016. He is currently working on molecules with a phosphorus atom confined in hemicryptophanes and their use as catalysts.

Dr. Damien Hérault received his PhD in 2004 from the University Claude Bernard Lyon 1. His work on polymer-supported chiral ligands was supervised by Profs. C. Saluzzo and M. Lemaire. He pursued postdoctoral studies on chiral organocatalysis at the Durham University with Prof. A. Whiting (2005–2007). Then he came back in France, at the University of Montpellier 2, to work with Profs. G. Cerveau and R.J.P. Corriu on sugar-based hybrid materials (2008–2009). He joined as lecturer the group of Prof. G. Buono at Ecole Centrale Marseille in 2009. Now, in the group of Prof A. Martinez, and his current research interests include phosphorus chemistry, chirality, hybrid material and asymmetric catalysis.

Dr. Jean-Pierre Dutasta gained his Doctorat d'Etat es-Sciences Physiques from the University of Grenoble, France, in 1980 for studies on synthesis, conformational analysis and NMR investigations of organo-phosphorus compounds with Prof. J.-B. Robert. He joined the Centre National de la Recherche Scientifique (CNRS) in 1979 and did a post-doctoral work in 1980–1982 at the University of California at Los Angeles under the supervision of Pr. D.J. Cram. He joined the Laboratory of Chemistry of the École Normale Supérieure de Lyon in 1988 with Prof. André Collet, where he was appointed Research Director. His research activities are mainly stereochemistry, NMR and supramolecular chemistry of cryptophanes, hemicryptophanes and phosphonate cavitands. He headed the supramolecular chemistry group until 2014, and is now CNRS Emeritus Research Director.

Prof. Dr. Alexandre Martinez obtained his Ph.D. from the University of Toulouse (France) in 2004 for his studies on asymmetric oxidation under the supervision of Dr. B. Meunier. He completed a postdoctoral work on the theme of supramolecular chemistry in 2004–2005 at the University of Geneva under the supervision of Prof. J. Lacour. He joined the Ecole Normale Superieure de Lyon in 2006 as a lecturer in the team of Dr. J.-P. Dutasta. Then, he obtained a position of full Professor at the Ecole Centrale Marseille in 2014. His research works are in the field of stereochemistry, catalysis, and supramolecular chemistry, he is particularly interested in hemicryptophane as host molecules.

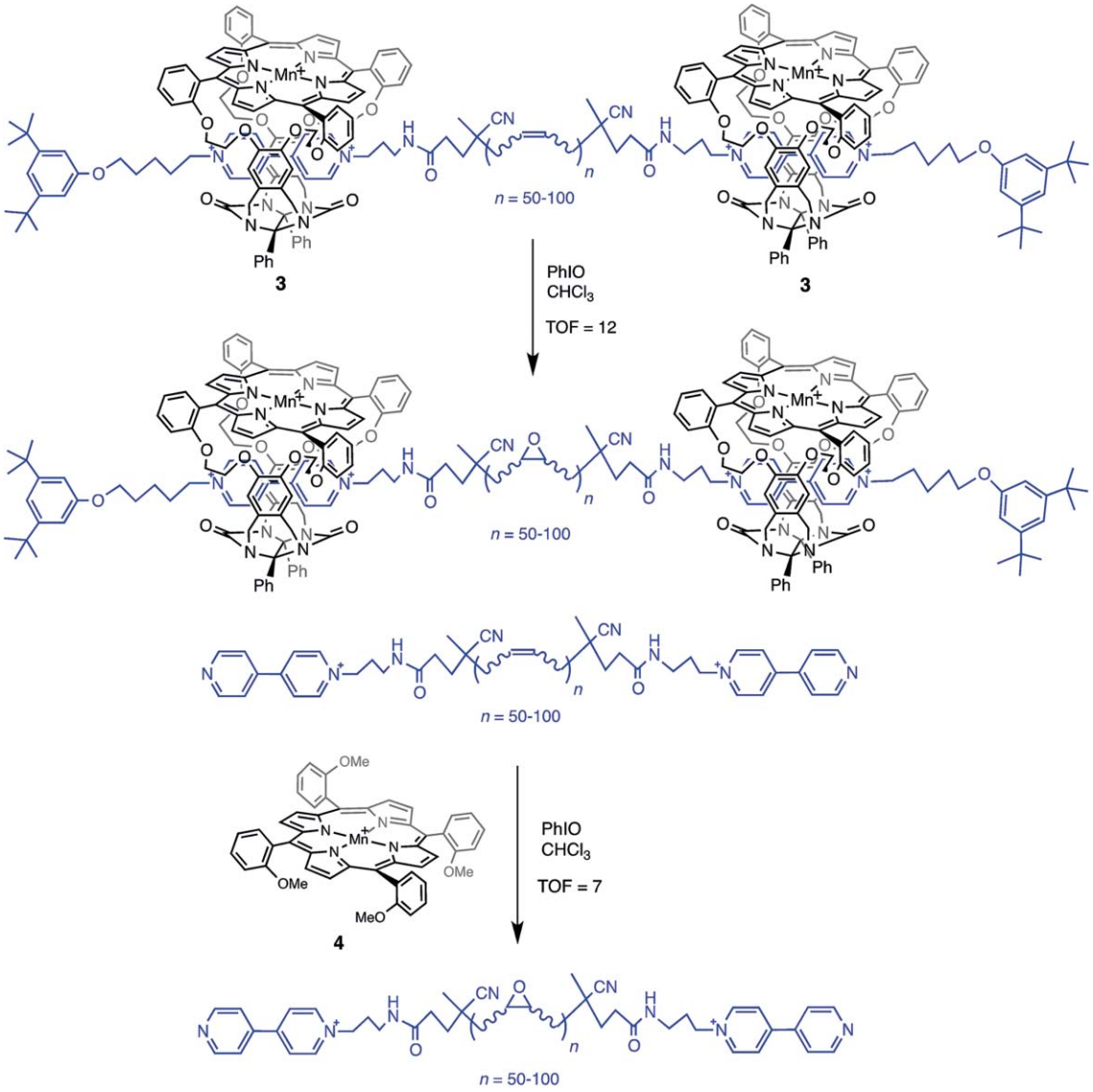

Figure 2. The bio-inspired Mn^{III}-porphyrin rotaxane **3** and its catalytic activity compared to that of **4**.

