ChemPubSoc Europe

DOI: 10.1002/cctc.201402726

A Double Conformationally Restricted Dynamic Supramolecular System for the Substrate-Selective Epoxidation of Olefins—A Comparative Study on the Influence of Preorganization

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Dedicated to Professor Christina Moberg on the occasion of her retirement and Professor Torbjörn Frejd on the occasion of his 70th birthday

A double conformationally restricted kinetically labile supramolecular catalytic system, the third generation, was designed and synthesized. We investigated the substrate selectivity of this system by performing competitive pairwise epoxidations of pyridyl- and phenyl-appended olefins. We compared the obtained substrate selectivities to previous less preorganized generations of this system. Five different substrate pairs were investigated, and the present double conformationally restricted system showed higher normalized substrate selectivities (pyridyl versus phenyl) for two of the substrate pairs than the previous less conformationally restricted generations. As for the preorganization of the components of the system, the catalyst, and the receptor part, it was shown that for each substrate pair there was one generation that was better than the other to generate substrate-selective catalysis.

Introduction

Despite the many successful examples of manmade homogeneous catalysts,[1] for example, in regioselective,[2] chemoselective, and enantioselective[3] transformations, very few address substrate selectivity.[4] One reason for this might be that those catalysts are designed and synthesized with the aim to catalyze a specific transformation for as broad a spectrum of substrates as possible.[4] Substrate-selective catalysts on the other hand are designed with the goal to display reactivity with only one substrate in a mixture containing several similar substrates. Another reason could be the hitherto lack of applications for substrate-selective catalysis.[4] However, one well-executed application of substrate-selective reactions is in the elucidation of reaction mechanisms for which the reaction is run in a competitive mode with carefully selected substrates to extract information about the mechanism.[4]

Although heterogeneous catalysis has appeared as a promising way to obtain substrate selectivity,[5] the mechanisms of heterogeneous catalysis are difficult to study,[6] which leads to difficulties in designing substrate-selective heterogeneous catalysts. In contrast, homogeneous catalysts are more amenable to design than heterogeneous ones owing to the higher mechanistic understanding of the former.[6] The masters of catalysis, the enzymes, are homogeneous catalysts that are able to swiftly transform one specific substrate in a mixture with others into one product with high enantio-, regio-, and chemoselectivity. Inspired by the efficiency of enzymes in these processes, supramolecular catalytic systems have been developed.[7] However, many suffer from poor turnover numbers,[7] and Sanders hypothesized that the fear of unfavorable entropy has brought supramolecular chemists in the direction of rigid systems that are too preorganized,[8] which leads to, among other things, mismatched transition states (TSs) and to product inhibition. To avoid these limitations on supramolecular catalysis, we wanted to use a kinetically dynamic catalytic cavity to achieve discrimination between substrates in homogeneous catalysis. Such an approach resembles the nonrigid catalytic cavities of enzymes, for which, for instance, product inhibition is limited and the catalytic cavity often self-assembled.

In the present study, we investigated how the degree of preorganization of the components of a dynamic supramolecular catalytic system influences the substrate selectivity in the ep-

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Supporting Information for this article is available on the WWW under http://dx.doi.org/10.1002/cctc.201402726.

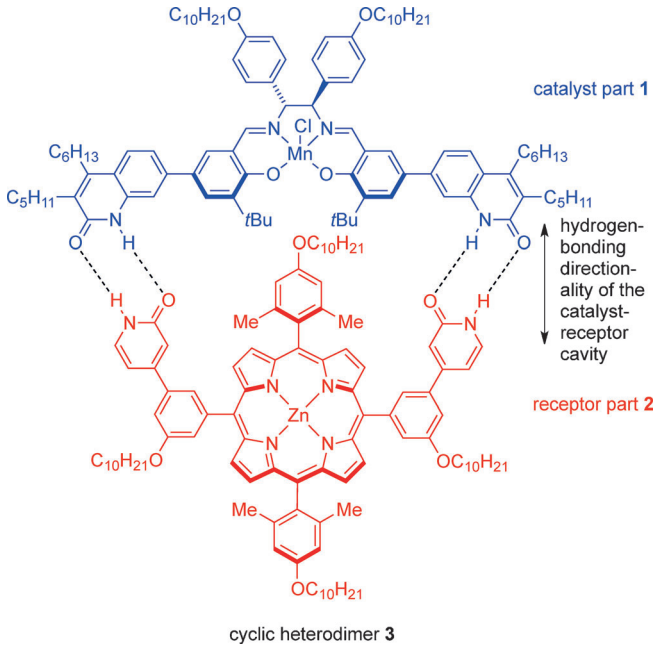


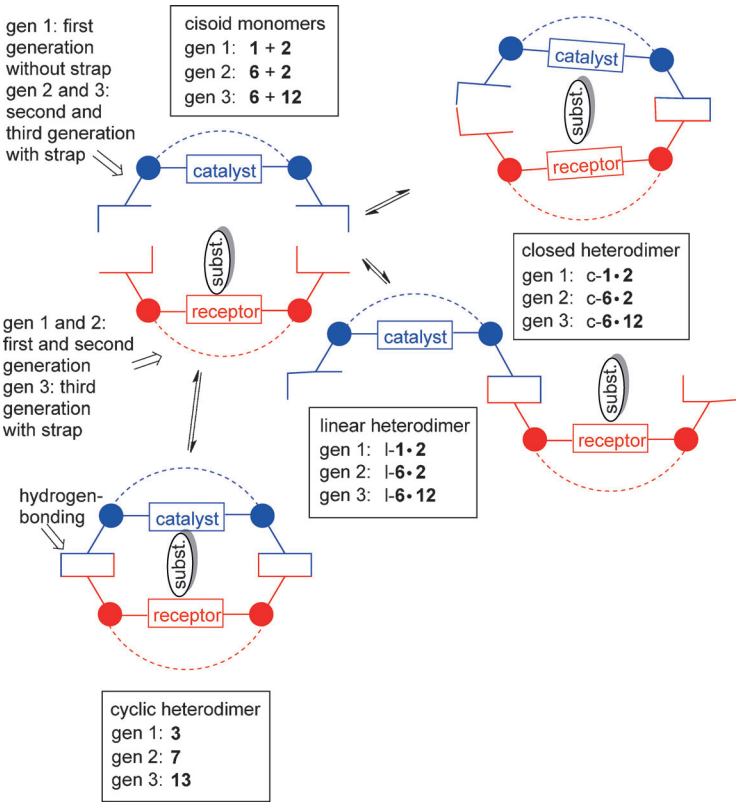
Figure 1. First generation of the supramolecular catalytic system, **1** + **2**. The supramolecular system is represented as so-designed substrate-selective cyclic heterodimer **3**.

oxidation of olefins. This was done by comparing the performance of the present, third-generation system (having the largest number of preorganized components) to the second generation (having an intermediate number of preorganized components) and the first generation (having the lowest number of preorganized components).

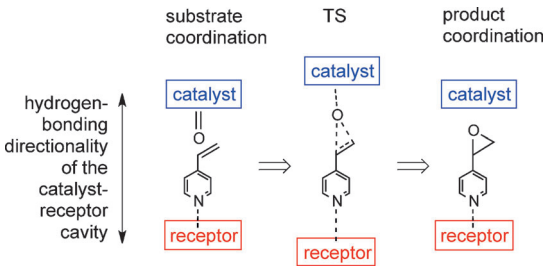
We took the first steps in this direction some years ago by designing and synthesizing catalytic Mn^{III}–salen complex **1** (Figure 1) on the basis of the Jacobsen–Katsuki (J-K) catalyst[9] and a receptor, Zn^{II}–porphyrin **2** (Figure 1), both designed to aggregate to a resulting cyclic heterodimer, supramolecular cavity **3** (Figure 1), constituting the first-generation system. The catalyst and receptor parts each contain the self-complementary and kinetically labile 2-pyridone motif, designed and geometrically positioned to promote the assembly of desired kinetically labile substrate-selective catalytic cavity **3** (Figure 1) at the expense of other self-assembled supramolecular species in solution,[10] according to the model **1** + **2** ⇌ **3** (schematically depicted in Scheme 1, cyclic heterodimer, gen 1).

To evaluate the system, the pairwise (1:1) competitive substrate-selective epoxidation of olefins was investigated for which the two substrates in each pair differed by only one atom (N or C). The epoxidation reaction was chosen, first, because there is a linear expansion–contraction in size upon going from substrate to product in that one oxygen atom is added during the reaction (Scheme 2). This expansion is in the same direction as that given by the two hydrogen-bonding systems, which allows the distance between the catalyst and receptor parts to linearly adjust accordingly owing to the dynamic nature of the hydrogen bond. This makes the epoxidation reaction the ideal reaction to be studied by our supramolecular catalytic cavity. Second, epoxides are important bulk chemicals that can be converted into different fine chemicals in a specific way by using one single synthetic transformation.[11] Third, olefins are obtained industrially as a mixture of different homologues in the cracking of oil. To be able to selectively epoxidize one of these homologues, instead of performing expensive and difficult separation of the very similar olefin homologues before the epoxidation, would be an important step toward the more sustainable production of epoxides.[4]

There are only a few examples of homogeneous substrate-selective catalysts that have been evaluated on the basis of their performance in competitive substrate-selective transformations.[4] However, for supramolecular catalysts, the epoxidation of alkenes constitutes the most commonly investigated type of reaction.[4] Hence, for use in epoxidation reactions, metalloporphyrins that discriminate substrates on the basis of their geometrical shape have been synthesized; the porphyrins have been decorated with large sterically encumbered groups[12] or have been part of a well-defined molecular basket.[13] More specific hosts such as metal-ion binding ligands[14a] and cyclodextrins[14b] have also been attached to metalloporphyrins. In addition, hydrogen-bonding recognition



Scheme 1. Schematic representation of the three generations of the dynamic supramolecular system and suggested substrate-selective supramolecular catalytic species in solution with a symbolic substrate inserted. Note: the distance between the catalyst and receptor parts is different between the opened and closed heterodimers.



Scheme 2. Proposed linear expansion and contraction of the catalyst–receptor cavity of the dynamic supramolecular system suggested to promote the different stages of the epoxidation of the pyridyl-appended olefin. This is possible because of the directionality of the hydrogen bonds attached to each unit (see Figure 1 and Scheme 1). The cartoon represents the dynamics of the so-designed substrate-selective cyclic heterodimer **3** (Figure 1).

elements have been attached to porphyrin-[15] and metallosalen-based[16] epoxidation catalysts. Finally, discrimination of substrates on the basis of the effective electron density at the catalytic center has also been observed.[17] However, no supramolecular catalyst for substrate-selective epoxidations, except ours, contains a catalyst part connected to a receptor part by hydrogen bonding and designed to generate a catalytic cavity. In fact, no such system has been developed at all and our first-generation system has for that reason been recognized as a new principle for the construction of supramolecular catalysts.[7b] For discrimination between substrates, we used the well-known interaction between pyridines and Zn^{II}–porphyrins.[18] Hence, to investigate the substrate selectivity of our supramolecular system, we incorporated one pyridyl moiety in one substrate and one phenyl moiety in the other, together constituting a substrate pair. Several substrates were constructed in silico, and the resulting TS structure in the epoxidation by using cavity **3** (Figure 1) containing the Mn=O reactive species was modeled by molecular mechanics (Figure 2).[19] It was found that (*Z*)-pyridyl-appended styrene **4a** (Scheme 3) made the least strained TS. Hence, compound **4a** became the pyridyl-appended alkene of choice to try in the substrate-selective epoxidation by using first-generation catalytic system **1**+**2**.

