



# Controlling the Activity of a Caged Cobalt–Porphyrin-Catalyst in Cyclopropanation Reactions with Peripheral Cage Substituents

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Abstract: In this study, three novel cubic cages were synthesized and utilized to encapsulate a catalytically active cobalt(II) mesotetra(4-pyridyl)porphyrin quest. The newly developed caged catalysts (Co-G@Fe<sub>8</sub>(Zn-L·1)<sub>6</sub>, Co-G@Fe<sub>8</sub>(Zn-L·2)<sub>6</sub> and Co-G@Fe<sub>8</sub>(Zn-L·3)<sub>6</sub>) can be easily synthesized and differ in exofunctionalization, which are either none, polar or apolar groups. This leads to a different polarity of the peripheral environment surrounding the cage, which affects the (relative) local concentration of the substrates surrounding the cage and hence indirectly influences the substrate availability of the catalysis embedded in the active site of the caged catalyst systems. The resulting increased local substrate concentrations give rise to higher catalytic activities of the respective caged catalyst in metalloradical catalyzed cyclopropanation reactions. Interestingly, the catalytic activity is the highest when the apolar cage catalyst (Co-G@Fe<sub>8</sub>(Zn-L·1)<sub>6</sub>) is used, and lowest with the polar analog (Co-G@Fe<sub>8</sub>(Zn-L·3)<sub>6</sub>). In addition, the catalytic activity of the cage without exo-functionalities (Co-G@Fe<sub>8</sub>(Zn-L·2)<sub>6</sub>) is nearly two times lower than that of Co-G@Fe<sub>8</sub>(Zn-L·1)<sub>6</sub> and three times higher than that of Co-G@Fe<sub>8</sub>(Zn-L·3)<sub>6</sub>, which further demonstrates the effect of the peripheral functionalities on the cyclopropanation reaction.

#### Introduction

Catalysis occupies a pivotal role in the modernization of our chemical industry, because it ensures more efficient use of natural resources and also aids in the minimization of waste production.<sup>[1]</sup> Traditionally, catalytic efficiency is controlled through ligand design, also known as the first coordination sphere.<sup>[2]</sup> Despite significant progress in the field of catalysis, there are still many reactions for which high catalytic efficiency cannot be achieved, and development of new approaches that lead to catalyst improvement are therefore important. In recent years, great efforts have been devoted to the development of supramolecular strategies as complementary approach to control catalytic performance.<sup>[3]</sup> Within this field, 'caged catalysts' have shown interesting prospects. A catalyst under confinement conditions often imposes reactivity and selectivity not observed in the bulk.<sup>[4]</sup> Thus far, many self-assembled capsules have

been developed as supramolecular catalysts, where catalytic activity and/or selectivity are controlled by the second coordination sphere.<sup>[5]</sup> Several studies have been reported were coordination cages with well-defined confined spaces impose so-called second coordination sphere effects, which can influence the activity and selectivity of the catalytic reaction.<sup>[6]</sup> An interesting feature of a reaction taking place in a confined space is the increased proximity of substrate(s) and the catalyst active site, thereby enhancing overall reaction rates by preorganization.<sup>[7]</sup> Secondly, selective substrate binding can lead to substrate selectivity and selective conversion of one of the substrates.<sup>[8]</sup> Thirdly, the pre-organization of a substrate in a higher energy conformation can accelerate the reaction and promote reactivity.<sup>[4b]</sup> Most importantly, the stabilization of a transition state or intermediate can alter reaction mechanisms and lead to reactivity not observed in the bulk.[9]

These supramolecular catalysts are inspired by the working principles of enzymes,<sup>[10]</sup> and in an effort to design and prepare catalysts with further control over chemical reactivity, enzymes can further serve as sources of inspiration. The active site of many enzymes is often located deep within the substrate binding cavity of the protein, and for any catalytic transformation to take place the substrate must diffuse through the body of the protein via a tunnel.<sup>[11]</sup> The difference with proteins where the active site is located on the surface is the additional protein-substrate interactions, as the substrate must diffuse through tunnel residues before binding to the active active site.<sup>[12]</sup> For example, the structure of cytochrome P<sub>450</sub>, which consists of a long hydrophobic tunnel, regulates the substrate access and product release.<sup>[13]</sup> Although these tunnels consist of highly complex molecular structures that contribute to enzyme function, less sophisticated abiological catalytic systems can mimic their properties and function for the development of catalysts with high efficiencies in terms of selectivity and/or activity.<sup>[14]</sup>

We previously demonstrated the effect of the secondcoordination sphere on catalysis, wherein a caged catalyst functionalized with apolar groups was shown to increase the catalytic activities in the cobalt-catalyzed cyclopropanation of styrene when compared to the free catalyst.<sup>[15]</sup> In this work, we demonstrate an unprecedented strategy for controlling catalytic

performance, in which differences in peripheral functionalization of cubic supramolecular cages hosting a cobalt catalyst influences the catalytic activity for cyclopropanation of styrene. To our best knowledge there are no previous examples reported wherein the periphery of a cage was shown to influence the activity of a (wo)man-made catalyst.

For the purpose of studying effects of the cage periphery, we explored three different caged catalyst with different exo-

polarities (Figure 1). The previously reported  $Fe_8(Zn-L\cdot1)_6$  cage is functionalized with apolar aliphatic tails (Figure 1, left),<sup>[15]</sup> the  $Fe_8$  (Zn-L·3)<sub>6</sub> cage is decorated with polar groups at the periphery (Figure 1, right) and the reference  $Fe_8(Zn-L\cdot2)_6$  cage (Figure 1, middle). We envisioned that the different peripheries of these caged systems could be used to control the affinity of caged catalyst for the substrate and thus lead to different activities. As such the cage serves as a mimic of the active site



#### Apolar

Polar

Figure 1. Modeled structures of Fe<sub>8</sub>(Zn-L·1)<sub>6</sub> (left), Fe<sub>8</sub>(Zn-L·2)<sub>6</sub> (middle), and Fe<sub>8</sub>(Zn-L·3)<sub>6</sub> (right), showing their inner cavity (red) and the different peripheral substituents (grey).

pocket of an enzyme whereas the periphery of the cage (light grey surface) provides a synthetic equivalent of the substrate binding site tunnel (Figure 1).

