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An Amphiphilic (salen)Co Complex – Utilizing Hydrophobic Interactions to Enhance the Efficiency of a Cooperative Catalyst

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Abstract: An amphiphilic (salen)Co(III) complex is presented that accelerates the hydrolytic kinetic resolution (HKR) of epoxides almost 10 times faster than catalysts from commercially available sources. This was achieved by introducing hydrophobic chains that increase the rate of reaction in one of two ways – by enhancing cooperativity under homogeneous conditions, and increasing the interfacial area under biphasic reaction conditions. While numerous strategies have been employed to increase the efficiency of cooperative catalysts, the utilization of hydrophobic interactions is scarce. With the recent upsurge in green chemistry methods that conduct reactions 'on water' and at the oil-water interface, the introduction of hydrophobic interactions has potential to become a general strategy for enhancing the catalytic efficiency of cooperative catalytic systems.

Keywords: Cooperative catalysis; self-assembly; preorganization; hydrolytic kinetic resolution; amphiphiles

Nature commonly exploits the pre-organization of functional groups to create highly effective catalytic systems.[1] This allows proximal functional groups to work cooperatively, achieving rate accelerations much greater than the sum of each of the groups acting on their own.[2] This emergent property has drawn the attention of chemists, and numerous cooperative catalytic systems have been reported over the last decades.[3] One example that stands out for its utility in both academic and industrial settings is the hydrolytic kinetic resolution (HKR) of terminal epoxides using (salen)Co complexes, first reported by Jacobsen and co-workers.[4] This reaction is an economically viable method for obtaining optically pure terminal epoxides and 1,2-diols from racemic mixtures of terminal epoxides (Figure 1b).[5] The cooperative system requires two Co(III) ions in the rate-determining-step, one acting as a Lewis acid to increase the electrophilicity of the epoxide whilst the other stabilizes the nucleophilic hydroxide anion.[6] The reaction can be conducted under neat conditions using only water as a reagent, or with addition of a water miscible solvent to generate a homogeneous system.

Cooperative catalysts require the participation of two or more functional groups in the rate-determining step, and thus benefit from pre-organization that brings the required functionality into proximity. This can be

a Previous work: different strategies for increasing the activity of cooperative catalysts

molecular scaffold   *dendrimers*   *attachment onto surfaces*   *hydrogen bonding*
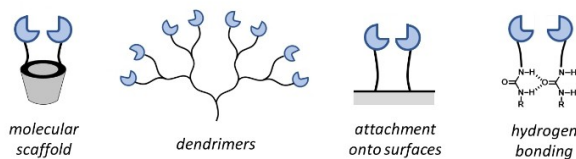
b This Work: enhancing cooperative catalysis by utilizing hydrophobic interactions

Enhanced cooperativity   *Increased interfacial area*
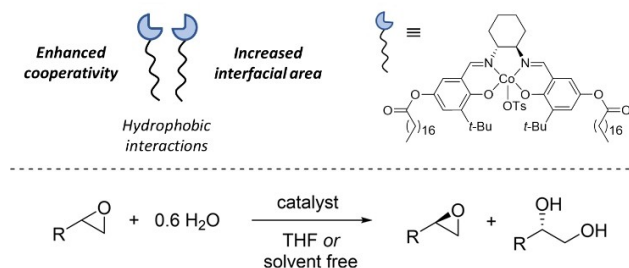
Hydrophobic interactions

Figure 1. Schematic representations of (a) previous strategies used to enhance the activity of cooperative catalysts and (b) utilization of hydrophobic interactions to enhance cooperativity in a self-assembled catalyst.

achieved by direct covalent linkage of the requisite groups onto a molecular scaffold[7] or by using more advanced strategies such as the incorporation of catalytic units into oligomers,[8] dendrimers,[9] the surfaces of particles and polymers[10] or by hydrogen bonded self-assembly.[11] All these strategies have been successfully utilized to generate catalytic systems with higher efficiencies than their monomeric counterparts (Figure 1a). Yet, one strategy seldom considered for the pre-organization of cooperative catalysts is the use of *hydrophobic* interactions (Figure 1b). The lack of examples in the literature is likely due to the fact that the majority of organic reactions are performed in organic solvents, where hydrophobic interactions are often disregarded. However, the recent drive for green synthetic methods can be expected to give greater emphasis on the utilization of hydrophobic interactions, with an evident shift towards performing reactions in benign solvents such as water,[12] on-water reactions,[13] and an increasing interest in reactions that occur at the water-oil interface.[14]