The Mn^{III}-porphyrin rotaxane complex **3** was synthesized by the group of Nolte in order to mimic natural enzymes such as T4 DNA polymerases (Figure 2).[36] The TOF is doubled with the supramolecular system **3**, when compared to its model parent **4**. Progressive epoxidation of the polybutadiene thread as well as the endohedral formation of manganese-oxo intermediate was clearly evidenced by a thorough investigation.[37–40]

In 2002, the group of Rebek used the resorcin[4]arene-based cavitand **5**, presenting a palladium complex oriented inward the cavity, and tested it as catalyst in allylic substitution reactions (Figure 3).[41] Whereas the model complex **6**, which lacks cavity, was unable to discriminate two different substrates, the encaged palladium complex was able to discriminate them efficiently, probably because the well-defined cavity can accommodate more easily a cyclohexyl group than a branched heptyl unit.

In 2017, Matt et al. reported the synthesis of a resorcinarene cavitand substituted with two N-anisyl-iminophosphoranyl moieties (Figure 4).[42] Hydrogenation of a 1:1 mixture of hex-1-ene and dec-1-ene using $[Rh(cod)_2]BF_4$ in the presence of **7** or **8** as catalyst led to a size-selective transformation of these α-olefins. Indeed, the model catalyst gave poor selectivity in favored of the hexane product, whereas the cavitand based catalyst provided much higher substrate selectivity, with a hexane/decane ratio of 5.4. The endohedral functionalization of the cavity of the ligand **7** by the rhodium metal could account for this improvement of the substrate discrimination.

The same group described the synthesis of a molecular capsule **9** built with two resorcin[4]arene moieties linked by a *meta*-xylyl spacer and including two phosphane ligand complexing a "*trans*-$PtCl_2$" unit (Figure 5).[43] This cage complex was tested as catalyst in the hydroformylation of styrene in the presence of $SnCl_2$. The confinement turns out to have a beneficial effect on both activity and regioselectivity: (i) conversions of 55 % and 40 % are reached with the container **9** and the model catalyst **10**, respectively. This better catalytic activity of **9** was

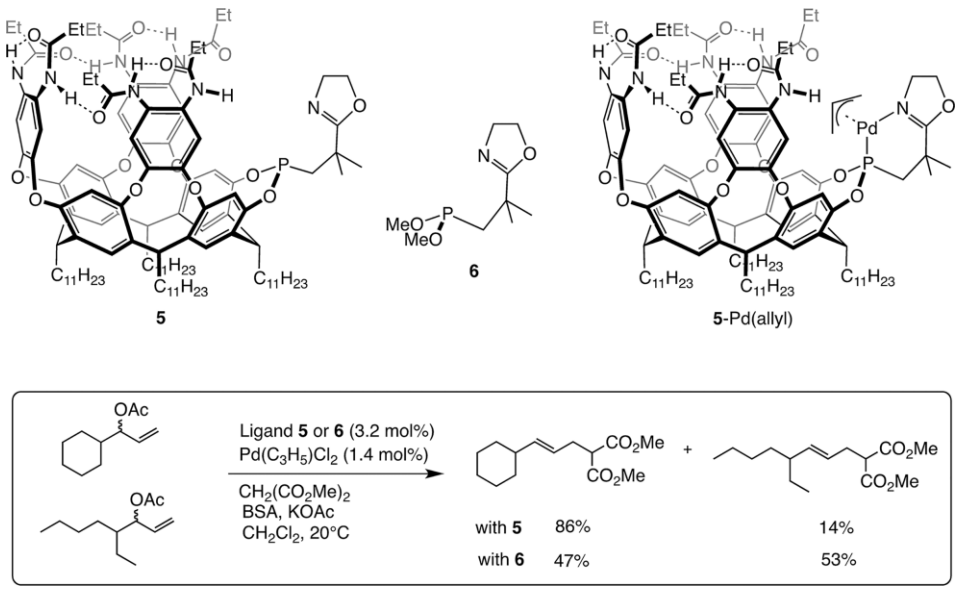

Figure 3. The resorcin[4]arene-based cavitand **5** and its model counterpart **6**. The catalytic activities of their palladium complexes have been compared using the allylic substitution as a benchmark reaction.

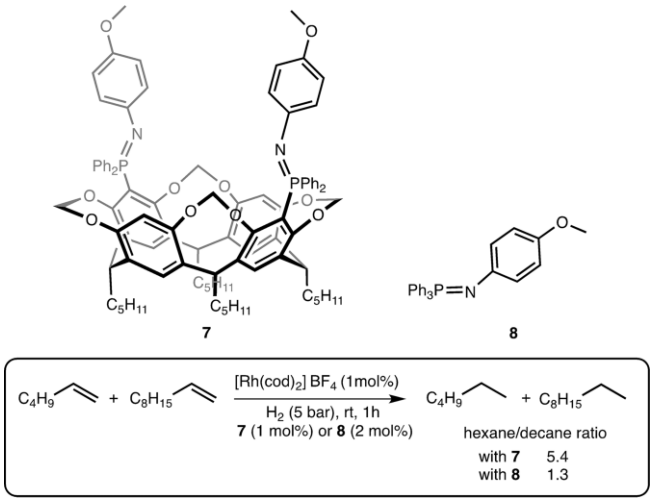

Figure 4. Cavitand **7** and its model counterpart **8** and their use in hydrogenation of alkenes.