#### **Results and Discussion**

Next to our previously reported apolar Fe<sub>8</sub>(Zn-L·1)<sub>6</sub> cage, we synthesized two new cages (Fe<sub>8</sub>(Zn-L·2)<sub>6</sub> and Fe<sub>8</sub>(Zn-L·3)<sub>6</sub>) without any peripheral functional groups and with polar peripheral substituents. This was done by following our recently reported synthetic protocol for the synthesis of Fe8(Zn-L·1)6 (Figure 2). For the preparation of the polar cage analog, component 3 was readily synthesized in one step in 65% yield by the nucleophilic aromatic substitution of 5-fluoro-2formylpyridine with Bis[2-(2-hydroxyethoxy)ethyl]ether (see Supporting information). The reaction between subcomponent Zn-L (6 equiv.), 2 or 3 (24 equiv.) and iron(II) triflimide (8 equiv.) in dry DMF at 70 °C overnight resulted in the formation of single discrete species via the complexation of iron with the formed pyridyl-imine functionality (Figure 2A and 2B). Typical shifts in the <sup>1</sup>H NMR spectra are in line with the formation of Fe<sub>8</sub>(Zn-L)<sub>6</sub> type cages. Importantly, <sup>1</sup>H NMR diffusion-ordered spectroscopy (DOSY) shows a narrow band with a diffusion constant of 3.4.10<sup>-</sup> 6 cm<sup>2</sup>s<sup>-1</sup> for Fe<sub>8</sub>(Zn-L·2)<sub>6</sub> and 2.9·10<sup>-6</sup> cm<sup>2</sup>s<sup>-1</sup> for Fe<sub>8</sub>(Zn-L·3)<sub>6</sub> confirming the formation of a single species in solution that is much larger than the corresponding subcomponents (Figure 2A and B). The value of the diffusion constant is in good agreement with the obtained diameters of the self-assembled cages (36 Å for  $Fe_8(Zn-L\cdot 2)_6$  and 43 Å for  $Fe_8(Zn-L\cdot 3)_6$ ) based on molecular modeling studies (vide infra).

High resolution electrospray ionization mass spectrometry (HR-ESI-MS) reveals various peaks belonging to the two new cubic cages ( $Fe_8(Zn-L\cdot2)_6$  and  $Fe_8(Zn-L\cdot3)_6$ ) with different charges, in line with the formation of the desired multicationic species (Figure 2A and B). For each cage, the experimental spectra and simulated isotope patterns overlap perfectly, unambiguously confirming the formation of  $M_8L_6$  cage structures. Our efforts to grow single crystals suitable for X-ray diffraction were unsuccessful (solvent layering and vapor diffusion at different temperatures only led to solid powders, not suitable for X-ray). Cage  $Fe_8(Zn-L\cdot1)_6$  was synthesized by following the same synthetic protocol and all analytical data are in line with the formation of a species identical to the previously reported cage.<sup>[15]</sup>

To confirm that the central cavity size of  $Fe_8(Zn-L\cdot2)_6$  and  $Fe_8(Zn-L\cdot3)_6$  is similar to  $Fe_8(Zn-L\cdot1)_6$  and able to bind metalloporhyrins such as the catalytically active paramagnetic Co-tetrapyridyl porphyrin (Co-G) or the non-catalytic diamagnetic model compound Zn-tetrapyridyl porphyrin (Zn-G), we performed molecular modeling studies. The molecular model of  $Fe_8(Zn-L\cdot1)_6$  was used to generate the new coordinates with different peripheral functionalization, and the geometry was optimized using a semi-empirical extended tight-binding method ((GFN2-xTB).<sup>[16]</sup> This provided an estimated volume of 3300 Å<sup>3</sup> and 3250 for  $Fe_8(Zn-L\cdot2)_6$  and  $Fe_8(Zn-L\cdot3)_6$ , respectively. As anticipated the obtained models reveal similar cavity volumes for

Fe<sub>8</sub>(Zn-L·2)<sub>6</sub> and Fe<sub>8</sub>(Zn-L·3)<sub>6</sub> as the Fe<sub>8</sub>(Zn-L·1)<sub>6</sub> cage and

therefore have an optimal internal volume to bind Co-G or Zn-G.

We first explored encapsulation of the diamagnetic Zn-G guest

in the new cages, as the resulting assemblies can be readily

studied by NMR techniques (in contrast to encapsulation studies

of paramagnetic Co-G). The overnight reaction of pre-formed

Fe<sub>8</sub>(Zn-L·2)<sub>6</sub> in DMF with 1 equivalent of Zn-G, results in a 4:2

splitting of the <sup>1</sup>H-NMR signals of the cage, consistent with

6

•Observed •Theoretica

H<sub>2</sub>N<sup>'</sup> [(Fe<sub>8</sub>(Zn-L•2)<sub>6</sub>]<sup>7+</sup>

1623.0598

1623.0

Hol

1624.0

1625.0

8

1622.0

(B)

### **FULL PAPER**

(A)

desymmetrization of the host induced by binding of the guest. Additionally, the <sup>1</sup>H NMR peaks of the free **Zn-G** disappeared and three new strongly upfield shifted guest peaks appeared a 6.59, 5.6, and 2.49 ppm indicating internal binding of **Zn-G** (Figure 3B). When **Fe<sub>8</sub>(Zn-L-3)**<sub>6</sub> was stirred in the presence of **Zn-G**, the empty cage and free **Zn-G** were still in solution and no new signals belonging to the encapsulated guest were observed by HR-ESI-MS and NMR spectroscopy. In contrast, a

[(Fe<sub>8</sub>(Zn-L•2)<sub>6</sub>]<sup>14+</sup>

671.7

•Observed •Theoretica

672.3

m/z

671 4970

671.