We recently performed conceptual studies to demonstrate that self-assembly driven by hydrophobic interactions is an effective strategy to improve the efficiency of cooperative catalysts in aqueous and semi-aqueous systems.[15,16] In addition to being more synthetically accessible than catalysts attached to molecular scaffolds, dendrimers or nanoparticles, the modularity of the system allowed facile optimization of the catalyst system when two different catalytically active building blocks were used.[17] The weak and reversible nature of hydrophobic interactions also allowed design of systems where control of the self-

assembly process can lead to stimuli-responsive and switchable catalytic properties.[15a]

While noteworthy as proof-of-concept studies, the above examples did not catalyze a practically useful reaction. To demonstrate that introduction of hydrophobic interactions can be a general method for increasing the efficiency of cooperative catalysts, we embarked on demonstrating this effect on the (salen) Co complexes used in the hydrolytic kinetic resolution (HKR) of terminal epoxides (Scheme 1).[4] We were drawn to this reaction as it is a widely employed process with a well-established cooperative mechanism.[6]

Amphiphilic analogues of (salen)Co complex (**1**) were made by replacing the two *tert*-butyl groups with fatty acid esters (Scheme 2). Synthesis of the salen ligands was achieved in five steps starting from 2-*tert*-butylhydroquinone, using a synthetic route adapted from one previously used to access an oligomeric (salen)Co complex.[8a] By changing the fatty acid employed in the fourth step of this sequence, three amphiphilic analogues (**2**–**4**) were made containing different degrees of hydrophobicity.

The catalytic activity of (salen)Co complex **4** was first investigated in the HKR of epichlorohydrin under solvent-free conditions (Figure 2). Water acts as a reagent in this reaction and was added to the epoxide substrate and complex **4**, forming a biphasic mixture. The mixture was stirred vigorously at room temperature and aliquots were taken at specific time intervals and analyzed by chiral GC to determine the reaction conversion.[4a] Under these neat conditions, complete chiral resolution ($>99\%$ *e.e.*) of epichlorohydrin was achieved within 70 min using 0.10 mol% of complex **4**, whereas 37% *e.e.* was observed with complex **1** under the same conditions (Figure 2). Analysis of the initial rates revealed an almost ten-fold rate difference between complex **1** ($k_{obs} = 0.86\,\mathrm{h}^{-1}$) and complex **4** ($k_{obs} = 8.2\,\mathrm{h}^{-1}$), with the k_{obs} determined from plots of $-\ln([\text{epoxide}]/[\text{epoxide}]_0)$ versus time (see SI). A positive correlation between the reaction rate and the
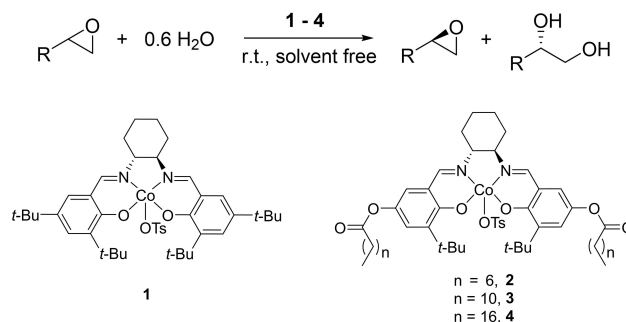
Scheme 1. Jacobsen's (salen)Co complex **1** and modified (salen)Co complexes **2**–**4** with incorporation of sidechains with differing lengths.
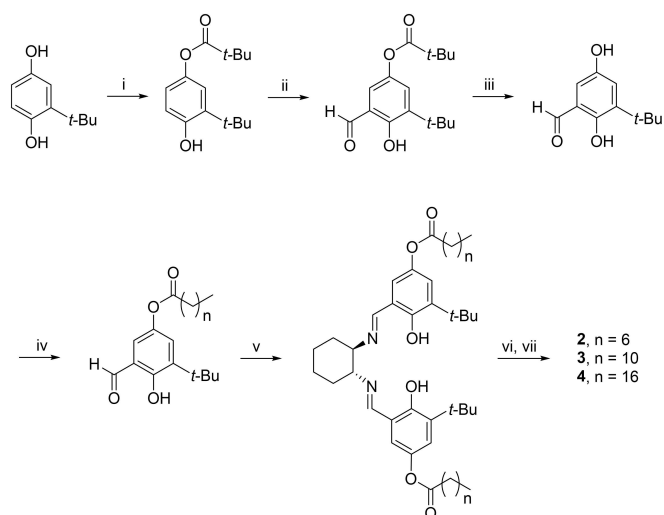
Scheme 2. Synthesis of amphiphilic (salen)Co(III) complexes **2**–**4**. i) DMAP (0.15 equiv.), imidazole (2 equiv.), pivaloyl chloride (1.2 equiv.), CH_2Cl_2, quantitative; ii) 2,6-lutidine (2 equiv.), $SnCl_4$ (0.5 equiv.), paraformaldehyde (9 equiv.), toluene, 89%; iii) KOH (10 equiv.), $EtOH/H_2O$ (1:1), 76%; iv) carboxylic acid (1 equiv.), DMAP (0.2 equiv.), EDC (1.2 equiv.), DMF/CH_2Cl_2 (1:5), n=6, 82%; n=10, 52%; n=16, 88%; v) (1R,2R)-(−)-1,2-diaminocyclohexane (0.5 equiv.), K_2CO_3 (2 equiv.), H_2O/THF (1:4), n=6, 43%; n=10, 65%; n=16, 67%; vi) $Co(OAc)_2 \cdot 4H_2O$ (1 equiv.) MeOH/toluene (1:1), n=6, 50%; n=10, 36%; n=16, 95%; vii) p-PTSA.H_2O (1 equiv.) MeOH/toluene/CH_2Cl_2 (10:3:10), n=6, 62%; n=10, 68%; n=16, 64%.
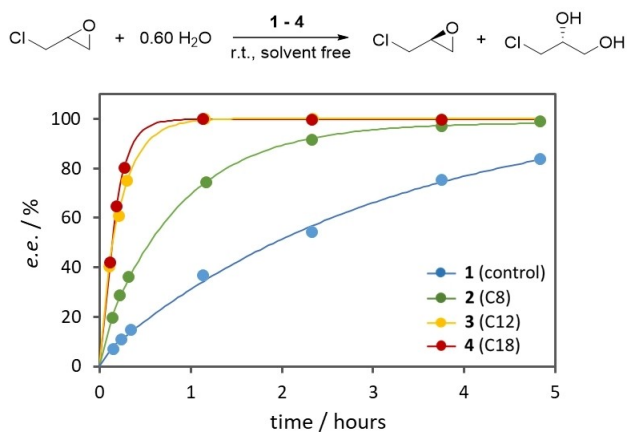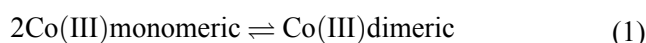