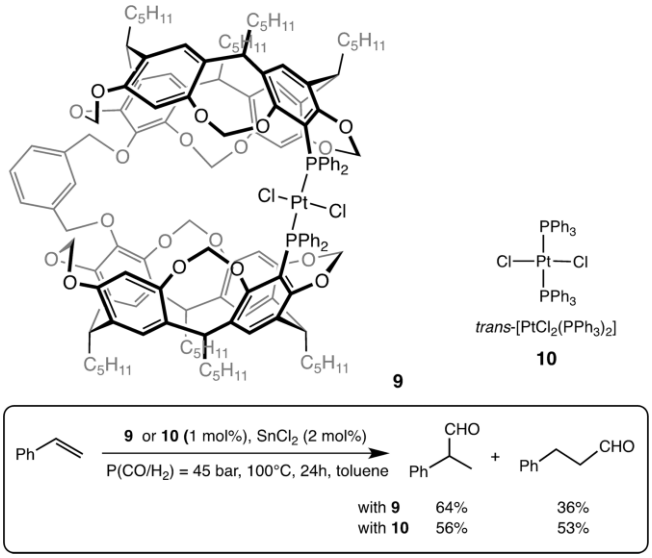

Figure 5. Capsule **9** and its model counterpart **10** and their used in hydroformylation of styrene.

attributed to the formation, inside the cavity, of a hydrido intermediate with a distorted trigonal bipyramidal structure. (ii) The selectivity towards the branched aldehyde is also improved probably because of specific orientations and conformations of the intermediately formed Pt-alkyl units in the confined space of the molecular cavity.

Recently, the Sollogoub's group managed to obtain gold complexes of NHC-capped cyclodextrins (ICyDs) (α-ICyD-AuCl **11** and β-ICyD-AuCl **12** complexes; Figure 6).[44] The encapsulation of the gold ion in the heart of the cavity was nicely demonstrated by a set of NMR and electrochemistry experiments. Besides the interesting enantioselectivities obtained (59 % *ee* with **12**), the most striking point is the switch of ring-size selectivity when the cage is used as catalyst in the ring cyclisation of enynes: with the model catalyst **13** and the cage complex **11** the five-membered ring product is the major one, whereas the six-membered ring compound is favored with the confined gold catalyst **12**. Then, a family of seventeen carbene-capped CDs metal complexes have been synthesized. Depending on the size and shape of the cavity strong changes in the regio- and enantio-selectivity were observed. In particular, using the β-ICyD-AuCl **12**, a remarkable *ee* of 80 % was reached.[45]

In 2017, the same group reported the two NHC-capped α- and β-cyclodextrins copper(I) complexes α-ICyD-CuCl **14** and β-ICyD-CuCl **15** (Figure 7) with different cavity size.[46] The two complexes were compared to study the regioselectivity induced by the cyclodextrin (CD) cavity on the hydroboration of aromatic alkynes. Interestingly, sterically hindered ligand α-ICyD gives rise to linear products, while the larger β-ICyD derivative favors branched compounds. They demonstrated that the