ż



24 N

8 Fe(NTf<sub>2</sub>)<sub>2</sub> 70 °C, DMF

7 6 Chemical shift (ppm)

24

OPEG<sub>4</sub>

5

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a *in situ* approach in which, **Zn-G** and **Zn-L**, **3**, and the iron(II) triflimide were mixed in the correct stoichiometric ratios yielded the encapsulated catalyst, as no <sup>1</sup>H-NMR signals of the free guest (**Zn-G**) could be identified. In addition, similar upfield shifted peaks as in **Fe**<sub>8</sub>(**Zn-L·2**)<sub>6</sub> were observed (6.58, 5.62 and 2.5 ppm, Figure 3C). The observed  $\Delta \delta$  values of **Zn-G** upon encapsulation in the two novel cages are consistent with previous encapsulation studies of **Zn-G** in **Fe**<sub>8</sub>(**Zn-L·1**)<sub>6</sub> and with similar cubic self-assembled cages.<sup>[17]</sup> HR-ESI-MS of **Zn-G** @**Fe**<sub>8</sub>(**Zn-L-2**)<sub>6</sub> and **Zn-G** @**Fe**<sub>8</sub>(**Zn-L-3**)<sub>6</sub> yields spectra with signals in line with the desired species and associated only to structures in which one molecule of **Zn-G** is encapsulated inside the molecular cube (**Zn-G**@**Fe**<sub>8</sub>(**Zn-L·2**)<sub>6</sub> and **Zn-G**@**Fe**<sub>8</sub>(**Zn-L·3**)<sub>6</sub> Figure 3B and C). Importantly, DOSY of the two cages

(Zn-G@Fe<sub>8</sub>(Zn-L·2)<sub>6</sub> and Zn-G@Fe<sub>8</sub>(Zn-L·3)<sub>6</sub>) features a uniquely observed product with the same diffusion constant (3.35·10<sup>-6</sup> cm<sup>2</sup>s<sup>-1</sup> and 2.86·10<sup>-6</sup> cm<sup>2</sup>s<sup>-1</sup>) as the empty cages (Fe<sub>8</sub>(Zn-L·2)<sub>6</sub> and Fe<sub>8</sub>(Zn-L·3)<sub>6</sub>), but now including the upfield NMR signals that are from protons of the Zn-G guest (Figure 3B and C). Interestingly, the preparation of Zn-G@Fe<sub>8</sub>(Zn-L·2)<sub>6</sub> can be done via either the encapsulation of Zn-G in Fe<sub>8</sub>(Zn-L·2)<sub>6</sub> or via the one-pot reaction of all the subcomponents, whereas the synthesis of Zn-G@Fe<sub>8</sub>(Zn-L·1)<sub>6</sub> and Zn-G@Fe<sub>8</sub>(Zn-L·3)<sub>6</sub> is only feasible by the one-pot synthetic protocol. We ascribe this to the more electron-rich O-functionalized building blocks used for the synthesis of Zn-G@Fe<sub>8</sub>(Zn-L·1)<sub>6</sub> and Zn-G@Fe<sub>8</sub>(Zn-L·3)<sub>6</sub> leading to stronger pyridine binding to iron and therefore decreasing the dynamicity of the pyridyl-imine iron(II) moieties.



Figure 3. (A) Synthetic procedures of M-G@Fe<sub>8</sub>(Zn-L·2)<sub>6</sub> (left) and M-G@Fe<sub>8</sub>(Zn-L·3)<sub>6</sub> (right). (B) Obtained (red) and calculated (black) HR-ESI-MS for the 9<sup>+</sup> (left) and 12<sup>+</sup> (right) species of Co-G@Fe<sub>8</sub>(Zn-L·2)<sub>6</sub> and (C) for 9<sup>+</sup> (left) and 12<sup>+</sup> (right) species of Co-G@Fe<sub>8</sub>(Zn-L·3)<sub>6</sub>. (B) <sup>1</sup>H-DOSY NMR of Zn-G@Fe<sub>8</sub>(Zn-L·2)<sub>6</sub> and of (C) Zn-G@Fe<sub>8</sub>(Zn-L·3)<sub>6</sub> showing diffusion constants of 2.86<sup>-10<sup>-6</sup></sup> cm<sup>2</sup>s<sup>-1</sup> and 3.35<sup>-10<sup>-6</sup></sup> cm<sup>2</sup>s<sup>-1</sup>, respectively. Guest peaks are indicated with a circle.

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With the optimized synthetic protocols for encapsulation of Zn-G in hand, and having established the characterization of the diamagnetic assemblies Zn-G@Fe<sub>8</sub>(Zn-L·1)<sub>6</sub>, Zn-G@Fe<sub>8</sub>(Zn-L·2)<sub>6</sub> and Zn-G@Fe<sub>8</sub>(Zn-L·3)<sub>6</sub> based on the non-catalytic metalloporphyrin Zn-G, we next explored the encapsulation of catalytically active and paramagnetic cobalt(II)-tetra(4-pyridyl)porphyrin Co-G via the same approach (Figure 3A). Confirmation of encapsulation of the catalysts came from the HR-ESI-MS of the assemblies, and the spectra reveal signals

corresponding to the expected elemental composition [(Co-G@Fe<sub>8</sub>(Zn-L·2)<sub>6</sub>)(NTf<sub>2</sub>)<sub>16</sub> - x(NTf<sub>2</sub>)]<sup>x+</sup> and [(Co-G@Fe<sub>8</sub>(Zn-L·3)<sub>6</sub>)(NTf<sub>2</sub>)<sub>16</sub> - x(NTf<sub>2</sub>)]<sup>x+</sup> of both caged-systems (**Co-G@Fe<sub>8</sub>(Zn-L·2)<sub>6</sub>** and **Co-G@Fe<sub>8</sub>(Zn-L·3)<sub>6</sub>** Figure 3B and C). Additional support for the formation of the host-guest systems was provided by EPR, which reveals typical signals for an isolated (non-interacting)  $S = \frac{1}{2} Co^{II}(por)$  species with clearly resolved cobalt hyperfine. In contrast, the EPR signal of free **Co-G** itself is