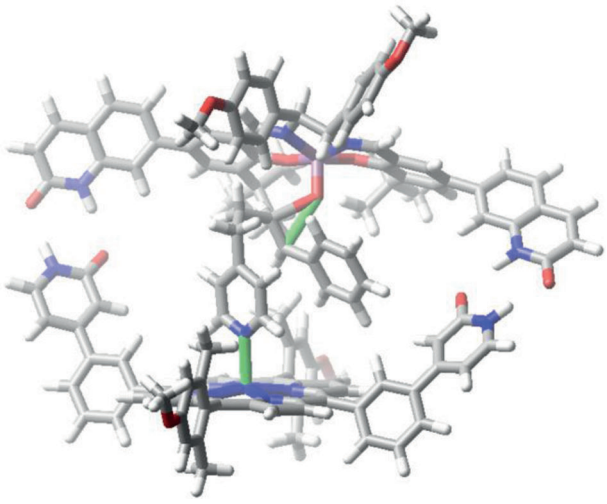
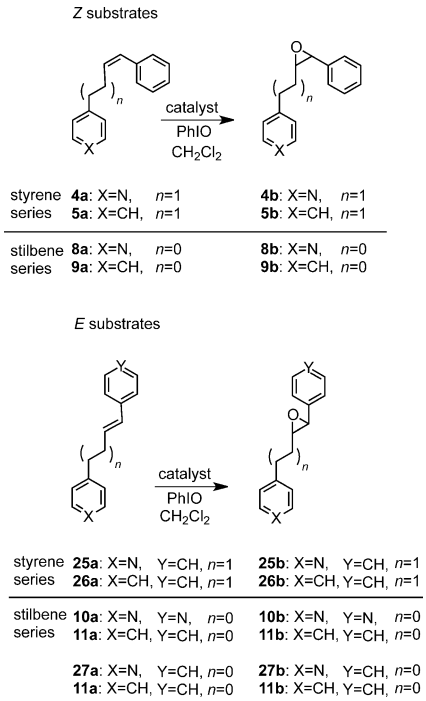


Figure 2. Molecular mechanics 3D representation of the TS in the epoxidation of receptor-bound substrate **4a** inside hydrogen-bonded cavity **3**.[19] Long alkyl-chain substituents are removed for clarity and ease of modeling. Zero-order bonds are colored green. This picture is also a model for the closed heterodimer (Scheme 1) that is assumed to be substrate selective.



Scheme 3. Competitive pairwise (1:1) epoxidation reactions in the styrene and stilbene series used to evaluate the substrate selectivity of the dynamic supramolecular catalytic system.

Indeed, a normalized[20] substrate-selectivity of 1.7 was observed in the pairwise (1:1) competitive epoxidation of (*Z*)-pyridyl-appended styrene **4a** over phenyl-appended **5a** (Scheme 3; Table 1, entry 11) by using system **1** (5 mM)+**2** (15 mM),[21,19] the highest for the first-generation system. This was rewarding, as according to the modeling, **4a** was the substrate that gave the least strained TS (see above). It was until then assumed that the model, **1**+**2**⇌**3** (schematically depicted in Scheme 1, gen 1), was valid, in which **3** constitutes a substrate-selective catalytic cavity. Owing to the hydrogen-bonding connection between the catalyst and receptor parts, the kinetic lability of the resulting catalytic cavity was supposed to generate a low-strain TS for the reaction and thus to give rise to a high turnover frequency in the catalytic cycle. The substrate selectivity was envisaged to arise from coordination of pyridyl-appended substrates to the *endo* side of receptor unit **2** in **3** to give rise to higher effective concentrations of pyridyl-appended substrates in the vicinity of **1** in **3** relative to the effective concentrations produced by substrates lacking a recognition element. The substrates and the products were expected to essentially display the same affinities with receptor unit **2**, which would possibly lead to product inhibition of the catalytic system. However, the reaction proceeded with good conversion,[19] and thus the similarities in affinities were rationalized to be overridden by the larger size of the epoxide products relative to the size of the alkene substrates. This is supposed to result in less-strong hydrogen bonding in the cata-

Table 1. Substrate selectivities obtained in the competitive pairwise (1:1) epoxidation of alkenes in the styrene and stilbene series catalyzed by the dynamic supramolecular systems.[a]

Entry	Catalyst (Concentration [mM])	Selectivity[b,c] (inherent or normalized/real)[20] **4a/5a**	**8a/9a**	**10a/11a**	**25a/26a**	**27a/11a**
1	**6** (5)	0.91	0.41	0.27	1.27	0.44
2	**28** (5)[19]	1.1	1.1	1.2	1.2	1.3
3	**6** (5)+**12** (5)	2.0/1.8	2.1/0.9	3.0/0.8	1.6/2.0	1.6/0.7
4	**6** (5)+**12** (12.5)	2.9/2.7	3.2/1.3	2.4[e]/0.6	2.1/2.6	2.2/1.0
5[d]	**6** (5)					0.51
6[d]	**6** (5)+**12** (5)					1.6/0.8
7	**6** (5)+**2** (5)[23]	1.8/1.6	2.1/0.8	2.2/0.6	2.0/2.5	1.2/0.55
8	**6** (5)+**2** (15)[23]	1.9/1.7	3.4/1.4	3.4/0.9	2.9/3.7	1.5/0.65
9[d]	**6** (5)+**2** (5)[23]	1.3/–			1.7/–	
10	**1** (5)+**2** (5)[19]	1.5/–	0.7/–	1.7/–	1.5/–	1.2/–
11	**1** (5)+**2** (15)[23]	1.7/–	0.6/–	2.4/–	1.6/–	1.4/–
12[d]	**1** (5)+**2** (5)[21]	1.3/–				

[a] General procedure: Catalyst part (3 μmol), receptor part (3, 7.5, or 9 μmol), substrate pairs (30 μmol each), PhIO (24 μmol), internal standard benzyl benzoate (15 μmol), CH_2Cl_2 (0.6 or 6 mL), RT. [b] See the Experimental Section and Ref. [20] for definitions. [c] Each experiment was repeated twice except for the experiment involving only the catalyst part, which was run only once. The selectivity was determined by GC analysis (double injections). The average result is reported. Accuracy = better than ±0.25. [d] 4-Ethylpyridine (90 μL, 0.72 mmol) was added. [e] This result was confirmed by repeating the reaction one more time according to [c].

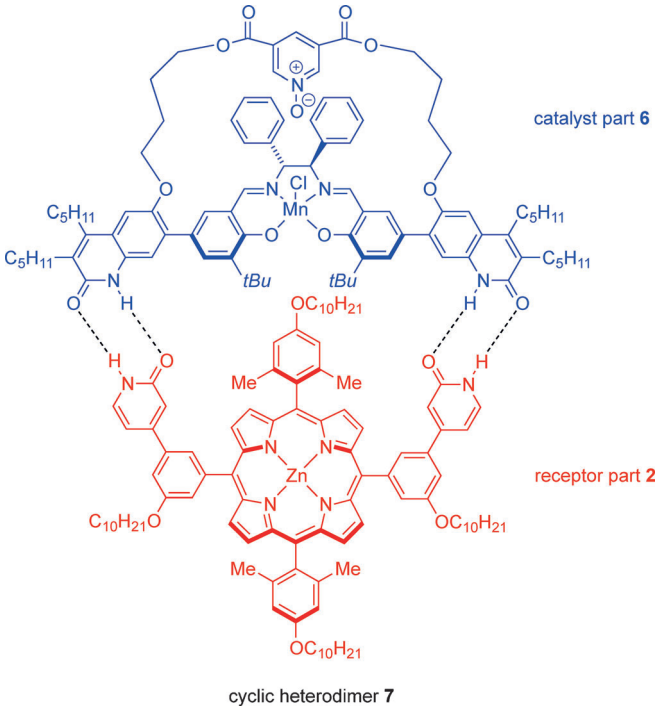


Figure 3. Second generation of the supramolecular catalytic system, **6**+**2**. The supramolecular system is represented as so-designed substrate-selective cyclic heterodimer **7**.

lyst–receptor product complex than in the corresponding catalyst–receptor substrate complex, which makes diffusion of the product from the catalytic cavity easier in the former case than in the latter; therefore, the catalytic cycle is pushed forward. The low but still significant substrate selectivity suggested a more complex system than the simple one represented by the **1**+**2**⇌**3** model (Figure 1). Analysis of the supramolecular system by NMR titrations followed by analysis of the existing equilibria and their quantification in terms of association constants showed that components **1** and **2** in $CDCl_3$ were not only in equilibrium with the catalytic cavity, cyclic heterodimer **3**, but also with linear homo-$\mathbf{1}_n$ and $\mathbf{2}_n$, noncyclic hetero-oligomers $\mathbf{1}_n\mathbf{2}_m$, (Scheme 1) and finally a trimer consisting of **2**, cyclo-$\mathbf{2}_3$ (Figure 6).[22,19] In fact, the degree of polymerization was low, so most of the oligomers existed as dimers.[22,19] Another analysis suggested that the large molar fraction of heterodimers could, in a conformation as a closed heterodimer, c-**1**·**2**, act as a substrate-selective species.[19] On the basis of the equilibrium analysis, we argued that to increase the substrate selectivity, the most straightforward action would be to increase the concentration of cyclic heterodimer **3**. By forcing components **1** and **2** into a *cisoid* conformation, a higher ratio of the substrate-selective cavity, the cyclic heterodimer, relative to that of other supramolecular species should be formed within the equilibrium system (Scheme 1).

Following this line, we managed to install a strap in catalytic part **1** to obtain catalytic part **6** (Figure 3).[23] Assumingly, this would thus lead to a higher molar ratio of the so-designed substrate-selective cavity (see above), compound **7**, in the second-generation system (Figure 3), according to **6**+**2**⇌**7** (schematically depicted in Scheme 1, gen 2), relative to that of previous system **1**+**2**. It was also assumed that the strap would somewhat hamper unselective catalysis from taking place on the *exo* side of **7**. To further assure this point, a pyridine *N*-oxide moiety was incorporated into the strap. Previously, a pyridine *N*-oxide had been strapped to a Mn^{III}–salen complex and its coordination to Mn^{III} was demonstrated by X-ray diffraction analysis of a crystal of the compound.[24] At the same time, it was proven that the presence of the pyridine *N*-oxide moiety in the strap did not affect the reactivity or the selectivity of the epoxidation reaction. In our case, we simply wanted the pyridine *N*-oxide strap to block the manganese ion from making a Mn=O species having the oxygen atom residing on the *exo* side of the catalyst–receptor complex, which would lead to unselective epoxidations. Rewardingly, in line with our expectations, this second-generation catalytic system, **6**+**2**, furnished higher substrate selectivity than the corresponding first-generation catalytic system, **1**+**2**; it reached a normalized substrate selectivity[20] of 3.4 for the competitive pairwise (1:1) epoxidation in the stilbene series of both (*Z*)-pyridyl **8a**/(*Z*)-phenyl **9a** and (*E*)-pyridyl **10a**/(*E*)-phenyl **11a** (Scheme 3; Table 1, entry 8).[23] Those were the highest substrate selectivities in the entire investigation of the second-generation system.

On the basis of a simple equilibrium analysis and to obtain an even higher ratio of the substrate-selective cyclic heterodimer, the next clear action is to also force the receptor part into a *cisoid* conformation by installing a strap on receptor part **2** (see above), which would lead to strapped receptor part **12**. Hence, herein we present the synthesis of strapped receptor

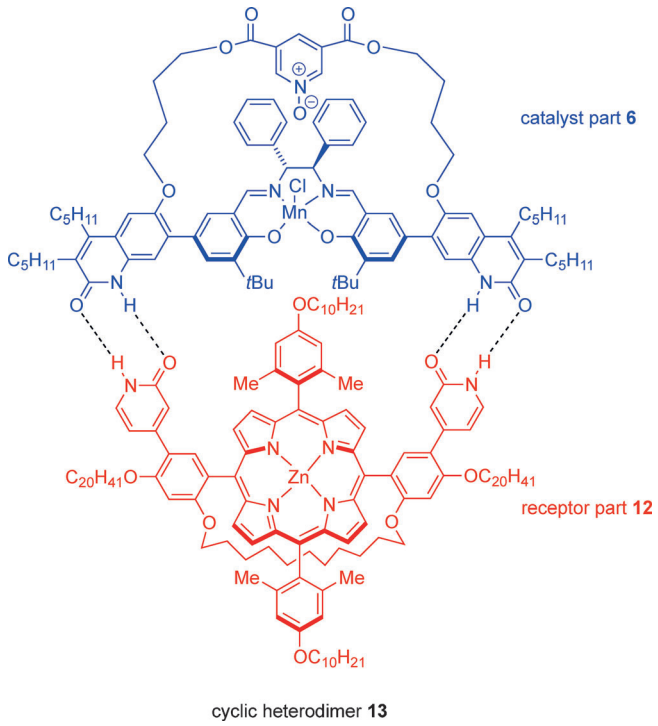


Figure 4. Third generation of the supramolecular catalytic system, **6**+**12**. The supramolecular system is represented as so-designed substrate-selective heterodimer **13**.

unit **12** to give the third-generation catalytic system, **6**+**12** (Figure 4), which is expected to result in a higher concentration of substrate-selective cavity **13** (Figure 4), according to **6**+**12**⇌**13** (schematically depicted in Scheme 1, gen 3), relative to that of the catalytic cavities of the earlier generations, cavities **3** and **7** (Figures 1 and 3).