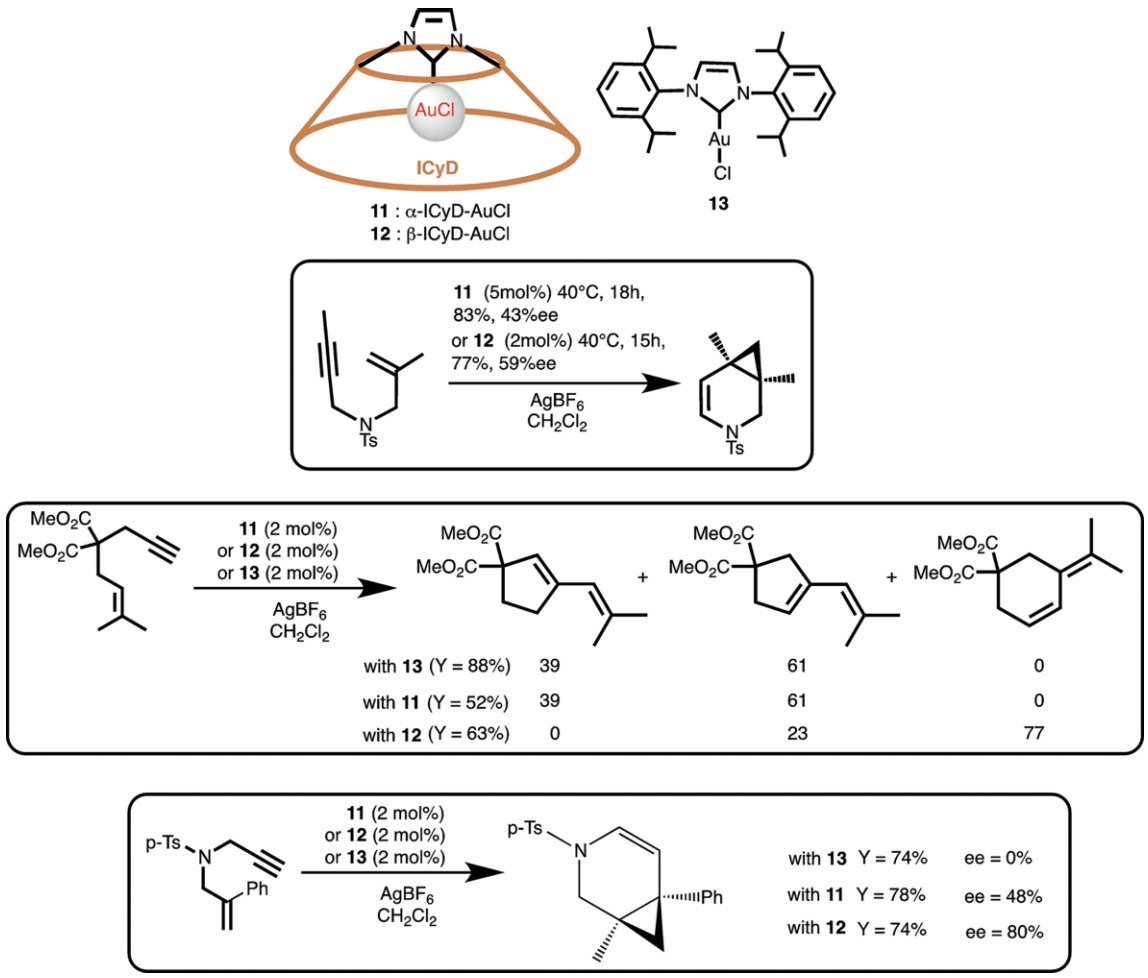

Figure 6. Endohedral gold-carbene cyclodextrin complexes **11** and **12** and their use in cycloisomerization.

regioselectivity is governed by the difference of the shape of the catalysts. Besides the conventional "parallel" mechanism, they proposed in this study a new "orthogonal" mechanism,

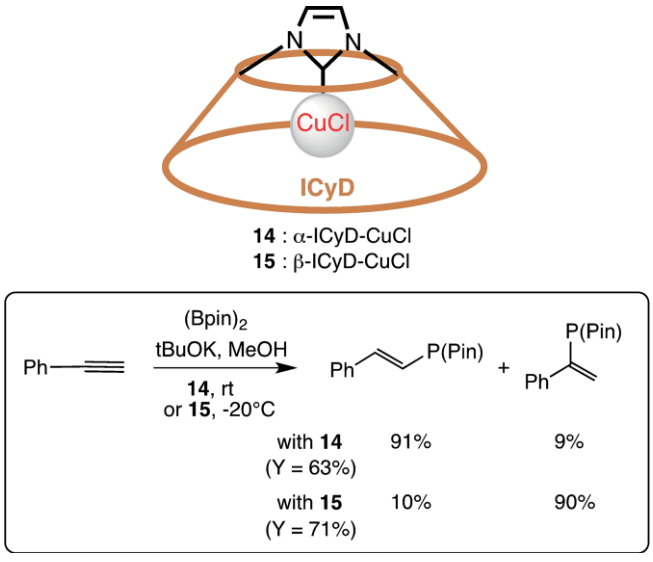

Figure 7. Copper-carbene cyclodextrin complexes **14** and **15** and their use in hydroboration.

which is consistent with DFT calculations. Thus, changing the shape of the cavity induces a switch of both the mechanism and the regioselectivity of the reaction.

In 2009, we described the synthesis of a hemicryptophane host including an endohedral oxido-vanadium unit (compound **16**, Figure 8).[47] This supramolecular catalyst turned to be efficient and selective for the oxidation of sulfides into sulfoxides with yields up to 95 %. When compared to the model complex **17**, which lacks cavity, the cage catalyst displayed rate constant up to six times higher, showing that the confinement of the oxido-vanadium site, improved the catalytic activity. Furthermore, a turnover number up to 180 was reached, highlighting that the hemicryptophane cage can be considered as a new class of supramolecular transition-metal based catalysts.

More recently, a new set of hemicryptophane cages including an oxidovanadium site, was reported in order to further improve their catalytic performance in sulfoxidation reactions (Figure 8).[48] The binaphtol units introduced in the linkers of **18** were expected to isolate more efficiently the heart of the cavity from the bulk of the solvent and thus, should lead to an improved confinement effect. These new hemicryptophane complexes are indeed much more efficient than those previously reported. Reaction rates in the oxidation of thioanisole are fivefold and 33-fold faster with the hemicryptophane cata-