Table 1. Control experiments and optimization of the reaction conditions or the cyclopropanation of styrene in cages. <sup>[a], [b]</sup>										
	$ \begin{array}{c} & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & \\ & & & \\ & & & & \\ & & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & $	a <b>talyst</b> (0.25 r Solvent, Δ, 3	mol %) 30 h ₽1	- o +o P2						
Entry	Catalyst	<i>T</i> [°C]	Conversion [%]	P1 [%]	P2 [%]					
1	Fe <sub>8</sub> (Zn-L·1) <sub>6</sub>	40		_	_					
2	Fe <sub>8</sub> (Zn-L·1) <sub>6</sub>	65		_	_					
3	Fe <sub>8</sub> (Zn-L·2) <sub>6</sub>	40		_	_					
4	Fe <sub>8</sub> (Zn-L·2) <sub>6</sub>	65		_	_					
5	Fe <sub>8</sub> (Zn-L·3) <sub>6</sub>	40	-	_	—	I				
6	Fe <sub>8</sub> (Zn-L·3) <sub>6</sub>	65	_	_	—					
7	Zn-G@Fe <sub>8</sub> (Zn-L·1) <sub>6</sub>	40	_	_	—					
8	Zn-G@Fe <sub>8</sub> (Zn-L·1) <sub>6</sub>	65		_	_					
9	Zn-G@Fe <sub>8</sub> (Zn-L·2) <sub>6</sub>	40	-	_	—					
10	$Zn-G@Fe_8(Zn-L\cdot 2)_6$	65	-	_	—					
11	Zn-G@Fe <sub>8</sub> (Zn-L·3) <sub>6</sub>	40	_	_	—					
12	$Zn-G@Fe_8(Zn-L\cdot 3)_6$	65	-	—	—					
13 <sup>[c]</sup>	Co-G@Fe8(Zn-L·1)6	40	90	76	14					
14	Co-G@Fe8(Zn-L·1)6	65	95	78	17					
15	Co-G@Fe <sub>8</sub> (Zn-L·1) <sub>6</sub>	40	96	84	12					
16[ <sup>c]</sup>	Co-G@Fe8(Zn-L·2)6	40	65.5	57	8.5					
17	Co-G@Fe <sub>8</sub> (Zn-L·2) <sub>6</sub>	65	70	58	12					
18	Co-G@Fe <sub>8</sub> (Zn-L·2) <sub>6</sub>	40	73	67.5	5.5					
19 <sup>[c]</sup>	Co-G@Fe <sub>8</sub> (Zn-L·3) <sub>6</sub>	40	51	45	6					
20	Co-G@Fe <sub>8</sub> (Zn-L·3) <sub>6</sub>	65	57	48.5	8.5	I				
21	Co-G@Fe <sub>8</sub> (Zn-L·3) <sub>6</sub>	40	63.5	60	3.5					

[a] Reaction conditions: Catalyst (0.25 mol %) with respect to **S2**, Styrene (**S1**, 0.16 mmol), ethyl diazoacetate (**S2**, 0.08 mmol) in DMF-d<sub>7</sub> (1 mL), 30 h under N<sub>2</sub> atmosphere. [b] Conversion of **S2** and yields with respect to **S2** were determined by <sup>1</sup>H NMR spectroscopy, using 1,3,5-trimethoxybenzene as internal standard. [c] **S2** was added without prior stirring of styrene and the catalyst.

very broad and does not show any hyperfine couplings due to self-aggregation causing substantial signal broadening as a result of spin-spin exchange coupling interactions.<sup>[17b]</sup> Encapsulation of **Co-G** within the cage assemblies leads to much sharper signals because the protective environment of the cage prevents self-aggregation. Interestingly, the formation of three different caged-systems with different exo-polarities shows that our strategy can be used to encapsulate metalloporphyrins with different metals (Zn and Co) inside cages with polar, apolar, and no peripheral functionalization.

Having established the preparation of three novel caged catalyst systems, we investigated the solubility in order to find a compatible solvent to perform our catalysis studies. Cages  $Co-G@Fe_8(Zn-L\cdot2)_6$  and  $Co-G@Fe_8(Zn-L\cdot3)_6$  proved to be

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soluble in DMF, acetone and acetonitrile, whereas **Co-G@Fe**<sub>6</sub>(**Zn-L-1**)<sub>6</sub> is soluble in a wide range of solvents (dimethylformamide, acetone, tetrahydrofuran, dichloromethane, toluene, and dichloromethane/hexane mixtures). As such, we focussed our catalysis investigation on utilizing DMF, as all the cages are soluble in this solvent and we have previously shown that DMF is a suitable solvent for these type of cobalt catalyzed cyclopropanation reactions.

Next, we conducted a series of control experiments, and optimized the reaction conditions. The results are summarized in Table 1. In a typical reaction, S1 (2 equiv.) and the catalyst were dissolved in DMF and stirred for 30 minutes before the addition of the diazo compound S2 (1 equiv.), as it generally led to lower dimer P2 formation (Table 1, entries 13, 16, 19 vs 15, 18, 21). Importantly, Fe<sub>8</sub>(Zn-L·1)<sub>6</sub>, Fe<sub>8</sub>(Zn-L·2)<sub>6</sub> Fe<sub>8</sub>(Zn-L·3)<sub>6</sub> and Zn-G@Fe<sub>8</sub>(Zn-L·1)<sub>6</sub>, Zn-G@Fe<sub>8</sub>(Zn-L·2)<sub>6</sub>, Zn-G@Fe<sub>8</sub>(Zn-L·3)<sub>6</sub> are not catalytically active, as performing the reaction at 40 or 65 °C did not vield any product (Table 1, entries 1-12). Following investigations on the effect of the temperature, a better catalytic performance was found when the reaction was done at 40°C vs 65 °C. (Table 1, entries 14, 17, and 20 vs 15, 18, and 21). Similar observations were obtained for all the caged catalysts (Co-G@Fe<sub>8</sub> (Zn-L·1)<sub>6</sub>, Co-G@Fe<sub>8</sub> (Zn-L·2)<sub>6</sub> and Co-G@Fe<sub>8</sub> (Zn-L·3)<sub>6</sub>), displaying an optimal reaction temperature of 40 °C, and revealing the importance of stirring the styrene with the supramolecular catalysts prior to addition of the diazo compound **S2** for our catalysis investigations.