Results and Discussion

Synthesis

Synthesis of catalyst part 6

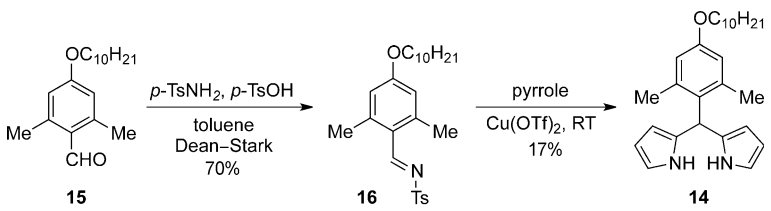
The synthesis of catalyst part **6** is described in our previous paper on the second-generation supramolecular catalytic system.[23]

Synthesis of receptor part 12

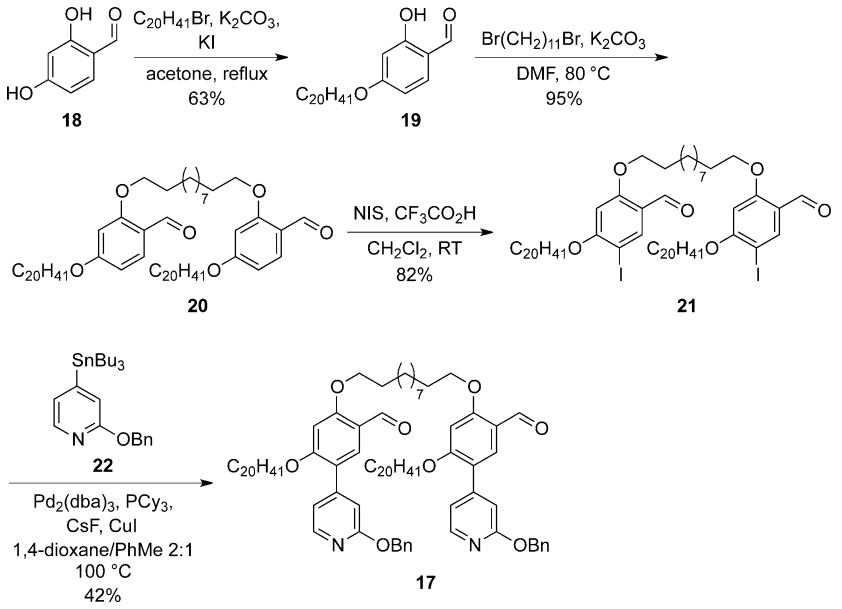
The synthesis of the receptor part, strapped Zn^{II}–porphyrin **12**, commenced by the synthesis of dipyrromethane **14** (Scheme 4), which was needed in the porphyrin condensation step. The synthesis of **14** started from known 2,6-dimethyl-4-decyloxybenzaldehyde (**15**).[19] Hence, compound **15** was condensed with *p*-toluenesulfonamide (*p*$TsNH_2$) to furnish tosylimine **16** in 70% yield. Dipyrromethane **14** was obtained in 17% yield by using the general methodology developed by Temelli and Unaleroglu,[25] which involved condensation of **16** with pyrrole in the presence of $Cu(OTf)_2$ Tf = CF_3SO_2 and application of the workup and purification procedures that we developed specifically for **14**. The overall sequence not only resulted in an overall higher yield of **14**, but also allowed the synthesis of **14** on a larger scale and with a simpler purification procedure than its original synthesis.[19]

The synthesis of required dialdehyde **17** for the condensation with dipyrromethane **14** to yield the porphyrin product started from commercially available 2,4-dihydroxybenzaldehyde (**18**, Scheme 5). Treatment of **18** with 1-bromoicosane by using conditions similar to those previously reported[26] furnished expected, less sterically encumbered regioisomer **19** in 63% yield. Strapping of **19** was performed by treating **19** with 1,11-dibromoundecane in the presence of potassium carbonate to give **20** in 95% yield. In the following step, compound **20** was subjected to *N*-iodosuccinimide (NIS) together with trifluoroacetic acid (TFA) to yield bisiodinated product **21** exclusively as the desired regioisomer in 82% yield. Compound **21** was used as an electrophile in a palladium-catalyzed double Stille cross-coupling reaction[27] with stannate **22**[19] as the nucleophile to furnish double-coupling product **17** in 29–42% yield. The yield of **17** varied presumably as a result of the presence of variable trace amounts of water in the reaction mixture. Support for this scenario was the identification of products from the competing iodine–hydrogen exchange reaction taking place on **21**, as moniodo-**21** and **20** were identified by ESI-MS. In fact, the highest yield was obtained if **21** and **22** were suspended in toluene and the resulting suspension was evaporated to dryness prior to the reaction to remove as much trace amounts of water as possible.

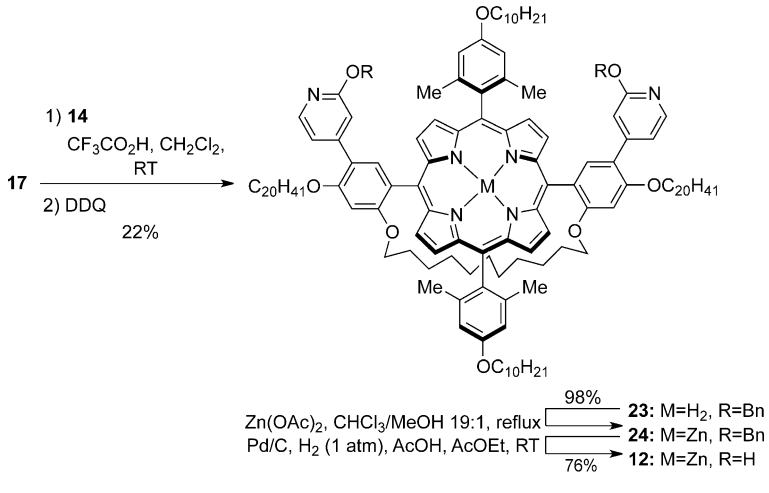
In the porphyrin condensation, aldehyde **17** was treated with dipyrromethane **14** in the presence of TFA, and the intermediate was oxidized with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) to yield porphyrin **23** in 16–22% yield (Scheme 6). Zn^{II} was inserted into **23** to furnish Zn^{II}–porphyrin **24** in 98% yield by using a standard protocol. Finally, palladium-mediated bis-de-*O*-benzylation of **24** under atmospheric pressure of H_2 gave target compound **12** in 76% yield after fast chromatography to avoid decomposition of the product. Noteworthy, the proton resonances of the methyl groups of the



Scheme 4. Synthesis of dipyrromethane **14** required for the porphyrin condensation reaction.



Scheme 5. Synthesis of aldehyde **17** required for the porphyrin condensation. Cy = cyclohexyl, dba = dibenzylideneacetone.



Scheme 6. Final steps in the synthesis of receptor part **12**: porphyrin condensation, zinc insertion, and deprotection.

aromatic rings at the *meso* position of **12** appeared at two different chemical shifts, which indicated that **12** was forced into a *cisoid* conformation at least on the timescale of the ^{1}H NMR spectrometer. For **2** on the other hand, the corresponding proton resonances of the methyl groups appeared at the same chemical shift, indicating that they are identical.[19] Another piece of evidence for the *cis* conformation of **12** is that the strap experiences ring current from the porphyrin ring, which places the resonances of its methylene protons at negative chemical shifts in the ^{1}H NMR spectrum.

Synthesis of the substrates

The substrates were obtained either from commercial sources (for **9a**, **10a**, **11a**, and **27a**) or were synthesized (for **4a**,[19] **5a**,[19] **8a**,[28] and **26a**).[29] Substrate **25a** was synthesized following a general procedure[30] and was characterized in our previous paper.[23]

Methodology

The catalysis

See the Experimental Section for details. To evaluate the substrate selectivity of a catalyst, the most correct method is to employ the substrates in competitive experiments.[4] In our case, we wanted to evaluate the effect on the substrate selectivity of having a pyridine auxiliary attached to an olefin in comparison to having a benzene auxiliary attached to an olefin in the epoxidation reaction. Discrimination between five olefinic substrate pairs (pyridyl- versus phenyl-appended) by catalytic system **6**+**12** on the basis of the interaction with the Zn^{II} moiety of the system was investigated in competitive pairwise (1:1) reactions. During the initial time of a reaction, the consumption of the substrate is linear with time. Thus, performing the competitive reactions in this linear region allows for the use of the ratio of the consumption of each substrate to be equivalent to the relative rate (the initial-rate method),[31] and thus, the substrate selectivity can be obtained directly. In our previous studies, we observed that a good compromise between reaction time and initial rate conditions in our systems was to terminate the reaction at approximately 40% conversion of each substrate.[23] Thus, 0.40 equivalents of the oxidant, PhIO, was added to each reaction, and to be able to calculate the consumption of each substrate, an internal standard (IS), benzyl benzoate, was added to each reaction mixture. It turned out that 40% conversion was reached after 24 h in almost all cases, and at that time the reaction was terminated by transferring the crude mixture to a silica column. Then, the organic starting materials and products were eluted together with the internal standard. The resulting sample was evaporated to dryness.

Analyzing the substrate consumption and product formation

See the Experimental Section for details. The consumption of the starting material was determined by gas chromatography (GC): a small amount of the dry sample was dissolved in diethyl ether, in which the Zn^{II}–porphyrin receptor part was insoluble; then, the solution was filtered through a microfilter and injected into the GC. The rest of the sample was dissolved in $CDCl_3$ and analyzed by ^{1}H NMR spectroscopy [except for

Table 2. Epoxide formation in CH_2Cl_2 at RT.[a]

Entry	Catalyst (concentration [mM])	Substrate pair	Total epoxide product[b] [%]	Epoxide selectivity pyridyl/phenyl[c]	Pyridyl epoxide *Z*/*E*
1	**6** (5)	**8a**/**9a**	67	0.77	1:0.7
2	**6** (5) + **12** (5)	**8a**/**9a**	92	1.60/1.23	1:0.6
3	**6** (5)	**27a**/**11a**	85	n.d.[d]	n.d.[d]
4	**6** (5)	**4a**/**5a**	79	0.53	n.d.[d]

[a] Each experiment was repeated twice except for the experiment involving only the catalyst part, which was run only once. The selectivity was determined by ^{1}H NMR spectroscopy. [b] The molar ratio of the total amount of epoxide products from both (*Z*)- and (*E*)-epoxides of both the pyridyl and phenyl substrates divided by the total amount of substrates consumed and multiplied by 100. The amount of epoxide was determined at approximately the same total conversion of the substrates, 40%. [c] Based on inherent or normalized/real values,[39] see text. [d] Overlapping peaks precluded determination of epoxide distribution.