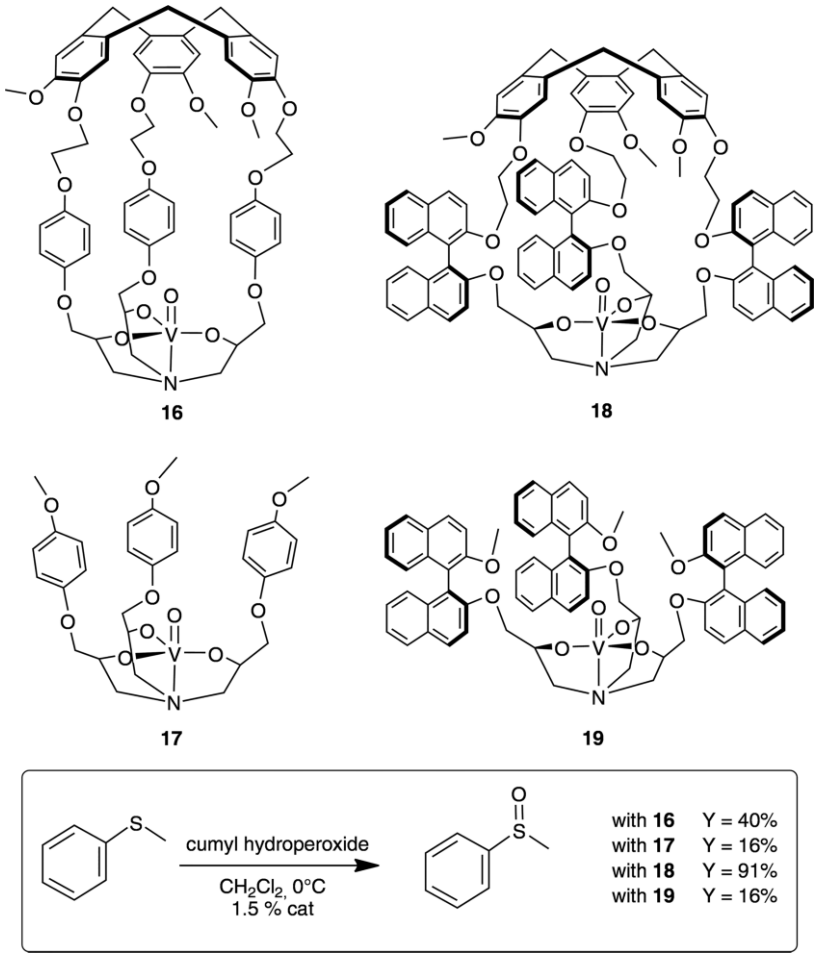

Figure 8. Oxidovanadium@hemicryptophane hosts **16** and **18** and their model complexes **17** and **19** used as catalysts in the oxidation of thioanisol.

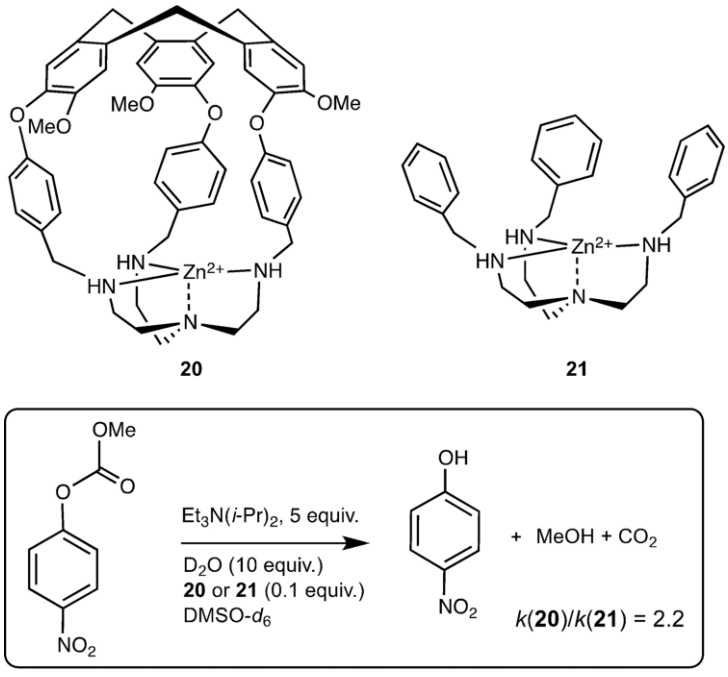

Figure 9. Zn@hemicryptophane supramolecular complex **20** and the model compound **21** tested as catalyst for the hydrolysis of methyl *para*-nitrophenyl carbonate.

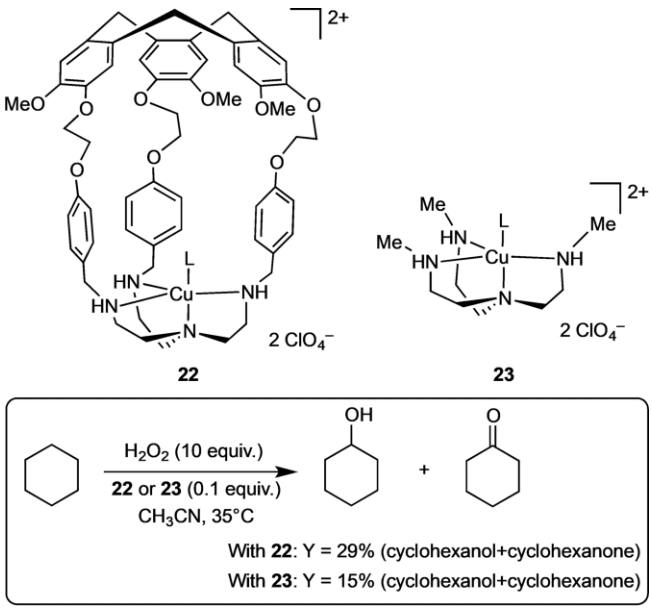

Figure 10. Cu^{II}@hemicryptophane **22** caged catalyst and its model counterpart **23** used for the oxidation of cyclohexane to cyclohexanone and cyclohexanol (L = MeOH).

lysts **18** than with the cage **16** and the model **19**, respectively. Moreover, a TON of 10000 was reached with **18**, underlining the remarkable catalytic activity and stability of this supramolecular catalyst. The key role played by the cavity was evidenced by a competitive inhibition experiment using $Me_4N^+Pic^-$ as competitive guest. While its addition has no influence on the catalytic activity of the model complex, it dramatically affects the reaction rate of the cage catalyst, probably by preventing the access of the cavity to the substrate. Both Michaelis–Menten kinetic and substrate selection were also observed, showing an enzyme-like behavior of the cage catalyst.

Makita et al. have reported a zinc(II) complex trapped into the cavity of a hemicryptophane, and its use as a catalyst for the hydrolysis of methyl *para*-nitrophenyl carbonate (MPC) (Figure 9).[49,50] The supramolecular catalyst turned out to be more efficient than the model since a k(**20**)/k(**21**) ratio up to 2.2 was measured. Based on DFT calculations, the cavity was proposed to avoid the inhibition by the solvent DMSO, which cannot coordinate to the Zn^{II} inside the cage.