With optimized reaction conditions for the three caged catalysts Co-G@Fe<sub>8</sub> (Zn-L·1)<sub>6</sub>, Co-G@Fe<sub>8</sub> (Zn-L·2)<sub>6</sub> and Co-G@Fe<sub>8</sub> (Zn-L-3)6, we studied the catalytic performance in terms of stability, activity, and selectivity. Table 2 shows the catalytic results for the cyclopropanation of S1 by using caged catalysts (0.25 mol %) with a hydrophobic (Co-G@Fe<sub>8</sub>(Zn-L·1)<sub>6</sub>), neutral (Cohydrophilic G@Fe<sub>8</sub>(Zn-L·2)<sub>6</sub>), and (Co-G@Fe<sub>8</sub>(Zn-L·3)<sub>6</sub>) peripheral environment. As we previously showed that Co-G@Fe8(Zn-L·1)6 outperforms both [Co(TPP)] and the free catalyst (Co-G), as encapsulation of Co-G leads to steric protection of cobalt-porphyrin catalyst (Co-G) from pyridinecobalt coordination and therefore hinders self-deactivation via the blockage of the catalytic cobalt center. We ascribe the increased conversion when using Co-G@Fe<sub>8</sub>(Zn-L·1)<sub>6</sub> compared to [Co(TPP)] to the increased local concentration of ethyl diazoacetate S2 and styrene S1 in the hydrophobic periphery environment of the cage, and hence also inside the cage, when compared to the bulk. In agreement with this hypothesis, interestingly, the enhanced performance of Co-G@Fe<sub>8</sub>(Zn-L·1)<sub>6</sub> is accompanied with more dimer P2 formation when compared to [Co(TPP)] and the guest catalyst (Co-G).

Table 2. Cyclopropanation of styrene with different cages and guests. <sup>[a], [b]</sup>											
Entry	Catalyst	Conversion [%]	P1 [%]	P2 [%]	P1/P2	TON <sup>[c]</sup>					
1	Co-G@Fe <sub>8</sub> (Zn-L·1) <sub>6</sub>	96	84	12	7	384					
2	Co-G@Fe <sub>8</sub> (Zn-L·2) <sub>6</sub>	73	67.5	5.5	12	292					
3	Co-G@Fe <sub>8</sub> (Zn-L·3) <sub>6</sub>	63.5	60	3.5	17	254					
4	Co-G	5	3	2	1.5	10					
5	[Co(TPP)]	71	70	1	70	284					

[a] Reaction conditions: Catalyst (0.25 mol %) with respect to S2, ethyl diazoacetate (S2, 0.32 mmol) and styrene (S1, 0.64 mmol) in solvent (1 mL), 40  $^{\circ}$ C, 30 h under N<sub>2</sub> atmosphere. [b] Conversion of S2 and yields with respect to S2 were determined by NMR spectroscopy, using 1,3,5-trimethoxybenzene as internal standard, and averaged from three measurements. [c] Turnover number (TON) was determined by dividing the conversion through the catalyst loading (conv/0.25).

Having concluded that the caged catalyst with apolar exofunctionalities (Co-G@Fe<sub>8</sub>(Zn-L·1)<sub>6</sub>) enhances catalytic activities compared to the non-encapsulated catalysts (free Co-G and [Co(TPP)]), we were interested to investigate the effect of the peripheral groups on the catalytic performance. The use of the exo-decorated cage analog Co-G@Fe<sub>8</sub>(Zn-L·3)<sub>6</sub> with 24 PEG-4 groups, in the cyclopropanation reaction, lowered the conversion to 63.5% (TON=254, Table 2, entry 2). Interestingly, P2 formation was decreased, as Co-G@Fe<sub>8</sub>(Zn-L·3)<sub>6</sub> suppressed dimerization by 2-fold compared to Co-G@Fe8(Zn-L·1)<sub>6</sub> (Table 2, entries 1 and 3). Compared to [Co(TPP)], the polar cage catalyst (Co-G@Fe<sub>8</sub>(Zn-L·3)<sub>6</sub>) results in lower conversions and cyclopropane yields (Table 2, entries 3 and 5), and a higher amount of dimer product P2 (1% vs 3.5%).

Further evidence that this is an effect of the cage periphery was obtained by the use of a cage without exo-funtionalities (Co-G@Fe<sub>8</sub> (Zn-L·2)<sub>6</sub>). Importantly, this catalyst system converted S2 to cyclopropane P1 in a yield of 67.5% (TON=292, Table 2, entry 2), which is lower than Co-G@Fe<sub>8</sub>(Zn-L·1)<sub>6</sub> and higher

than Co-G@Fe<sub>8</sub> (Zn-L·3)<sub>6</sub> (Table 2, entries 1 and 2). The apolar cage catalyst Co-G@Fe<sub>8</sub>(Zn-L·1)<sub>6</sub> leads to a P1/P2 ratio of 7, whereas this ratio is 12.3 and 17 for the non-functionalized Co-G@Fe<sub>8</sub>(Zn-L·2)<sub>6</sub> and polar Co-G@Fe<sub>8</sub>(Zn-L·3)<sub>6</sub> analogs, respectively (Table 2, entries 1, 2 and 3). Remarkably, the selectivity towards the desired product P1 decreases upon increasing the polarity of the cage periphery. These results indicate that the peripheral modification of the cage from polar to apolar increases the catalytic performance of the system in the cyclopropanation reaction. We ascribe this to a different local concentration of ethyl diazoacetate and styrene in the two cages, thus leading to different catalytic activities for the formation of both P1 and P2.