(*Z*)-stilbene analogue **8a** (Scheme 3) that was analyzed by ^{1}H NMR spectroscopy in [D_6]DMSO as a result of *E*/*Z* isomerization caused by residual HCl in $CDCl_3$]. Owing to overlapping signals, the substrate consumption could not be analyzed by ^{1}H NMR spectroscopy except in one case (see below). For the same reason, the ratio of epoxide product versus other oxidation products could only be determined by ^{1}H NMR spectroscopy in a few cases (Table 2). For the analysis of substrate consumption by GC and/or ^{1}H NMR spectroscopy, a chromatogram and a spectrum, respectively, was recorded before and after the reaction. In the chromatogram and the spectrum, respectively, the area of each peak/signal of the substrate was normalized with the area of the internal standard, which allowed the correct determination of substrate consumption by subtracting the normalized area of each of the two substrates in each reaction before and after the reaction.

Validation of the GC methodology

For one substrate, (*Z*)-stilbene analogue **8a**, its consumption could be determined by both GC and ^{1}H NMR spectroscopy (see the Supporting Information), as one proton resonance did not overlap with any other signal. The difference in the so-determined conversion of **8a** was less than 3% between the two methodologies, which thus validated the use of the GC methodology.

Determination of the substrate selectivity

First, the inherent substrate selectivity[20] was determined by running the reaction with only the catalyst part. The inherent substrate selectivity is a measure of the rate difference in the epoxidation of the pairwise substrates caused by the difference in the electronic and steric interactions of each substrate with the catalyst part alone in the TS. Then, the reaction was run with both the catalyst part and the receptor part to obtain the real substrate selectivity.[20] However, a more accurate measure of the ability of the dynamic catalytic system to discriminate between the two substrates owing to the presence of the receptor is the normalized substrate selectivity.[20] The normalized substrate selectivity was obtained as the quota between the real and the inherent substrate selectivities, thus taking into account the substrate selectivity between the two substrates that the catalyst part itself has induced.

Catalysis

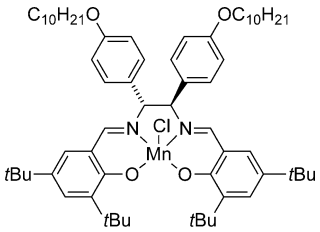
Substrate selectivity

The same substrate pairs (Scheme 3) that were investigated with the first generation, **1** + **2** (Figure 1), and the second generation, **6** + **2** (Figure 3), of the supramolecular catalytic system were investigated with the third-generation catalytic system, **6** + **12** (Figure 4), involving substrates from both the styrene and the stilbene series and of both *Z* and *E* configuration. For solubility reasons, the highest concentration of strapped receptor **12** was 12.5 mM compared to 15 mM for unstrapped receptor **2**.

In general, the first-generation system is not discussed because it generated much lower substrate selectivities than the second- and third-generation systems.

Catalyst part alone

First, the inherent reactivity difference between the substrates with catalyst part **6** itself was determined. As can be seen in Table 1, entry 1, the inherent substrate selectivity varied in such a way that the closer the pyridyl-appended group was to the alkene double bond in the substrate and the more pyridyl groups attached, the lower the reactivity. Thus, the stilbene series of substrates (Scheme 3) demonstrated the lowest reactivity as seen in the lowest inherent selectivity values. On the basis of this observation one might expect that the substrate having the highest electron density on the double bond would react the fastest with the electrophilic Mn=O species of the catalyst part of the supramolecular system. In fact, the J-K epoxidation partly involves a radical mechanism that results in a C–C bond in the TS, and this explains the formation of both (*E*)- and (*Z*)-epoxides from an alkene starting material with a specific stereochemistry.[32] However, the major mechanism involves concerted addition of the double bond to the Mn=O species,[33] which leads to an epoxide product with conserved stereochemistry. By running the competitive pairwise (1:1) reactions with the use of a congener of the J-K catalyst, compound **28**[19] (Figure 5), as the catalyst, inherent substrate selectivities very close to 1 were observed (Table 1, entry 2); this demonstrates that the electron density on the double bond of the substrate had in reality very little influence on the inherent substrate selectivity. Thus, one possible conclusion about the inherent substrate selectivity of catalyst part **6** alone, which exhibits much more pronounced inherent selectivities than **28** in the competitive pairwise (1:1) epoxidations of the investigated substrate pairs, is that **6** forms aggregates with pyridyl-appended substrates by (2-quinolidone)N–H···N(pyridine) hydrogen bonding. These aggregates might be able to exercise sub-



28

Figure 5. Congener **28** of the Jacobsen–Katsuki catalyst employed as a reference compound.

strate selectivity by being more reactive with one substrate than the other. Notably, the influence of the geometry of the double bond does not have such a large impact on the inherent substrate selectivity of **6**, as the substrate pairs of the same chemical composition but of different geometrical isomers, **4a**/**5a** and **25a**/**26a** (Scheme 3; Table 1, entry 1) on the one hand and **8a**/**9a** and **27a**/**11a** (Table 1, entry 1) on the other hand, show very similar inherent substrate selectivities.

Owing to the complex nature of the system with many different supramolecular aggregates present, as seen in the equilibrium analysis of **1**+**2**,[22] and for which the structure of each species is not well defined, all the rationalizations must be treated with caution. Nevertheless one attempt to explain the observed substrate selectivities of the catalytic part alone will be given: one conclusion about the aggregation of the first generation of the supramolecular catalytic system is that a large amount of its components exists as monomers and linear dimers at the concentration at which the catalytic reactions are run, for example at 5 mM for **6**,[22,19] At the same time, there is a large excess amount of substrate relative to that of the catalyst, and consequently a pyridyl-appended substrate is always reversibly coordinated to the 2-quinolidone moiety on each arm of catalyst **6** through (2-quinolidone)N–H···N(pyridine) hydrogen bonding between the pyridine unit of the substrate and one of the 2-quinolidone units of catalyst part **6**. Consequently, the pyridyl-appended substrate molecules will be somewhat delayed in their itinerary to the catalytic center of **6** relative to the phenyl-appended substrates. Thus, the phenyl-appended substrates will react faster, and this will result in a substrate selectivity (pyridyl- versus phenyl-appended substrates) of <1. The one exception is substrate **25a**, the most elongated of the substrates investigated, which reacted faster than phenyl congener **26a** (Table 1, entry 1). This result might be explained by the possibility that if **26a** hydrogen bonds reversibly to one of the 2-quinolidone moieties of catalyst **6** through (2-quinolidone)N–H···N(pyridine) hydrogen bonding between the pyridine and the 2-quinolidone moieties, the double bond of **26a** is placed more or less in the vicinity of the catalytic center of **6** relative to the vicinity of the other substrates and the epoxidation thus occurs more swiftly.

Catalyst part + receptor part

The normalized substrate selectivities (pyridyl- vs. phenyl-appended olefins) of the five substrate pairs in Table 1 were found to be 2.1–3.2 (mean 2.5) by using the third-generation dynamic catalytic system, **6**+**12**; 1.5–3.4 (mean 2.6) by using the second-generation system, **6**+**2**; and 0.6–2.4 (mean 1.5) by using the first-generation system, **1**+**2**, for which the catalyst concentration was 5 mM and the receptor concentration was 12.5 mM for **12** and 15 mM for **6** and **2**, respectively (Table 1, entries, 4, 8, and 11). Thus, taking our first-generation system as a reference point, it is clear that it is more important for our dynamic supramolecular catalytic system to have the catalyst part preorganized than the receptor part to obtain high substrate selectivity. This can be explained by considering that the strap on the catalytic part, in addition to preorganizing the catalyst part into a *cisoid* conformation to form a cyclic cavity, also blocks the *exo* side of the self-assembled cavities from participating in catalysis, and this hampers unselective catalysis.

The analyses below are based on the assumption that both systems **6**+**12** and **6**+**2** have the same type of supramolecular components as system **1**+**2**. For system **1**+**2**, the molar ratio of noncyclic heterodimer, closed c-**1·2** and linear l-**1·2** (Scheme 1), increases upon the addition of an excess amount of the receptor part on the basis of the equilibrium analysis of system **1**+**2**, whereas the molar ratio of cyclic heterodimer **3** is constant.[22,19] At this stage, this is the best assumption that can be done. Thus, all the conclusions must be treated with caution. We can also assume that because of the double strapping there is a higher molar ratio of the cyclic heterodimer in system **6**+**12** than in either **6**+**2** or **1**+**2**. Another assumption is that c-**1·2** is more substrate selective than l-**1·2** (Scheme 1).

Stilbene series

We started the investigation of the substrate selectivity of the third-generation catalytic system, **6**+**12**, by studying the competitive pairwise (1:1) epoxidation between the same two substrate pairs that gave the best result with the second-generation catalytic system, **6**+**2**, that is, (*Z*)-pyridyl **8a**/(*Z*)-phenyl **9a** and (*E*)-pyridyl **10a**/(*E*)-phenyl **11a**, both pairs in the stilbene series of substrates (Scheme 3).

For (*Z*)-stilbene pair **8a**/**9a**, the normalized substrate selectivity was the same as that for systems **6**+**12** and **6**+**2**, both at equal ratios of the catalyst and receptor parts, namely, 2 (Table 1, entry 3 vs. 7), and with an excess amount of the receptor part, namely, 3 (Table 1, entry 4 vs. 8). Given that the substrate selectivity increases in the same way for the two systems and that the absolute values are the same, this indicates that for substrate pair **8a**/**9a**, the substrate-selective catalytic species is the same, that is, c-**6·12** and c-**6·2**, respectively (see above). As an approximation, the equilibrium analysis of system **1**+**2** was used to rationalize this result.[22] This analysis showed that the molar ratio of cyclic cavity **3** was not affected by the increase in the concentration of the receptor part but that the molar ratio of the catalyst part bound to the receptor part as the next neighbor in hetero-oligomers, was doubled.[19] At the same time, the degree of polymerization was low.[22] This indicates that the substrate-selective catalyst for **8a**/**9a**

was the closed-heterodimer, c-**6·12** in the third-generation system and c-**6·2** in the second-generation system (Scheme 1), both of which generated the same substrate selectivity. It is also likely that the substrate selectivity induced by c-**6·12** and c-**6·2** is similar owing to their similar structures.

For (*E*)-stilbene pair **10a**/**11a**, **11a** containing two pyridyl groups, the normalized substrate selectivity showed abnormal behavior in that higher normalized substrate selectivity was obtained at a lower receptor concentration for **6**+**12** (Table 1, entry 3 vs. 4), whereas system **6**+**2** displayed the common higher normalized substrate selectivity at a higher concentration of receptor relative to that at a lower concentration (Table 1, entry 8 versus 7). The abnormal result might be explained by considering that with an excess amount of receptor part **12**, strapped in a *cisoid* conformation, **12** is perfectly preorganized to form a strong aggregating cyclic trimer, cyclo-(**12**)$_3$ (Figure 6). According to the equilibrium analysis of system **1**+**2**,[22] cyclic trimer cyclo-**2**$_3$ is one of the supramolecular aggregates in solution. Accordingly, there is also some cyclo-**2**$_3$ in excess amount of **2** also in system **6**+**2**, but because **2** is not as preorganized as **12**, it exists to a much smaller extent than cyclo-(**12**)$_3$ in system **6**+**12** (Figure 6). Now,

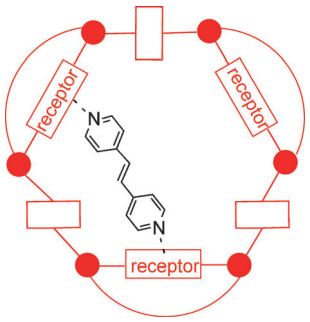


Figure 6. Proposed residing state of (*E*)-dipyridylstilbene congener **10a** bonded inside cyclo-(**12**)$_3$ in system **6**+**12** with an excess amount of **12**.

substrate **10a** might fit well into the cavity of cyclo-(**12**)$_3$, resulting in complex cyclo-(**12**)$_3$·**10a**, which then might constitute a resting state for **10a**, and this would retard the rate at which molecules of **10a** can reach any of the substrate-selective catalytic species; this paves the way for the epoxidation of phenyl-appended substrates **11a** (Scheme 3).