Oxidation of unreactive C–H bonds, catalyzed by transition metal complexes, arouses a considerable interest as it can provide an easy and cheap access to valuable oxygenated products from alkanes of petroleum and natural gas. Among the supramolecular complexes presenting a well-defined cavity above the metallic site, mainly copper(II), very few examples display a catalytic activity in C–H oxidation of exogenous substrates. The Cu^{II}@hemicryptophane complex **22** represents one of the rare supramolecular complexes capable of oxidation of cyclohexane under mild conditions and using hydrogen peroxide as stoichiometric oxidant (Figure 10).[51,52] A direct comparison with the model compound **23** demonstrates that the cage structure protects the supramolecular catalyst from degradation, leading to yields two times higher. Moreover, the confined catalyst **22** was able to discriminate more efficiently cyclohexane from adamantane than the model **23**, probably because adamantane is too big to enter inside the cavity of **22**. This result opens up the way for a larger use of confined catalysts in C–H bond oxidation.

3. Confined Organo-Catalysts

Supramolecular catalysts based on the confinement of organo-catalysts into covalent molecular cages have been described. These nano-reactors present an endohedral functionalization of the inner space of their cavity without any metal in their catalytic site or in their framework. As in the previous section, only examples involving covalent cages including an organo-catalytic center will be presented.

The group of Rebek Jr. reported the synthesis of cavitand **24**. The molecular cage, functionalized with a Kemp's triacid derivative, displays a carboxylic acid pointed inward a deep open-ended cavity (Figure 11).[53] The cavity imposes a specific folding of the substrate in the vicinity of the catalytic site, as a consequence a remarkable regioselectivity in the cyclization reaction of alcohol **25** into **26** was achieved when the cavitand **24** was used as catalyst. Furthermore, the rate constant is more than 50 times higher with the supramolecular catalyst than with its related model compound **27**. These remarkable confinement effects were attributed to the true endohedral functionalization of the molecular cage.

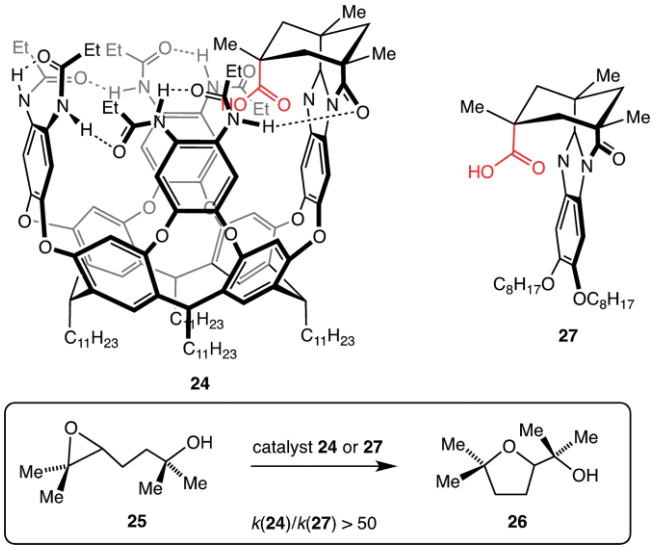

Figure 11. Cavitand **24** and its model counterpart **27** used as catalyst in the cyclization reaction of alcohol **25** into **26**.

Chen et al. synthesized two robust endohedral-functionalized organic cages via dynamic covalent chemistry, bearing three phenol hydroxyl groups inside the cavity (Figure 12, cage **28**).[54] Compared with model catalyst **29** which lacks a cavity, the cage catalysts demonstrated excellent catalytic activities in the Friedel–Craft reaction with a wide range of substrates. For instance, in the reaction of *trans*-β-nitrostyrene with 1-methylindole, a yield of 86 % was obtained in the presence of cage catalyst **28**, while only 17 % yield was obtained in the presence of model analogue **29**. Besides, the authors proposed that the

reaction occurred inside the cavity: when steric bulky substrates were used as reactants very low yields were reached, indicating that the cage catalyst presents a remarkable substrate-size selectivity.

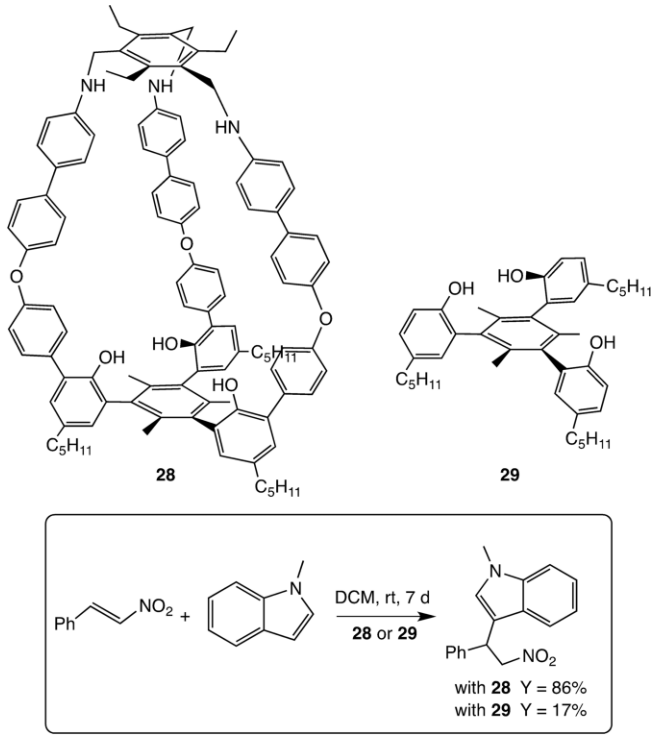

Figure 12. Cage **28** and model compound **29** used as catalysts in the Friedel–Craft reaction.