To gain more insight on the effect of the cage periphery, the reaction was monitored over time by <sup>1</sup>H NMR spectroscopy, from which the kinetic profiles in DMF for Co-G@Fe<sub>8</sub>(Zn-L·1)<sub>6</sub>, Co-G@Fe<sub>8</sub>(Zn-L·2)<sub>6</sub>, Co-G@Fe<sub>8</sub>(Zn-L·3)<sub>6</sub> and [Co(TPP]] were obtained (Figure 4). As the peripheral environment of the three novel cages differs in polarity, different kinetics are expected for

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each catalyst system. As shown in Figure 4, Co-G@Fe<sub>8</sub>(Zn-L·1)<sub>6</sub> is substantially more active than Co-G@Fe<sub>8</sub>(Zn-L·2)<sub>6</sub> and Co-G@Fe<sub>8</sub>(Zn-L·3)<sub>6</sub>, as evidenced by the initial TOF at 15% conversion (Figure 4). This indicates a higher degree of substrate accumulation in Co-G@Fe<sub>8</sub>(Zn-L·1)<sub>6</sub> compared to both Co-G@Fe<sub>8</sub>(Zn-L·2)<sub>6</sub> and Co-G@Fe<sub>8</sub>(Zn-L·3)<sub>6</sub>, thus leading to higher catalytic activity due to higher local concentrations of both

**S1** and **S2**. As is clear from Figure 4, reaction rates for both cyclopropanation and carbene dimerization are enhanced. The presence of 24 icosyl groups in the periphery of the cage (**Co-G@Fe<sub>8</sub>(Zn-L·1)**<sub>6</sub>) leads to higher substrate affinity for the periphery, and thereby the interior of the cage, and demonstrates the influence of the peripheral polarity of the cage



Figure 4. (A) Reaction profile of  $Co-G@Fe_8(Zn-L-1)_6$ , (B)  $Co-G@Fe_8(Zn-L-2)_6$ , (C)  $Co-G@Fe_8(Zn-L-3)_6$  and (D) [Co(TPP)] in the cyclopropanation of styrene at 0.25 % catalyst loading. (E) Plot of TOF<sub>ini</sub> for the formation of P1 calculated at 15% conversion. Data is obtained by fitting the initial part of the reaction rate curve of  $Co-G@Fe_8(Zn-L-1)_6$ ,  $Co-G@Fe_8(Zn-L-2)_6$ , C

on the catalytic rates. This trend shows that the exohydrophobicity of the cage framework has an indirect, but nonetheless significant impact on the affinity of the substrate towards the inner environment of the cage. If correct, inverse

polarity is expected to lead to slower catalytic rates in the cyclopropanation reaction. Indeed, lower activity is observed with the increased peripheral polarity of Co-G@Fe8(Zn-L·3)6, due to lower local substrate concentration in the cavity of the cage. Importantly, the catalytic activity of the cage with no exofunctionalities (Co-G@Fe8(Zn-L·2)6) is nearly two times lower than Co-G@Fe8(Zn-L·1)6 and three times higher than that of Co-G@Fe<sub>8</sub>(Zn-L·3)<sub>6</sub> (Figure 4E). Additionally, the catalytic activity of the confined catalyst Co-G@Fe8(Zn-L·2)6 compared to the non-encapsulated catalyst [Co(TPP)] is similar, whereas the activity of Co-G@Fe8(Zn-L·3)6 is 2 times lower than that of [Co(TPP)]. As cages Co-G@Fe<sub>8</sub>(Zn-L·1)<sub>6</sub>, Co-G@Fe<sub>8</sub>(Zn-L·2)<sub>6</sub> and Co-G@Fe<sub>8</sub>(Zn-L·3)<sub>6</sub> similarly confine the catalyst (Co-G), we attribute the differences in activity to different (relative) substrate affinities to the periphery of the cage catalysts, and thereby the interior of the cages, as a result of the peripheral functionalities.

#### Conclusion

In conclusion, we prepared three novel cubic cages that can bind catalytically active cobalt(II) meso-tetra(4-pyridyl)porphyrin. The cages differ in exo-decoration, which can be polar or apolar tails. By encapsulation of cobalt porphyrins as catalysts, this strategy provides three supramolecular caged catalyst systems with only different peripheral environment, which effect was probed in catalysis. For the cyclopropanation of styrene with ethyl diazoacetate, we observed an effect of these peripheral groups on the catalytic activity, with the exo-functionalized cage catalyst with apolar icosyl groups providing a higher activity (TOF<sub>ini</sub>) compared to the free bulk catalyst and cages with no or polar exo-functionalization (Co-G@Fe8(Zn-L·2)6 and Co-G@Fe<sub>8</sub>(Zn-L·3)<sub>6</sub>). The catalytic activity of the non exofunctionalized cage catalysts (Co-G@Fe<sub>8</sub>(Zn-L·2)<sub>6</sub>) was nearly two times lower than Co-G@Fe8(Zn-L·1)6 and three times higher than that of Co-G@Fe<sub>8</sub>(Zn-L·3)<sub>6</sub>. Remarkably, the peripheral modification of the cage catalysts from polar to apolar increases the catalytic activities in the cyclopropanation reaction and dimerization. We ascribe this effect to different (relative) substrate affinities to the cage that lead to different substrate local concentrations and thus to altered catalytic activities. The affinity of the substrates proved to be the highest when the apolar decorated cage (Co-G@Fe<sub>8</sub>(Zn-L·1)<sub>6</sub>) is used and the lowest for the polar analog (Co-G@Fe<sub>8</sub>(Zn-L·3)<sub>6</sub>).