The third stilbene pair, *E* substrates **27a**/**11a**, showed normal behavior in that the normalized substrate selectivity increased upon going from system **6**+**2** to system **6**+**12** (Table 1, entry 3 vs. 7 and entry 4 vs. 8); the selectivity increased from 1.6 to 2.2 if an excess amount of the receptor part was present in system **6**+**12**. This substrate selectivity is higher than that for the earlier generations of the system and increases as we have observed with an excess amount of the receptor part. This indicates that the substrate-selective catalyst for **27a**/**11a** is closed-heterodimer c-**6·12** in the third-generation system and c-**6·2** in the second-generation system (Scheme 1) on the basis of the same reasoning as that for substrate pair **8a**/**9a** (see above) with one exception: the substrate selectivities of c-**6·12** and c-**6·2** are somewhat different and/or there is also a contribution from cavity **13** in the third-generation system.

Styrene series

The normalized substrate selectivity of the third-generation catalytic system, **6**+**12**, was investigated in the competitive pairwise (1:1) epoxidation of the styrene series of substrates. For (*Z*)-styrene pair **4a**/**5a**, the normalized substrate selectivity was about the same as that for system **6**+**2** if equal amounts of the catalyst part and receptor part were employed (Table 1, entry 3 vs. 7), but the selectivity increased considerably for system **6**+**12**, relative to that for system **6**+**2**, when the receptor part was in excess amount, from 2.0 to 2.9 for the former system (Table 1, entries 3 and 4), but almost nothing for the latter system, which stayed at 1.8–1.9 (Table 1, entries 7 and 8). This indicates that the substrate-selective catalyst for **4a**/**5a** is closed-heterodimer c-**6·12** in the third-generation system on the basis of the same reasoning as that for substrate pair **27a**/**11a** (see above). However, according to the same analysis, also the second-generation system should result in a higher substrate selectivity when the concentration of the receptor part is increased. Thus, one conclusion could be that there is a high content of c-**6·2** in the system, but the TS is not optimal for **4a**. An alternative conclusion could be that the substrate-selective catalyst is instead l-**6·2**, which generates low selectivity owing to the large distance between the catalyst and receptor parts (Scheme 1).

For the second substrate pair in the styrene series, *E* substrates **25a**/**26a**, the normalized substrate selectivity decreased with higher preorganization of the catalytic system, for both equal amounts of the catalyst part and receptor part as well as for an excess amount of the receptor part. However, in both systems **6**+**12** and **6**+**2** it increased when the receptor part was in excess amount. This points toward that cavity c-**6·12** in the third-generation system and cavity c-**6·2** in the second-generation system are the substrate-selective catalysts, and the resulting TSs are a little bit different between the cavities of both generations; this explains the difference in substrate selectivity. Alternatively, the substrate-selective species for this substrate pair could be linear heterodimer l-**6·12** for the third-generation system and l-**6·2** for the second-generation system. This result seems plausible, as both **25a** and **26b** are the largest substrates in this series, and as such, they could experience difficulties in entering the proposed catalytic cavity c-**6·12** in the third-generation system and c-**6·2** in the second-generation system.

Further analysis of the catalytic experiments

In general, owing to the complex nature of the system with many different supramolecular aggregates present, as seen in the equilibrium analysis of system **1**+**2**,[22,19] and for which in addition the structure of each supramolecular species in the system is not well defined, all rationalizations must be treated with caution. However, now in the third-generation system, **6**+**12**, for which both the catalyst and the receptor parts are

forced into a *cisoid* conformation, postulated substrate-selective catalytic cavities **13** (Figure 4 and Scheme 1) and c-**6·12** should be the major species in solution. Thanks to molecular modeling (Figure 2), we have a good indication that **13** should exert substrate selectivity in the epoxidations of at least some of our designed substrates such as **4a** versus **5a** (Figure 2). Moreover, compound **13** is the only substrate-selective species for which we have some idea of its structure and conformation and hence becomes the basis for the reasoning. In addition, it seems logical that the conformation of substrate-selective closed heterodimer c-**6·12** should be similar to that of **13** (Scheme 1) but with only one pyridone hydrogen-bonding motif in operation.

Rewardingly, the substrate selectivity for the epoxidation of (*Z*)-styrene pair **4a**/**5a**, for which the first-generation dynamic supramolecular system was designed with substrate-selective catalytic cavity **3** as the proposed unique supramolecular species in solution (Figure 2), was higher than that for corresponding *E* substrates **25a**/**26a** for system **6**+**12** (Table 1, entry 3 and entry 4), for which c-**6·12** (Scheme 1), close in conformation to **13** (Figure 4 and Scheme 1), were the suggested substrate-selective species. Simply changing the position of the phenyl group of **4a** to the "*E* position" (=compound **25a**) (using Figure 2 as a starting point) leads to a case in which the phenyl group clashed with the interior of catalytic cavity c-**6·12**, thus explaining the lower substrate selectivity of **25a**/**26a** compared to **4a**/**5a**. Interestingly, in system **6**+**2**, the above-mentioned selectivity was reversed, in that substrate selectivity for **25a**/**26a** was higher than for **4a**/**5a** in system **6**+**12** (Table 1, entry 7 vs. 3 and entry 8 vs. 4), which indicates that there are small differences in the TSs of the epoxidation reaction involving the cavity compounds of both systems as catalysts or that the linear heterodimers are the substrate-selective catalysts (see above).

For the two substrate pairs in the stilbene series, for which the pyridyl-appended substrate contains one pyridyl group, the result was that the *Z* substrate pair, **8a**/**9a**, showed a higher substrate selectivity than the *E* substrate pair, **27a**/**11a**, by using system **6**+**12** (Table 1, entries 3 and 4). The same trend was also observed for system **6**+**2**; however, it was not as pronounced, which supports the view that there are fewer substrate-selective species in the latter system than in the former system and that the observed substrate selectivity arises from the closed heterodimer. Finally, the third-generation system was also better than the previous generations in generating good substrate selectivity for **4a** and a geometrically very different substrate, **27a** (in competition with **11a**).

For the substrate pairs **8a**/**9a**, **10a**/**11a**, and **25a**/**26a**, the resulting TSs in the third-generation system was not optimal to obtain good substrate selectivity relative to that obtained for the earlier generations, for which, presumably, the more conformationally flexible closed heterodimer, c-**6·2**, was able to generate higher substrate selectivities for these substrates than c-**6·12**.

To make stronger statements about the origin of the substrate selectivity of the second- and third-generation systems and to suggest improvements in the design for a fourth-generation system, complete analysis of the system regarding all possible equilibria in each of these systems must be conducted, similar to the one that was executed for the first-generation system.[22,19] Of special importance in this context will be to verify that in the third- and second-generation systems there is a substantial amount of the cyclic catalytic cavities present, as assumed in the preliminary conclusions in the present work. However, it seems as though having a large amount of the catalytic cavities present does not lead to high substrate selectivity for all the investigated substrate pairs. However, the catalytic cavities in the complicated equilibrium mixture are the only species for which we can make some predictions about the structure and thus a prediction about the TS of the epoxidation reaction (Figure 2). Hence, continuing our efforts to increase the amount of the cyclic heterodimer and the closed heterodimer in a future fourth system is highly desirable. A clear structural change would be to lock the free rotation between the pyridone unit and the attached phenylene unit of porphyrin receptor **12** (Figure 4). That would lead to the loss of a smaller amount of conformational entropy upon aggregation with the catalyst part and stronger bonding and thus more of the desired cavity species. To evaluate if the closed heterodimer has a strong influence on the substrate selectivity, the catalyst and receptor parts should be modified to contain only one hydrogen-bonding moiety per part, which would thus ensure the formation of the closed heterodimer as the only substrate-selective cavity compound.

Real substrate selectivities

For practical uses of substrate-selective catalysts, it is more relevant to look at the real substrate selectivity.[20] In the third-generation system, **6**+**12**, the real substrate selectivity for pyridyl-appended substrates was ≥ 1 in four of five cases compared to three of five cases for the second-generation system, **6**+**2** (Table 1, entry 4 vs. 8). Notably, the obtained highest real substrate selectivity was for substrate pair styrene **25a**/**26a**, which reached a real substrate selectivity of 3.6 for system **6**+**2**. However, one should remember that the inherent substrate selectivity was positive in this case, 1.27 (Table 1, entry 1), unique to the series of substrates in the studies, thus we started from a case in which the substrate selectivity was already in favor of the pyridyl-appended substrate.

Inhibition studies

Adding a large amount of 4-ethylpyridine to the pairwise epoxidation reaction of **27a** versus **11a** by using system **6**+**12** did not affect the normalized substrate selectivity, as was the case for systems **6**+**2** and **1**+**2** (Table 1, entries 6, 9, and 12), for which the substrate selectivity decreased. This observation might be explained by the fact that this large excess amount of Lewis base will occupy all of the available Zn^{II} sites in the receptor part of systems **6**+**2** and **1**+**2**, which would make the pyridyl-appended substrates competing with 4-ethylpyridine for the binding sites. However, if both the catalytic part and the receptor part are strapped, a high amount of cavities of

c-**6**·**12** and **13** are formed that hampers binding of 4-ethylpyridine on the *exo* side of **12** in c-**6**·**12** and **13**, which makes it easier for the pyridyl-appended substrate to coordinate on the *endo* side because no 4-ethylpyridine, residing on the *exo* side, needs to be substituted to reach the square pyramidal coordination mode between the Zn^{II}–porphyrin and the pyridyl-appended substrate. Specifically, this result is in agreement with the proposition above that for substrate pair **27a**/**11a** in the third-generation system, the substrate selective species is c-**6**·**12**.

Turnover number (TON)

Despite the success of the J-K epoxidation, the overall utility of this catalyst is limited by its facile deactivation,[34] which is caused by the formation of Mn^{IV}–μ-oxo dimers[35] and irreversible ligand oxidation.[36] Thus, it is of interest to find out how the addition of receptor **12** to catalyst **6** affects the TON. Thus, first catalyst part **6** (5 mM), pyridyl-appended substrate **27a** (20 equiv.), and PhIO (1.5 equiv.) were stirred at room temperature for 1 week in CH_2Cl_2 to ensure that the reaction had reached completion (see the Experimental Section for details). After 1 week, the TON was determined to 9. Repeating the reaction in the presence of receptor part **12** (5 mM) increased the TON to 13. Thus, **12** provided some shelter for catalyst part **6**. The observed low TON for system **6**+**12** should be regarded in perspective that substrate **27a** is a large substrate that is sterically encumbered and possesses a coordinating functionality. A similar approach was already taken by Nguyen and Hupp; they added Zn^{II}–TPP (TPP = tetraphenylporphyrin) to a double 4-pyridyl-appended Mn^{III}–salen complex, which resulted in a rather open Mn catalyst with two big side walls. The TON increased from 51 to 92 by adding Zn^{II}–TTP and by using the standard compound, styrene, as the substrate.[34] In comparison, the TON in the epoxidation of styrene with PhIO in CH_2Cl_2 by using the catalyst part of the first-generation system, compound **1** (1 mM), and an equimolar amount of pyridine *N*-oxide was determined to be 149.[19] By adding a fourfold excess amount of receptor **2** to the original mixture of **1** and pyridine *N*-oxide, reaching the composition of the first generation of our supramolecular catalytic system, the TON was raised to 162.[19] A further comparison was provided by a congener of J-K catalyst, compound **28**, and the TON was determined to be 37 in the epoxidation of styrene[34] but in the absence of pyridine *N*-oxide. The reason for the lower TON in the case of **6**+**12** might be that *E* alkenes (**27a** is an *E* alkene) are epoxidized more slowly than *Z* alkenes,[37] and during this time the catalyst is deactivated, which results in a small amount of consumed *E* alkene. Nevertheless, for both catalysts **6** and **1**, the addition of a "cap", receptor parts **12** and **2**, respectively, protected the catalytic Mn site from forming catalytically inactive Mn^{IV}–μ-oxo dimers as was, for instance, demonstrated by Hupp in epoxidations of alkenes by using self-assembled capped Zn^{II}–porphyrin–Re molecular squares as catalysts.[38]