Figure 2. Hydrolytic kinetic resolution of epichlorohydrin utilizing complexes **1** to **4** under solvent free conditions. [Catalyst] = 0.10 mol%, epichlorohydrin (1 equiv.), H_2O (0.6 equiv.).

length of the added sidechain was also observed (2.4 h^{-1} for complex **2** and 6.5 h^{-1} for complex **3**).

To provide insight into the origin of this rate acceleration, we measured the kinetic profile of complexes **4** and **1** under different reactions conditions.

The experiments were first conducted under homogenous conditions, to allow direct comparison to prior studies demonstrating the cooperativity of these catalysts in the HKR (Figure 3a).[6,7b,11a,18,19] This required addition of THF to the reaction mixture to form a fully miscible reaction mixture. The plot of the k_{obs} of the reaction against [catalyst]^2 confirmed the second-order dependence of the rate on catalyst concentration, confirming that a cooperative mechanism is operative with complex **4**. The higher activity of complex **4** can be seen by the much steeper curve compared to complex **1** and the origin of this increase can be rationalized in a similar way as to a treatment by Hong.[11a] Firstly, we can assume that formation of the active catalyst results from dimerization of monomeric Co(III) complexes (equation 1). The rate of the reaction is proportional to the dimeric complex (equation 3) and can be expressed in terms of the concentration of the monomer (equation 4). A second assumption is that the concentration of the active dimeric species is much lower than the concentration of the monomeric catalyst (and hence the observation of second order dependence typical for non-covalently-linked, cooperative systems).[20] This allows simplification of the expression to be directly proportional to the total Co(III) complex concentration (equation 6). This equation shows that there is a direct relationship between the rate of the reaction and the equilibrium constant K_2, describing the equilibrium between the dimeric and monomeric forms of the (salen)Co(III) complex.