#### **Experimental Section**

**General considerations:** All reactions involving air- or moisturesensitive compounds were carried out under nitrogen using standard Schlenk and vacuum line techniques. Unless noted otherwise, all reagents were of commercial grade and used without further purification. Dry DMF was kept under N<sub>2</sub> over molecular sieves. Styrene was filtered over basic alumina prior to use. <sup>1</sup>H NMR spectra were recorded on a Bruker AMX 400, Varian Mercury 300, Bruker DRX 500, Bruker DRX 300 or spectrometer, and they are referenced to the solvent residual signal (5.32 ppm for CD<sub>2</sub>Cl<sub>2</sub>, 7.32 ppm for CDCl<sub>3</sub>, 8.03 ppm for DMF-d7, 1.32 ppm for CD<sup>3</sup>CN and 2.08 ppm for toluene-d8). The temperature and the magnetic gradient were calibrated prior the measurement for 2D <sup>1</sup>H-DOSY NMR. High-resolution mass spectra were recorded on a HR-ToF Bruker Daltonik Gmbh Impact II, as ESI-ToF MS capable of a resolution of at least 4000 FWHM, coupled to a Bruker cryospray unit. The detection was done in positive-ion mode and the source voltage was between 4 and 6 kV. The flow rate was 18 uL/hr. The machine was calibrated prior to every measurement via direct infusion of a TFA-Na solution. For geometry optimizations of cages and caged-catalysts, Grimme's GFN2-xTB (Geometry, Frequency, Noncovalent, extended tight, binding) software was used.<sup>[16]</sup> Figures and images of the geometry-optimized structures were generated with UCSF Chimera software.<sup>[18]</sup> EPR spectra were recorded on a Bruker EMX X-band spectrometer equipped with an ER 4112HV-CF100 helium cryostat.

3: PEG-4 (1.7 mL, 9.73 mmol), cesium carbonate (3.2 g, 9.74 mmol), and dry DMF (230 mL) were added to a Schlenk flask under N2. The mixture was stirred at 100 °C for 1 h, after which 5-fluoropicolinaldehyde (1.2 g, 9.6 mmol) was added. The reaction mixture was heated at 100°C for 18 h, followed by cooling down to room temperature. The brown suspension was filtered through a celite pad and the DMF was removed under reduced pressure. The crude product was purified by flash column chromatography (SiO<sub>2</sub> Ethyl acetate/MeOH (100:1 to 100:5, v/v) which afforded the desired product 2 (1.9 g, 65%) as a yellow oil. <sup>1</sup>H-NMR (400 MHz, 298 K, CDCl<sub>3</sub>)  $\delta$  (ppm) = 9.98 (d, J = 0.8 Hz, 1H), 8.46 (d, J = 2.8 Hz, 1H), 7.95 (d, J = 8.7 Hz, 1H), 7.34 (ddd, J = 8.8, 2.8, 0.7 Hz, 1H), 4.30 - 4.27 (m, 2H), 3.92 - 3.89 (m, 2H), 3.75 - 3.65 (m, 11H), 3.62 -3.59 (m, 2H). <sup>13</sup>C NMR (101 MHz, 298 K, CDCl<sub>3</sub>) δ (ppm) = 61.68, 68.21, 69.37, 70.29, 70.53, 70.64, 70.90, 72.52, 77.06, 120.80, 123.34, 138.94, 146.35, 158.36, 192.01. HR-MS (ESI) theoretical calculation for C14H21NO6, m/z [M+H]\*: 300.1402, experimental result m/z [M+H]\* = 300.1387.

Fe<sub>8</sub>(Zn-L·2)<sub>6</sub>: Zn-L (0.144 g, 0.150 mmol) together with picolinaldehyde (0.062 g, 0.57 mmol), iron(II)triflimide (0.118 g, 0.191 mmol) and dry DMF (11 ml) were added to a Schlenk flask. The mixture was degassed by three cycles of freeze-pump-thaw, and heated at 70 °C for 18 h. The reaction mixture was cooled down to room temperature and stirred for 1 h. The purple-red solution was passed through a short pad of celite and precipitated in diethyl ether. The precipitates were collected by filtration and washed with diethyl ether (10 ml) and DCM (10 ml). The solids were collected by washing the filter with acetonitrile (100 ml) and the solvent was removed under reduced pressure afford Fe<sub>8</sub>(Zn-L·2)<sub>6</sub> as dark purple solid. (0.255 g, 80%). <sup>1</sup>H NMR (300 MHz, Acetonitrile-d<sub>3</sub>) δ (ppm) = 9.07 (s, 24H), 8.88 (s, 34H), 8.65 (d, J = 7.6 Hz, 28H), 8.51 (s, 24H), 8.42 -8.32 (m, 38H), 8.18 (dd, J = 19.0, 7.5 Hz, 44H), 8.03 (d, J = 8.2 Hz, 48H), **7.**87 (s, 36H), 7.53 (d, J = 5.3 Hz, 24H), 5.69 (d, J = 7.7 Hz, 60H). <sup>13</sup>C NMR (75 MHz, Acetonitrile-d<sub>3</sub>) δ 174.90, 158.48, 156.04, 149.70, 149.62, 142.97, 139.81, 137.88, 135.12, 131.64, 131.18, 129.88, 127.99, 1265.4, 124.6, 122.

Fe8(Zn-L·3)6: Zn-L (0.100 g, 0.095 mmol) together with 3 (0.114 g, 0.38 mmol), iron(II)triflimide (0.078 g, 0.127 mmol) and dry DMF (12 ml) were added to a Schlenk flask. The mixture was degassed by three cycles of freeze-pump-thaw, and heated at 70 °C for 20 h. The reaction mixture was cooled down to room temperature and stirred for 1 h. The purple-red solution was passed through a short pad of celite and precipitated in diethyl ether. The precipitates were collected by filtration and washed with diethyl ether (100 ml) and DCM (100 ml). The solids were collected by washing the filter with acetonitrile (100 ml) and the solvent was removed under reduced pressure to afford Fe<sub>8</sub>(Zn-L·3)<sub>6</sub> as dark purple solid. (0.292 g, 77%).<sup>1</sup>H NMR (500 MHz, Acetonitrile-d<sub>3</sub>) δ (ppm) 8.95 (s, 24H), 8.86 (d, J = 7.7 Hz, 38H), 8.58 (d, J = 8.9 Hz, 28H), 8.44 - 8.27 (m, 42H), 8.27 - 8.09 (m, 44H), 8.00 (s, 74H), 7.20 (s, 18H), 5.71 (s, 42H), 4.37 (s, 42H), 3.88 (s, 62H), 3.81 - 3.35 (m, 330H). <sup>13</sup>C NMR (75 MHz, Acetonitrile-d<sub>3</sub>) δ (ppm) = 173.44, 146.78, 135.77, 135.55, 132.77, 132.25, 128.51, 126.41, 125.21, 123.11, 122.9, 72.56, 71, 69.56, 61.85.