Product selectivity

Although the study of the product selectivity[39] was not the major issue in this investigation, some information can be obtained from the ^{1}H NMR spectra originally intended to be used to determine the conversions of the substrates (see the Experimental Section and the Supporting Information), but overlapping proton resonances in the spectra made it difficult to use ^{1}H NMR spectroscopy for this purpose. From the studies of the J-K epoxidation of olefins, it is known that besides epoxides, other oxidation products are also formed such as aldehydes and alcohols.[40] For systems **1**+**2** and **6**+**2**, a rough estimation of the amount of epoxide formed was 70%.[19,21,23] Owing to the difficult assignment and overlapping proton resonances in the ^{1}H NMR spectra, we were only able to determine the total formation of epoxide and the distribution, pyridyl/phenyl and (*Z*)-pyridyl/(*E*)-pyridyl, respectively, for a few substrate pairs when **6**+**12** was used as the catalytic system (Table 2, see the Experimental Section and the Supporting Information for details). Fortunately, in one case, a comparison between the epoxidation involving only the catalyst part **6**, and the combined catalyst–receptor system **6**+**12**, could be made, namely, for the *Z* substrates in the stilbene series, **8a**/**9a**. For this system, as seen in Table 2, entries 1 and 2, the total amount of epoxide relative to that of the other products was substantially increased in the system containing both the catalyst part and the receptor part, **6**+**12**, in comparison to the case in which **6** alone was employed in CH_2Cl_2 (5 mM of each components); this indicates that with the receptor present, the catalytic system is more specific to the formation of epoxide than to the formation of other products or that the system consisting of a catalyst part and a receptor part simply experiences a longer lifetime so that more epoxide is formed. The system was not analyzed for other products so we do not know which case is the correct one. On the basis of this one unique observation, it is of course impossible to make generalizations for the other substrates. As seen in the same entries, a radical mechanism is most probably involved to a large extent on the basis of the high degree of formation of both the *Z* and *E* diastereoisomers of the pyridyl-appended epoxide, (*Z*)-**8b**/(*E*)-**8b**(**27b**), by employing stilbene **8a** (*Z* diastereoisomer) as the starting material. The observed *Z*/*E* ratio is not affected by the presence or absence of the receptor part, as seen in Table 2, entries 1 and 2. The other entries in Table 2 are included just to report the full study by including the cases for which product-selectivity values were possible to extract by analyzing the reaction mixtures of the competitive epoxidations in Scheme 3 by ^{1}H NMR spectroscopy.

Conclusions

The purpose of the present work was to increase the substrate selectivity of a dynamic supramolecular catalytic system for the epoxidation of pyridyl- versus phenyl-appended substrates by increasing the preorganization of the catalyst part and receptor part by having each part into a *cisoid* conformation in an attempt to increase the amount of the proposed substrate-se-

lective cavity. The present system, the third generation, was compared to the two previous less preorganized generations of the catalytic system.

Specifically, the third-generation system showed results that might be explained by the formation of a high amount of the substrate-selective cavities, that is, designed cyclic heterodimer **13** and, maybe above all, closed heterodimer c-**6·12** (Scheme 1). Thus, the pyridyl-appended substrate that was designed to best fit the catalytic cavity of the designed catalytic cyclic heterodimers, (*Z*)-styrene **4a**, gave a higher substrate selectivity over phenyl-appended congener **5a** than the earlier less preorganized systems. This was also true for geometrically very different **27a** (in competition with **11a**). However, for the three other substrates, the resulting transition states of each of the reactions catalyzed by the cyclic heterodimers of the third-generation system were not optimal to obtain good substrate selectivity relative to that obtained with earlier generations. Thus, the overall conclusion about the substrate selectivity of the dynamic supramolecular system with respect to the studied epoxidation reaction and the given substrate pairs is that each substrate pair needs a specific level of preorganization of the components to give optimal substrate selectivity. However, the results show that to obtain good substrate selectivity it is better to have the catalyst part preorganized than the receptor part. This can be explained by considering that the strap, in addition to preorganizing the catalyst part into a *cisoid* conformation to form cyclic cavities, also blocks the *exo* side of the self-assembled cavities from participating in catalysis, which thus hampers unselective catalysis.

To obtain firmer statements about the origin of the substrate selectivity of the second- and third-generation systems and to suggest improvements in the design for a fourth-generation system, complete analysis of the system regarding all possible equilibria in each of these systems has to be conducted, just like the one that was executed for the first-generation system.[19,22] Such analyses are currently underway in our laboratory.

Nevertheless, we showed that the present dynamic supramolecular catalytic systems can generate substrate selectivity and turnover numbers in an important organic transformation involving structurally advanced substrate pairs. Our results might have bearing on the construction of other supramolecular catalysts and is a contribution to the ongoing discussion about the need for preorganization in supramolecular catalytic systems.[8]

Experimental Section

General

All chemicals were used as received, unless otherwise stated. CuI was recrystallized from saturated aqueous potassium iodide and then dried for 1 week under vacuum (0.4 mbar) at 80 °C prior to use. CH_2Cl_2 was distilled from CaH_2 and stored over 4 Å molecular sieves. Pyrrole was distilled from CaH_2 at reduced pressure. Dry 1,4-dioxane was purchased from Acros Organics. Toluene was dried by distillation over sodium/benzophenone ketyl prior to use. Acetone was dried over Na_2SO_4. For petroleum ether (PE), the 40–60 °C fraction was used. PhIO was prepared by the hydrolysis of commercially available diacetoxyiodobenzene following a literature procedure.[41] The glassware used for anhydrous conditions was dried in an oven for 24 h at 140 °C. Column chromatography was performed with Acros Organics (40–60 μm, 60 A) silica. TLC analyses (Merck 60 F254 sheets) were visualized under UV light (254 or 366 nm). Catalytic reaction mixtures were filtered through an Acrodisc CR 13 mm syringe filter with a 0.2 μm polytetrafluoroethylene membrane. GC was performed with a Hewlett Packard (5890 A) instrument (Agilent Technologies, Santa Clara, CA, USA). The following protocol was used: VA-1 column, 30 m × 0.25 mm × 0.25 μm (Varian Chromatography System, Walnut Creek, CA, USA), helium as carrier gas, flow gradient was from 0.5 to 3 mL min^{-1} with a ramp of 0.1 mL min^{-1}, oven the temperature from 140 to 185 °C with a ramp of 2 °C min^{-1}, then to 220 °C with a ramp of 10 °C min^{-1}, then hold for 6 min. NMR spectra were recorded with a Bruker DRX400 NMR spectrometer; ^{1}H NMR spectra were recorded at 400 MHz and ^{13}C NMR spectra were recorded at 100 MHz in $CDCl_3$ or [D_6]DMSO. Chemical shifts are reported in ppm relative to an internal standard of residual chloroform ($\delta = 7.26$ ppm for ^{1}H NMR; $\delta = 77.16$ ppm for ^{13}C NMR) and residual DMSO ($\delta = 2.50$ ppm for ^{1}H NMR). The NMR assignment of the synthesized molecules was performed with the aid of coupling constants and 2D correlation NMR experiments. HRMS was performed with a Waters micromass Q-Tof instrument. A. Kolbe, Mikroanalytisches Laboratorium, Germany, performed the elemental analyses.

Syntheses

4-Decyloxy-2,6-dimethylbenzaldehyde *N*-tosyl imine (16): *p*-Toluenesulfonamide (30.9 g, 0.180 mol) and *p*-toluenesulfonic acid (1.5 mmol) were added to a solution of **15**[19] (8.7 g, 0.030 mol) in toluene (290 mL). The mixture was heated at reflux under Dean–Stark conditions overnight. The mixture was cooled to RT before water was added. The formed precipitate was filtered off, and the aqueous phase was extracted with toluene. The combined organic layer was washed with water and brine, dried with magnesium sulfate, and evaporated under reduced pressure. Heptane was added to the crude product, which was collected as an orange oil, and the crystallization of **16** started immediately at RT. The mixture was placed in the fridge for a few hours and was then collected on a filter to afford the title compound (9.6 g 70%) as white crystals. M.p. 42.1–42.9 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 9.41$ (s, 1H), 7.90 (d, $^3J_{H,H} = 8.40$ Hz, 2H), 7.34 (d, $^3J_{H,H} = 8.00$ Hz, 2H), 6.63 (s, 2H), 4.01 (t, $^3J_{H,H} = 6.80$ Hz, 2H), 2.62 (s, 6H), 2.44 (s, 3H), 1.82–1.75 (m, 2H), 1.44–1.25 (m, 14H), 0.91–0.87 ppm (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 168.03, 163.20, 146.24, 143.89, 136.51, 129.94, 129.65, 127.65, 127.33, 121.55, 115.67, 68.16, 31.89, 29.54, 29.31, 29.04, 26.08, 25.93, 22.84, 22.68, 22.50, 21.62, 14.12 ppm; HRMS (FAB): *m/z*: calcd. 444.2494 $[M+1]^+$; found: 444.2564; elemental analysis calcd (%) for $C_{26}H_{37}NO_3S$ (443.64): C 70.39, H 8.41, N 3.16; found: C 70.68, H 8.06, N 3.08.

5-(4-Decyloxy-2,6-dimethylphenyl)dipyrromethane (14): $Cu(OTf)_2$ (0.904 g, 2.50 mmol) was added to a solution of **16** (9.5 g, 20.6 mmol) in freshly distilled pyrrole (34 mL, 490 mmol). The solution turned black immediately. The mixture was stirred at RT overnight. The solution was filtered through a pad of silica, eluting with EtOAc. Pyrrole was removed by bulb-to-bulb distillation to collect a black solid crude product. The crude product was purified by chromatography (PE to PE/EtOAc = 9:1; $h = 10$ cm, $d = 5$ cm). A final crystallization (PE/EtOAc = 19:1) at −20 °C furnished the title compound (1.4 g, 17%) as an off-white solid. $R_f = 0.59$ (PE/EtOAc = 8:2). The spectroscopic data of the title compound were in agree-

ment with the published ones;[19] elemental analysis calcd (%) for $C_{27}H_{38}N_2O$ (406.60): C 79.76, H 9.42, N 6.89; found: C 79.66, H 9.09, N 6.87.

2-Hydroxy-4-(icosyloxy)benzaldehyde (19): K_2CO_3 (2.8 g, 20 mmol) and KI (323 mg, 2.0 mmol) were added to a solution of **18** (2.7 g, 20 mmol) and 1-bromoicosane (7.2 g, 20 mmol) in dry acetone under an atmosphere of N_2. The resulting mixture was heated at reflux for 40 h. After this time, the mixture was filtered while warm through a filter paper, and the collected filtrate was concentrated under reduced pressure. CH_2Cl_2 (100 mL) and aqueous HCl (1 M, 100 mL) were added. The phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (100 mL). The combined organic layer was concentrated to dryness under reduced pressure, and the furnished concentrate was purified by column chromatography ($CHCl_3$/PE = 1:8 to 1:7 to 1:4; h = 15 cm, d = 5 cm) to furnish the title compound (5.3 g, 63%) as a white solid. R_f = 0.35 (EtOAc/hexane = 1:3); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 11.48 (s, 1H), 9.70 (s, 1H), 7.41 (d, $^3J_{H,H}$ = 8.8 Hz, 1H), 6.52 (dd, $^4J_{H,H}$ = 2.3 Hz, $^3J_{H,H}$ = 8.8 Hz, 1H), 6.41 (d, $^4J_{H,H}$ = 2.3 Hz, 1H), 4.00 (t, $^3J_{H,H}$ = 6.6 Hz, 2H), 1.82–1.75 (m, 2H), 1.48–1.40 (m, 2H), 1.33–1.25 (m, 32H), 0.88 ppm (t, $^3J_{H,H}$ = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 194.41, 166.60, 164.67, 135.31, 115.13, 108.92, 101.17, 68.74, 32.07, 29.85, 29.82, 29.81, 29.79, 29.72, 29.68, 29.51, 29.45, 29.06, 26.06, 22.84, 14.26 ppm; HRMS (ESI): m/z: calcd for $C_{27}H_{46}O_3$: 441.3345 $[M+Na]^+$; found: 441.3334; elemental analysis calcd (%) for $C_{27}H_{46}O_3$ (418.65): C 77.46, H 11.07; found: C 77.41, H 11.05.