Proazaphosphatranes Verkade's superbases are very efficient basic or nucleophilic organo-catalysts: when compared to most other organo-catalysts, higher yields and better selectivities are reached while working under milder conditions (Figure 13).[55,56]

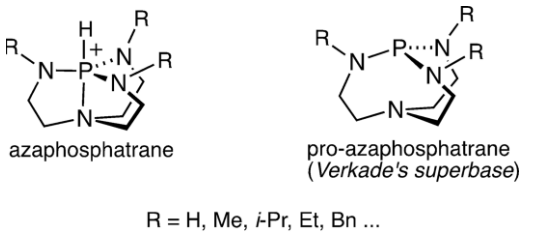

Figure 13. Structures of azaphosphatranes and pro-azaphosphatranes (Verkade's superbase).

When the Verkade's superbase was encapsulated in a hemicryptophane host (compound **30**, Figure 14),[57] it was shown that the confinement both slightly increases the basicity of the proazaphosphatrane unit, and dramatically decreases the rate of proton transfer. Although the encaged Verkade's superbase **30** is seven times more basic than its model parent **31**, its protonation rate is one hundred times slower. Makita et al. reported the synthesis of the hemicryptophane **32** encaging an azaphosphatrane unit.[58] Due to the more rigid structure of this host, the endohedral proton was strongly shielded by the cage structure, hence the authors were unable to deprotonate the azaphosphatrane despite the various strongly basic conditions used.

In order to investigate the role of size and shape of the cavity on the rate and thermodynamic of the protons transfer, two new encaged proazaphosphatranes **33** and **34** were synthesized (Figure 14).[59] The confinement was found to strongly affect the pK_a values: the basicity of the Verkade's superbase is either dramatically improved or strongly decreased, depending on the cage structure. For instance, the basicity of the encaged superbase **33** is 30 times lower than that of its model parent **35** (K_a of 4.42×10^{-32} and 1.26×10^{-33}, respectively). This behavior is in sharp contrast with that of the encaspulated superbase **34**, which is more than 100 times more basic than the model counterpart **36**. The following general trend can be observed: an increase of cavity size (from **30** to **33** and **34**) is associated with a decrease of the rate of proton transfer, as a consequence, the rate of protonation of the highly basic species **34** is 500 000 times slower than that of its model counterpart. The X-ray molecular structures of the host compounds allow rationalizing this unexpected behavior: from **30** to **33** and **34**, the cavity becomes longer but also less wide and the naphthalene linkers of **34** prevent the access to the reactive center, making its protonation kinetically blocked. This underlines how the space available above the basic unit can affect the kinetics and thermodynamics of proton transfer.

The confined superbase **30** has been tested as organo-catalyst in the base-catalyzed Diels–Alder reaction shown in Figure 14.[60] It displays a good catalytic activity, since a quantitative yield was obtained when anthrone and dimethylfumarate were used as substrates, whereas only 38 % yield is reached with trimethylamine as catalyst. The direct comparison with the model superbase **31** shows that the rate of the reaction is twice slower with the cage catalyst **30**. The decrease of the reactivity is much less pronounced than that observed for proton transfer, rendering this system still efficient for organo-catalysis. Moreover, it was found that the confinement improves the diastereomeric excess (*de*): *de* of 78 % and 42 % (both in favor of the *endo* product) were obtained with the cage catalyst **30** and its corresponding model **31** in the reaction between 3-hydroxy-2-pyrone and *N*-methylmaleimide. The increase of the amount of *endo* product with the supramolecular superbase, is consistent with previous reports suggesting that catalysts presenting a deep and narrow cavity lead to an improvement of the *endo*/*exo* ratio, probably because the cavity above the reactive center favors the most compact geometry.[61,62] Thus, the confinement of organocatalyst in the tight space of a hemicryptophane cavity can improve the stereoselectivity of the targeted reaction.

Although Verkade's superbases have been widely used as organo-catalyst or stoichiometric reactants in various reactions, their conjugated acid, the azaphosphatranes, have aroused little interest. However, these robust cations were recently reported to catalyze, under mild conditions (1 bar, 100 °C), the conversion of CO_2 and epoxides into carbonates (Figure 15).[63] Azaphosphatranes encapsulated in a hemicryptophane host (compounds **37**–**40**) have been also tested as catalysts for this reac-