**Zn-G**@**Fe**<sub>8</sub>(**Zn-L**·2)<sub>6</sub>: To an oven-dried Schleck flask under nitrogen atmosphere were added **Fe**<sub>8</sub>(**Zn-L**·2)<sub>6</sub> (0.080 g, 0.006 mmol), **Zn-G** (4.1 mg, 0.006 mmol) and dry DMF (4 ml). The mixture was degassed by three cycles of freeze-pump-thaw, and heated at 70 °C for 18 h. The reaction mixture was cooled down to room temperature and stirred for 1

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h. The purple-red solution was passed through a short pad of celite and precipitated in diethyl ether. The precipitates were collected by filtration and washed with diethyl ether (100 ml) and DCM (100 ml). The remaining solids on the filter were collected by washing the filter acetonitrile (100 ml). The solvent was removed under reduced pressure to afford **Zn-G@Fe<sub>8</sub>(Zn-L·2)**<sub>6</sub> as a dark purple solid. (0.059 g, 69 %). <sup>1</sup>H-**NMR** (400 MHz, Acetonitrile-*d*<sub>3</sub>)  $\delta$  (ppm) 9.12 – 8.86 (m, 48H), 8.63 (s, 34H), 8.48 (s, 28H), 8.41 – 8.22 (m, 50H), 8.21 – 7.66 (m, 134H), 7.51 (d, *J* = 19.9 Hz, 32H), 6.59 (s, 8H), 5.67 (dd, *J* = 17.9, 8.1 Hz, 34H), 5.6 (s, 8H) 2.49 (s, 8H).

Zn-G@Fe<sub>8</sub>(Zn-L·3)<sub>6</sub>: To an oven-dried Schleck flask under nitrogen atmosphere were added Zn-G (8.45 mg, 0.012 mmol), Zn-L (0.078 g, 0.075 mmol), 3 (0.090 g, 0.3 mmol), iron(II)triflimide (0.062 g, 0.1 mmol) and dry DMF (7 ml). The mixture was degassed by three cycles of freeze-pump-thaw, and heated at 70 °C for 18 h. The reaction mixture was cooled down to room temperature and stirred for 1 h. The purple-red solution was passed through a short pad of celite and precipitated in diethyl ether. The precipitates were collected by filtration and washed with diethyl ether (100 ml) and DCM (100 ml). The remaining solids on the filter were collected by washing with acetonitrile (150 ml). The solvent was removed under reduced pressure to afford Zn-G@Fe<sub>8</sub>(Zn-L·3)<sub>6</sub> as a dark purple solid. (0.169 g, 73 %). 1H-NMR (400 MHz, 298 K, Acetonitrile-d<sub>3</sub>) δ (ppm) = 8.99 (d, J = 15.6 Hz, 58H), 8.61 (dd, J = 17.2, 9.0 Hz, 48H), 8.35 (dd, J = 21.5, 7.1 Hz, 62H), 8.24 - 7.76 (m, 114H), 7.22 (d, J = 17.2 Hz, 30H), 6.58 (s, 8H), 5.73 (s, 46H), 5.62 (s, 8H), 4.37 (s, 42H), 3.88 (s, 58H), 3.75 - 3.42 (m, 286H), 2.50 (s, 8H).

**Co-G**@**Fe**<sub>8</sub>(**Zn-L**·2)<sub>6</sub>: To an oven-dried Schleck flask under nitrogen atmosphere were added **Fe**<sub>8</sub>(**Zn-L**·2)<sub>6</sub> (0.080 g, 0.006 mmol), **Co-G** (4 mg, 0.006 mmol) and dry DMF (4 ml). The mixture was degassed by three cycles of freeze-pump-thaw, and heated at 70 °C for 18 h. The reaction mixture was cooled down to room temperature and stirred for 1 h. The purple-red solution was passed through a short pad of celite and precipitated in diethyl ether. The precipitates were collected by filtration and washed with diethyl ether (100 ml) and DCM (100 ml). The remaining solids on the filter were collected by washing the filter acetonitrile (100 ml). The solvent was removed under reduced pressure to afford **Co-G**@**Fe**<sub>8</sub>(**Zn-L·2**)<sub>6</sub> as a dark purple solid. (0.062 g, 74 %).

**Co-G**@**F**e<sub>8</sub>(**Zn-L**·**3**)<sub>6</sub>: To an oven-dried Schleck flask under nitrogen atmosphere were added **Co-G** (8.8 mg, 0.013 mmol), **Zn-L** (0.081 g, 0.078 mmol), **3** (0.093 g, 0.31 mmol), iron(II)triflimide (0.064 g, 0.1 mmol) and dry DMF (7 ml). The mixture was degassed by three cycles of freeze-pump-thaw, and heated at 70 °C for 18 h. The reaction mixture was cooled down to room temperature and stirred for 1 h. The purple-red solution was passed through a short pad of celite and precipitated in diethyl ether. The precipitates were collected by filtration and washed with diethyl ether (100 ml) and DCM (100 ml). The remaining solids on the filter were collected by washing with acetonitrile (150 ml). The solvent was removed under reduced pressure to afford **Co-G**@**Fe**<sub>8</sub>(**Zn-L·3**)<sub>6</sub> as a dark purple solid. (0.191 g, 79 %).

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# Entry for the Table of Contents

**FULL PAPER** 



Three novel cubic cages were synthesized and utilized to encapsulate a catalytically active cobalt(II) meso-tetra(4-pyridyl)porphyrin guest. The different polarity of the peripheral cage substituents influences the substrate availability of the catalysts embedded in the active site of the caged catalyst systems. This is demonstrated on the on the cyclopropanation reaction wherein the catalytic activity is the highest when the apolar cage catalyst (Co-G@Fe<sub>8</sub>(Zn-L·1)<sub>6</sub>) is used, and lowest with the polar analog (Co-G@Fe<sub>8</sub>(Zn-L·3)<sub>6</sub>).

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