2,2′-[Undecane-1,11-diylbis(oxy)]bis[4-(icosyloxy)benzaldehyde] (20): 1,11-Dibromoundecane (1.32 mL, 5.65 mmol) was added to a suspension of **19** (4.73 g, 11.3 mmol) and K_2CO_3 (3.9 g, 11.3 mmol) in anhydrous DMF (300 mL) at RT under an atmosphere of N_2. After the addition, the temperature was increased to 80 °C, and the mixture was stirred for 10 h. Then, the mixture was allowed to reach RT before H_2O (400 mL) and CH_2Cl_2 (400 mL) were added. The two phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (2×400 mL). The combined organic layer was washed with brine (2×400 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification of the residue by column chromatography ($CHCl_3$/PE = 1:3 to 1:1 to 3:1 to 1:0; h = 14 cm, d = 5 cm) gave the title compound (5.3 g, 95%) as a white solid. R_f = 0.45 (EtOAc/PE = 1:9); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.32 (s, 2H), 7.78 (d, $^3J_{H,H}$ = 8.7 Hz, 2H), 6.50 (dd, $^4J_{H,H}$ = 2.1 Hz, $^3J_{H,H}$ = 8.7 Hz, 2H), 6.42 (d, $^4J_{H,H}$ = 2.1 Hz, 2H), 4.04–3.98 (m, 8H), 1.86–1.72 (m, 8H), 1.51–1.20 (m, 82H), 0.87 ppm (t, $^3J_{H,H}$ = 7.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 188.49, 165.90, 163.49, 130.27, 119.02, 106.31, 99.04, 68.57, 68.53, 32.05, 32.01, 29.83, 29.79, 29.72, 29.68, 29.63, 29.58, 29.50, 29.48, 29.42, 29.22, 29.14, 26.18, 26.09, 22.82, 22.82, 14.25 ppm; HRMS (ESI): m/z: calcd for $C_{65}H_{112}O_6$: 989.8537 $[M+H]^+$; found: 989.8538; elemental analysis calcd (%) for $C_{65}H_{112}O_6$ (989.58): C 78.89, H 11.41; found: C 78.91, H 11.39.

6,6′-[Undecane-1,11-diylbis(oxy)]bis[4-(icosyloxy)-3-iodobenzaldehyde] (21): TFA (1.11 mL, 14.5 mmol) was added dropwise to a solution of **20** (4.77 g, 4.82 mmol) and NIS (2.43 g, 10.6 mmol) in CH_2Cl_2 (175 mL) under an atmosphere of N_2 at RT. The resulting mixture was stirred for 20 h. After this time, the reaction was quenched with aqueous $Na_2S_2O_3$ (10% *w/v*, 150 mL). The phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (2×150 mL). The combined organic phase was dried ($MgSO_4$), filtered, and concentrated to dryness under reduced pressure. The obtained residue was purified by silica column chromatography ($CHCl_3$/PE = 1:1 to 3:1; h = 8 cm, d = 10 cm) to furnish the title compound (4.9 g, 82%) as a white solid. R_f = 0.53 (Et_2O/PE = 3:7); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.21 (s, 2H), 8.20 (s, 2H), 6.34 (s, 2H), 4.07–4.04 (m, 8H), 1.88–1.82 (m, 8H), 1.57–1.25 (m, 82H), 0.87 ppm (t, $^3J_{H,H}$ = 6.6 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 187.23, 163.87, 163.49, 138.97, 120.39, 96.35, 76.33, 32.07, 29.85, 29.81, 29.72, 29.68, 29.59, 29.51, 29.40, 29.11, 29.01, 26.15, 22.84, 14.28 ppm; HRMS (ESI): m/z: calcd for $C_{65}H_{110}I_2O_6$: 1241.6470 $[M+H]^+$; found: 1241.6537; elemental analysis calcd (%) for $C_{65}H_{110}I_2O_6$ (1241.38): C 62.89, H 8.93; found: C 62.66, H 9.03.

6,6′-[Undecane-1,11-diylbis(oxy)]bis{3-[2-(benzyloxy)pyridin-4-yl]-4-(icosyloxy)benzaldehyde} (17): Diodo compound **21** (1.0 g, 0.81 mmol) and stannate **22**[19] (1.5 g, 3.2 mmol) were suspended in PhMe (30 mL), and then the mixture was evaporated to dryness. The residue was dried under vacuum (0.4 mbar) overnight. CsF (539 mg, 3.55 mmol), CuI (307 mg, 1.61 mmol), and dry 1,4-dioxane/PhMe (2:1, 48 mL) were added to the solid residue, and the resulting suspension was degassed and a N_2 atmosphere was introduced. Then, PCy_3 (452 mg, 1.61 mmol) and $Pd_2(dba)_3$ (147.3 mg, 0.161 mmol) were added under a N_2 atmosphere. The mixture was heated to 100 °C for 72 h under a N_2 atmosphere. The mixture was allowed to reach room temperature, and the solvent was removed under reduced pressure. The furnished crude product was purified by column chromatography (Et_2O/PE = 1:4 to 2:5 to 3:7; h = 12 cm, d = 5 cm) to give the title compound (420 mg, 42%) as a white solid. R_f = 0.26 (CH_2Cl_2/Et_2O = 39:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.37 (s, 2H), 8.16 (d, $^3J_{H,H}$ = 5.5 Hz, 2H), 7.89 (s, 2H), 7.49–7.47 (m, 4H), 7.39–7.36 (m, 4H), 7.33–7.29 (m, 2H), 7.07 (dd, $^4J_{H,H}$ = 1.4 Hz, $^3J_{H,H}$ = 5.4 Hz, 2H), 7.00 (br s, 2H), 6.49 (s, 2H), 5.42 (s, 4H), 4.12 (t, $^3J_{H,H}$ = 6.2 Hz, 4H), 4.06 (t, $^3J_{H,H}$ = 6.6 Hz, 4H), 1.91–1.85 (m, 4H), 1.82–1.75 (m, 4H), 1.54–1.21 (m, 82H), 0.88 ppm (t, $^3J_{H,H}$ = 6.7 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 188.02, 163.96, 163.82, 162.66, 147.89, 146.18, 137.63, 130.54, 128.48, 127.84, 127.76, 120.90, 118.51, 118.06, 111.39, 96.17, 69.01, 68.89, 67.62, 32.03, 29.81, 29.76, 29.69, 29.62, 29.60, 29.52, 29.47, 29.40, 29.35, 29.14, 28.95, 26.17, 22.79, 14.23 ppm; HRMS (ESI): m/z: calcd for $C_{89}H_{130}N_2O_8$: 1355.9905 $[M+H]^+$; found: 1355.9934; elemental analysis calcd (%) for $C_{89}H_{130}N_2O_8$ (1356.00): C 78.83, H 9.66, N 2.07; found: C 78.84, H 9.65, N 2.06.

Porphyrin 23: A solution of TFA (32 mg, 281 μmol) in CH_2Cl_2 (0.2 mL) was added to a solution of **17** (95.2 mg, 70.2 μmol) and dipyrromethane **14** (56.9 mg, 140 μmol) in CH_2Cl_2 (28 mL) under a N_2 atmosphere at room temperature in a 50 mL round-bottomed flask covered with aluminum foil. The mixture was stirred for 55 min. After this time, DDQ (47.8 mg, 211 μmol) was added, and the mixture was stirred for an additional hour. Then, the solvent was removed under reduced pressure, and the residue was purified by silica column chromatography (Et_2O/hexane = 1:19 to 3:17; h = 13 cm, d = 2 cm) to furnish the title compound (32.9 mg, 22%) as a red solid. R_f = 0.37 (Et_2O/hexane = 1:3); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.80 (d, $^3J_{H,H}$ = 4.8 Hz, 4H), 8.65 (d, $^3J_{H,H}$ = 4.8 Hz, 4H), 8.18 (d, $^3J_{H,H}$ = 5.6 Hz, 2H), 8.14 (s, 2H), 7.45–7.43 (m, 4H), 7.39 (d, $^3J_{H,H}$ = 5.6 Hz, 2H), 7.34–7.24 (m, 8H), 7.01 (s, 4H), 6.97 (s, 2H), 5.40 (s, 4H), 4.28 (t, $^3J_{H,H}$ = 6.4 Hz, 4H), 4.23 (t, $^3J_{H,H}$ = 6.3 Hz, 4H), 3.88 (t, $^3J_{H,H}$ = 5.0 Hz, 4H), 1.99–1.85 (m, 8H), 1.88 (s, 3H), 1.85 (s, 3H), 1.65–1.27 (m, 102H), 0.94–0.87 (m, 16H), −0.25 to −0.31 (m, 4H), −1.14 to −1.22 (m, 4H), −1.84 to −1.91 (m, 4H), −2.52 (br s, 2H), −2.72 to −2.76 ppm (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.94, 160.91, 158.96, 157.82, 149.52, 145.92, 141.12, 140.76, 137.56, 136.67, 134.15, 128.52, 127.97, 127.82, 125.17, 119.51, 118.67, 117.43, 114.70, 112.95, 112.76, 111.64, 99.33, 70.77, 69.14, 68.20, 67.87, 32.08, 31.11, 29.89–29.80 (overlapping methylene carbon resonances), 26.77 26.60, 26.49, 26.43, 25.51, 24.87, 22.88, 22.85, 22.25, 22.05, 14.31, 14.28 ppm; HRMS (ESI): m/z: calcd for $C_{143}H_{196}N_6O_8$: 1064.2652 $[M+2H]^{2+}$; found: 1064.2638; elemental

analysis calcd (%) for $C_{143}H_{196}N_6O_8$ (2127.13): C 80.74, H 9.29, N 3.95; found: C 80.54, H 9.41, N 3.99.

Zn^{II}–porphyrin 24: A solution containing **23** (28 mg, 13.2 μmol) and $Zn(OAc)_2{\cdot}2H_2O$ (17.3 mg, μmol) in $CHCl_3$/MeOH (19:1, 30 mL) under a N_2 atmosphere was stirred at 64 °C for 4 h. The mixture was allowed to reach RT before the solvent was removed under reduced pressure. The residue was purified by silica column chromatography (Et_2O/PE = 1:3) to furnish the title compound (28.3 mg, 98%) as a red solid. R_f = 0.39 (Et_2O/hexane = 1:3); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.90 (d, $^3J_{H,H}$ = 4.7 Hz, 4H), 8.75 (d, $^3J_{H,H}$ = 4.7 Hz, 4H), 8.17 (s, 2H), 8.16 (d, $^3J_{H,H}$ = 5.4 Hz, 2H), 7.43–7.39 (m, 6H), 7.32–7.22 (m, 8H), 7.00 (s, 4H), 6.96 (s, 2H), 5.39 (s, 4H), 4.28 (t, $^3J_{H,H}$ = 5.3 Hz, 4H), 4.23 (t, $^3J_{H,H}$ = 5.6 Hz, 4H), 3.88 (t, $^3J_{H,H}$ = 5.5 Hz, 4H), 2.00–1.93 (m, 8H), 1.84 (s, 12H), 1.66–1.26 (m, 96H), 0.93–0.86 (m, 16H), −0.27 to −0.34 (m, 4H), −1.17 to −1.24 (m, 4H), −1.80 to −1.88 (m, 4H), −2.77 to −2.80 ppm (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.07, 160.83, 158.76, 157.65, 150.78, 150.21, 149.28, 146.05, 140.95, 140.60, 137.70, 136.61, 134.73, 132.07, 130.70, 128.49, 127.91, 127.75, 125.82, 119,39, 118.64, 118.50, 115.77, 112.87, 112.68, 111.56, 99.23, 70.70, 69.12, 68.18, 67.65, 32.08, 30.11, 29.89–29.52 (overlapping methylene carbon resonances), 28.00, 26.78, 26.72, 26.50, 26.44, 26.00, 24.85, 22.88, 22.85, 22.23, 22.09, 14.31, 14.28 ppm; HRMS (ESI+): *m/z*: calcd for $C_{143}H_{194}N_6O_8Zn$: 1094.7198 $[M+2H]^{2+}$; found: 1094.7191.