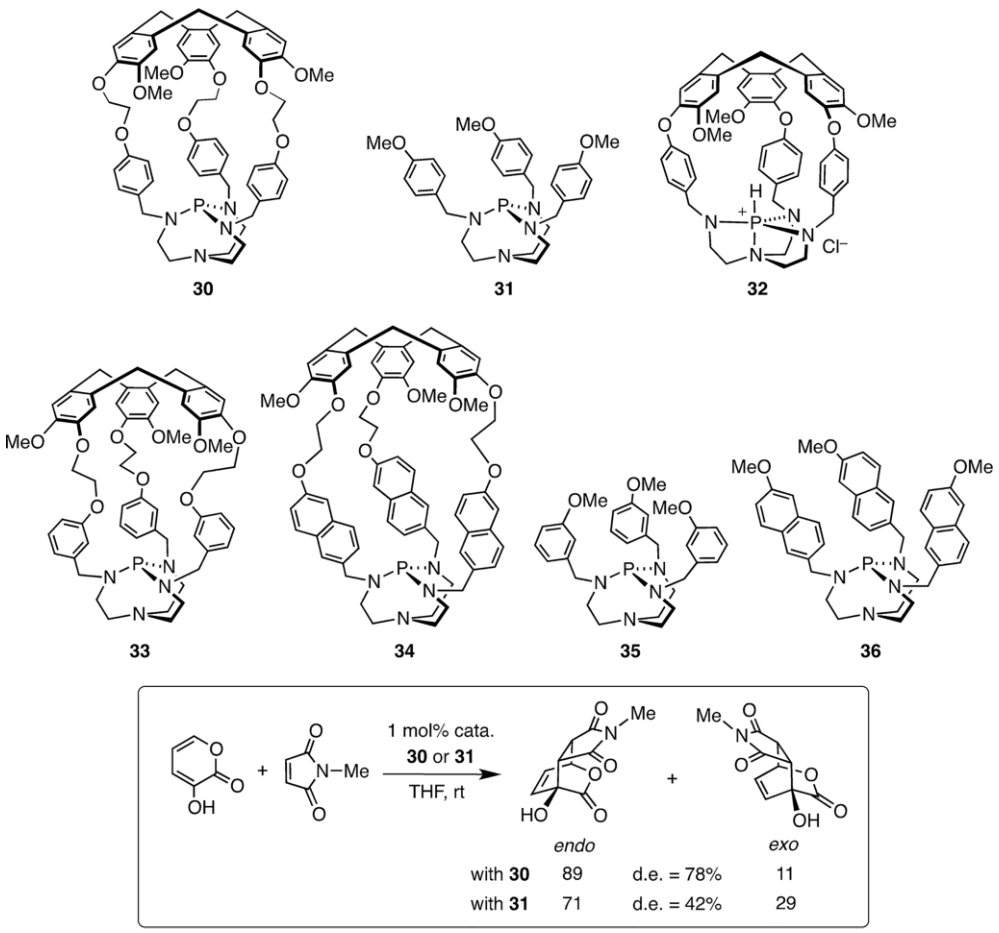

Figure 14. Structures of the encapsulated superbases **30**, **33**, **34**, of the encaged azaphosphatrane **32**, and their related model **31**, **35**, **36**. Insert: the compared selectivity of **30** and **31** when used as catalysts in a Diels–Alder reaction between 3-hydroxy-2-pyrone and *N*-methylmaleimide.

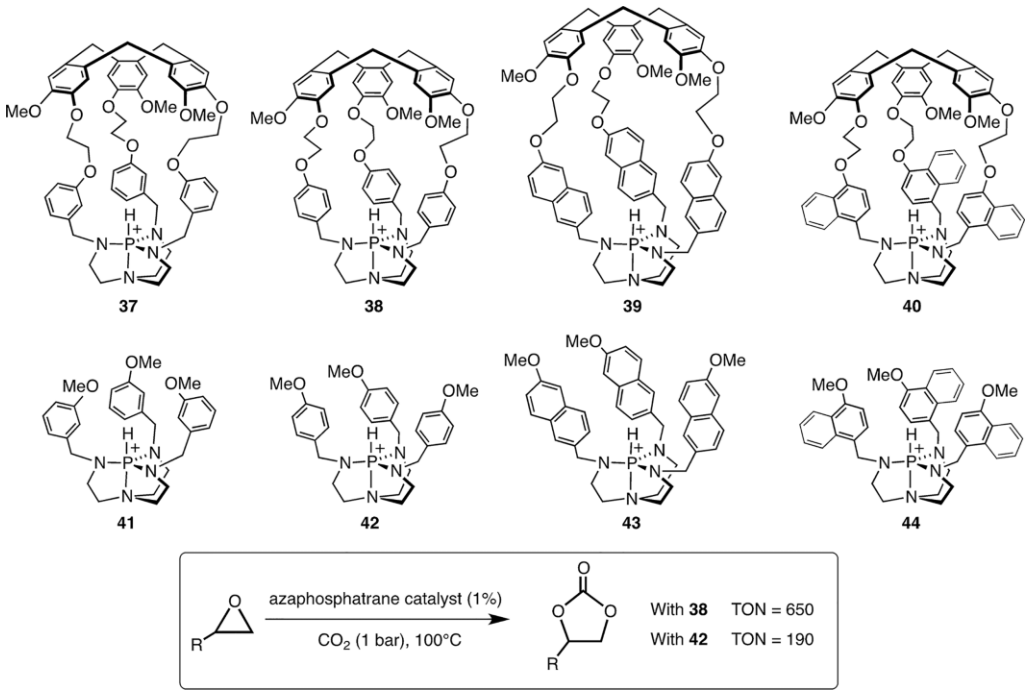

Figure 15. Structures of encaged azaphosphatranes, which differ by the size and shape of their cavity, and the corresponding model compounds used as catalysts for CO_2 conversion (chloride as counterion).

tion. When compared to the model compounds **41**–**44**, (Figure 15)[64] the confined catalysts, except **39**, exhibit improved stability and reactivity, probably because the shielding of the aromatic wall of the cavity protects the active site, avoiding some degradations. As a consequence, TON up to 700 can be reached, making **37**, **38** and **40** efficient supramolecular catalysts. Due to their flexibility and the lability of the host–guest complex, the carbonated product is easily released from the cavity, and these hemicryptophane catalysts do not suffer from product inhibition, as often observed with supramolecular catalysts. As mentioned above, supramolecular catalyst **39** displays a specific behavior: its catalytic activity is much lower than that of its model counterpart **43**, whereas this latter presents an activity similar to the other model catalysts. The helical arrangement of the naphthalene linkers above the reactive center precludes its access to the substrates (as already observed for proton transfer), accounting for the observed low reactivity.

4. Conclusion

In this review article we have described covalent cages including a reactive site oriented toward the molecular cavity. In each case, the catalytic activities of the resulting endohedral functionalized cages have been compared to those of the model catalysts lacking cavity. These comparisons highlight that an improvement on the reaction rate, stability of the catalyst, or selectivity of the reaction, can be induced by the confinement of the catalytic site. Although examples of host molecules with a well-defined cavity just above a reactive catalytic center, with catalytic activities directly compared to model catalysts, remain to some extend underexplored, we believe that this field of research will stimulate a blossoming interest, given the high potential of such an approach.

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