Zn^{II}–porphyrin 12, the receptor part: Pd/C (70 mg, 10% *w/v*) was added to a degassed solution of **24** (48 mg, 21.9 μmol) and AcOH (50 μL) in EtOAc (60 mL) under an atmosphere of N_2. The mixture was degassed, and a N_2 atmosphere was introduced. The mixture was degassed one more time, and an atmospheric pressure of H_2 was introduced by using a balloon. After 12 h, the solvent was removed under reduced pressure, and the residue was purified by very fast (≈20 min) silica column chromatography (CH_2Cl_2/MeOH = 39:1 to 19:1; h = 12 cm, d = 2 cm) to furnish the title compound (33.3 mg, 76%) as a pink solid. The title compound constituted the last pink band that eluted from the column. R_f = 0.25 (CH_2Cl_2/MeOH = 19:1); ^{1}H NMR (400 MHz, c = 4.15 mg mL^{-1} in $CDCl_3$ containing 2.4% *v/v* [D_5]pyridine): δ = 8.74 (d, $^3J_{H,H}$ = 4.7 Hz, 4H), 8.66 (d, $^3J_{H,H}$ = 4.7 Hz, 4H), 7.99 (br s, 2H), 7.24–7.21 (m, 4H), 6.94–6.93 (m, 6H), 6.88 (s, 2H), 6.75–6.73 (m, 2H), 4.25 (t, $^3J_{H,H}$ = 6.2 Hz, 4H), 4.16 (t, $^3J_{H,H}$ = 6.6 Hz, 4H), 3.82 (t, $^3J_{H,H}$ = 4.5 Hz, 4H), 1.96–1.90 (m, 8H), 1.76 (s, 3H), 1.71 (s, 3H), 1.59–1.23 (m, 100), 0.87–0.82 (m, 16H), −0.22 to −0.29 (m, 4H), −1.08 to −1.15 (m, 4H), −1.88 to −1.99 (m, 4H), −2.48 to −2.57 ppm (m, 2H), the NH peak of the pyridone moieties appeared at 11.89 ppm at c = 6 mg mL^{-1} in $CDCl_3$ containing 6% *v/v* of [D_5]pyridine; HRMS (ESI): *m/z*: calcd for $C_{129}H_{182}N_6O_8Zn$: 2008.3389 $[M+H]^+$, found: 2008.3418; elemental analysis calcd (%) for $C_{129}H_{182}N_6O_8Zn$ (2010.27): C 77.07, H 9.13, N 4.18; found: C 77.23, H 9.19, N 4.06.

Catalytic experiments

General procedure

Typically, five reactions were performed in parallel for each substrate pair. Thus, Mn^{II} catalyst **6** (3 μmol) was weighed into five 2 mL glass vials. Two of the glass vials were charged with Zn^{II}–porphyrin **12** (3 μmol), two other glass vials were charged with **12** (7.5 μmol), and the last glass vial was not charged with any amount of **12**. After the addition, a 2 mL stock solution in CH_2Cl_2 was prepared containing two substrates (0.24 mmol of each) and benzyl benzoate (internal standard, 0.12 mmol). For the inhibition experiment, 4-ethylpyridine (0.72 mmol) was also added to the stock solution. Then, stock solution (250 μL) and CH_2Cl_2 (350 μL) were added to each vial by means of a 250 μL Hamilton syringe. An aliquot (250 μL) of the stock solution was kept as a blank for the NMR and GC analyses. After the addition, the vials were subjected to ultrasonication until a clear homogeneous solution was obtained. Another set of five 2 mL glass vials were loaded with PhIO (24 μmol). The solutions were transferred to the vials containing PhIO by means of a cannula. The obtained mixtures were stirred for 24 h at RT. After this time, each reaction mixture was loaded on a silica pad (h = 2.5 cm, d = 0.5 cm) by means of a Pasteur pipette and eluted with EtOAc (50 mL) with the exception of substrate pair **10a**/**11a**, which was eluted with EtOAc/MeOH (5:1, 50 mL). After removal of the solvent under reduced pressure, the concentrate was dissolved in Et_2O (3 mL), in which the catalyst was insoluble, and filtered through a syringe filter to remove the residual catalyst. Then, an aliquot was taken for GC analysis and the remaining Et_2O was removed under reduced pressure. The so-obtained residue was dissolved in $CDCl_3$ (0.7 mL) for analysis by NMR spectroscopy with the exception of substrate pair **8a**/**9a**, which was dissolved in [D_6]DMSO (0.7 mL) prior to analysis by NMR spectroscopy. To determine the substrate selectivity, GC analysis was performed. Each injection for each sample (both for the blank and the mixture after reaction) was repeated twice. t_R = 11.0 (**9a**), 13.6 (**8a**), 16.8 (**11a**), 18.4 (**5a**), 18.5 (IS), 19.7 (**27a**), 21.1 (**26a**), 22.2 (**4a**), 22.4 (**10a**), 25.0 min (**25a**).

Determination of the substrate selectivity by GC

The conversion (*C*) of each substrate was calculated from the chromatograms by normalizing (N) the substrate (S) area (*A*) with the area of the IS both before the reaction (BR), $NA_{S,BR} = A_{S,BR}/A_{IS,BR}$, and after the reaction (AR), $NA_{S,AR} = A_{S,AR}/A_{IS,AR}$, and then subtracting the normalized substrate area after the reaction from the normalized substrate area before the reaction, and finally dividing the difference by the substrate area before the reaction, thus $C_S = (NA_{S,BR} - NA_{S,AR})/NA_{S,BR}$. The inherent substrate selectivity (ISS) and real substrate selectivity (RS), obtained in the absence and in the presence of receptor part, respectively, were calculated by dividing the conversion of the pyridine substrate (N) with the conversion of the competing substrate lacking a nitrogen atom (C); thus ISS and $RS = C_{s,N}/C_{S,C}$. The normalized substrate selectivity (NS) was finally obtained by dividing RS by ISS (NS = RS/ISS). Further details for the calculations of substrate selectivity are presented in the Supporting Information.

Determination of epoxide formation by ^{1}H NMR spectroscopy

A ^{1}H NMR spectrum was recorded before the reaction of the same stock solution used for the reaction. After the reaction, another ^{1}H NMR spectrum was recorded. The signal for the benzylic protons of the IS at δ = 5.39 ppm was integrated to 1 in the spectra recorded both before and after reaction. Estimation of the amount of consumed substrate (S) that had been converted into epoxide (E) was obtained from the formula: $A_{E,AR}/(A_{S,BR} - A_{S,AR})$. The following signals of substrates were integrated before and after reaction: for **8a**: δ = 6.90 (d, $^3J_{H,H}$ = 12.6 Hz, 1H), 6.66 ppm (d, $^3J_{H,H}$ = 12.6 Hz, 1H); for **9a**: δ = 6.67 ppm (s, 2H); for **11a**: δ = 7.14 ppm (s, 2H); for **27a**: δ = 7.04 ppm (d, $^3J_{H,H}$ = 16.3 Hz, 1H); for **4a**: δ = 5.55 ppm (dt, $^3J_{H,H}$ = 11.6 Hz, $^3J_{H,H}$ = 7.3 Hz, 1H); for **5a**: δ = 5.72 ppm (dt, $^3J_{H,H}$ = 11.7 Hz, $^3J_{H,H}$ = 7.1 Hz, 1H). The following signals of epoxides were integrated after the reaction: for (*Z*)-**8b**: δ = 4.59 (d, $^3J_{H,H}$ = 4.6 Hz, 1H), 4.54 ppm (d, $^3J_{H,H}$ = 4.6 Hz, 1H); for (*E*)-**8b** (**10b**): δ = 4.22 ppm (d, $^3J_{H,H}$ = 1.9 Hz, 1H); for (*Z*)-**9b**: δ = 4.48 ppm (s, 2H); for

(*E*)-**9b** (**11b**): $\delta = 4.11$ (s, 2H) (the signals of (*Z*)-**9b** and (*E*)-**9b** might be the opposite), 4.16 ppm (d, $^3J_{H,H} = 1.9$ Hz, 1H); for **11b** and **27b**: overlap of a multiplet at $\delta = 3.90$–3.87 ppm; for **4b**: $\delta =$ 4.01 ppm (d, $^3J_{H,H} = 4.2$ Hz, 1H); for **5b**: $\delta = 3.26$ ppm (dt, $^3J_{H,H} =$ 6.3 Hz, $^3J_{H,H} = 4.3$ Hz, 1H). Owing to the fact that the areas of different proton resonances were used to determine the amount of consumed substrate and produced epoxide, there is an uncertainty in the values, as each proton resonance has its own relaxation time, which thus causes different values of the integrated area depending on which resonance is integrated.

TON experiment of 6 and 6+12 by using 27a as substrate

Two 2 mL glass vials were charged with **6** (1.99 μmol each) and **12** (1.99 μmol each). In parallel, two other 2 mL glass vials were charged with only **6** (1.99 μmol each). A stock solution (1.5 mL) in CH_2Cl_2 was prepared containing **27a** (0.24 mmol) and the IS (0.12 mmol). Stock solution (250 μL) was added to the vials containing **6** and **6+12**, and the mixtures were then diluted with CH_2Cl_2 (150 μL) by means of a Hamilton syringe. After the addition, the vials were subjected to ultrasonication until a clear homogeneous solution was obtained. The solutions were transferred by means of cannula to four other glass vials each loaded with PhIO (59.7 μmol). The obtained mixtures were stirred for 7 days at RT. Then, the workup was performed in an identical way as that described under the "General procedure". The conversion of **27a** was calculated in the same way as that described in the section "Determination of the substrate selectivity by GC". To obtain the TON, the observed conversion of **27a** was multiplied by the molar amount of **27a** before the reaction and then divided by the molar amount of **6** present in each mixture. The two vials loaded with **6** gave TON = 8.1 and 10.3. The vials loaded with **6+12** gave TON = 12.8 and 13.8 (see the Supporting Information for details).

Acknowledgements

We thank the Swedish Research Council, the Royal Physiographic Society (Lund), and the Crafoord Foundation for financial support. H.N.A. and E.L. thank the Crafoord Foundation for postdoctoral fellowships, and E.S is grateful to the Carl Trygger Foundation for a postdoctoral fellowship. Mr. Clas Wesén and Prof. Ola Wendt, Lund University, are acknowledged for valuable discussions.

Keywords: epoxidation · supramolecular catalysis · hydrogen bonds · self-assembly · substrate selectivity

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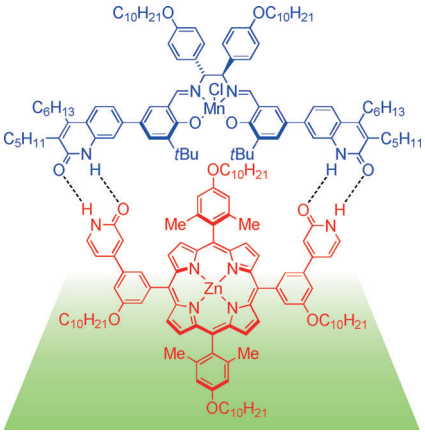
Received: September 10, 2014
Published online on ■■ ■■, 0000

FULL PAPERS

To be or not to be preorganized… A third generation of a kinetically labile supramolecular catalytic system was synthesized. Its substrate selectivity in the epoxidation of pyridyl- versus phenyl-appended olefins was compared to previous less preorganized systems in the series. The third generation showed higher substrate selectivities in two out of five cases.



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A Double Conformationally Restricted Dynamic Supramolecular System for the Substrate-Selective Epoxidation of Olefins—A Comparative Study on the Influence of Preorganization