$$2Co(III)monomeric \rightleftharpoons Co(III)dimeric \quad (1)$$

$$K_2 = [Co(III)dimeric]/[Co(III)monomeric]^2 \quad (2)$$
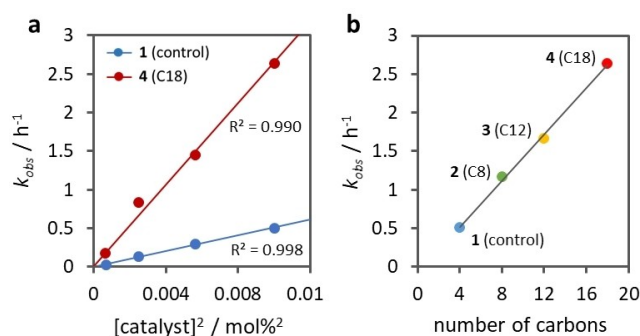
Figure 3. a) Initial rates of reaction for the HKR of epichlorohydrin at variable catalyst loadings under homogenous conditions. Red: complex **4**. Blue: complex **1**; b) Initial rates of hydrolytic kinetic resolution of epichlorohydrin in THF vs number of carbons in the salen sidechain, catalyst loading 0.1 mol%. Blue=catalyst **1**; green=complex **2**; yellow= complex **3**; red=complex **4**. Reaction conditions for both a and b: epichlorohydrin (1 equiv., 1 volume), THF (1 volume), H_2O (0.6 equiv.), rt, 400 rpm.

$$\text{rate} = \text{k}[\text{Co(III)dimeric}] \tag{3}$$

$$\text{rate} = \text{kK}_2[\text{Co(III)monomeric}]^2 \tag{4}$$

$$[\text{Co(III)total}] = 2[\text{Co(III)dimeric}] + [\text{Co(III)monomeric}] \tag{5}$$

$$\text{If } [\text{Co(III)dimeric}] \ll [\text{Co(III)monomeric}]$$

$$\text{Then rate} = \text{kK}_2 \,([\text{Co(III)total}]\text{-}2[\text{Co(III)dimeric}])^2 \approx \text{kK}_2[\text{Co(III)total}]^2 \tag{6}$$

If hydrophobic interactions were in fact an important factor in the formation of this cooperative catalyst, changes in the length of the hydrophobic chains should result in changes in the catalytic activity. To investigate this hypothesis, we examined the initial rates of (salen) Co complexes **2** and **3**. A positive linear relationship was found between the initial rates of the HKR reaction, and the number of carbon atoms present in the hydrocarbon sidechain of the (salen)Co complex (Figure 3b). This trend also rules out changes in activity due to electronic effects, which have been previously observed in other analogues.[11a] Small angle neutron scattering (SANS) experiments also excluded the formation of micellar aggregates with amphiphilic complex **4** (see SI, section 5),[21] which is in line with the observed second-order rate dependence on catalyst concentration.

To estimate the relative difference in magnitude between the dimerization constants of complexes **4** and **1**, the corresponding Ni(II) analogues **5** and **6** were synthesized (Table 1).[22] The ^{1}H NMR spectra of (salen)Ni(II) complexes **5** and **6** were measured at different concentrations in a mixture of THF-d_8 and D_2O to simulate the reaction conditions (see SI). Changes in the chemical shift of the aromatic protons were used to estimate their association constants.[23]

Non-linear least squares fitting of the ^{1}H NMR data into the monomer-dimer (MD) model estimated a dimerization constant of 1.43 ± 0.75 for complex **6** and 0.36 ± 0.75 for complex **5**. Alternatively, fitting into the equal K (EK) model estimated an association constant of 2.82 ± 2.19 for complex **6** and 0.68 ± 0.57 for complex **5**. Both models estimated the dimerization/association constant of functionalized complex **6** to be approximately 4 times that of complex **5**, which is consistent with the 5 times difference in rate observed between the two complexes (see Figure 3a).

While (salen)Co(III) complex **4** yielded faster rates than control complex **1** in the kinetic studies under homogeneous conditions, this rate enhancement (~5 times) was significantly lower than what was observed under neat, biphasic conditions (~10 times). We thus proceeded to examine the kinetics of the reaction under the biphasic conditions in which the HKR reaction is commonly utilized, and the initial rates of reaction were measured for a range of loadings of complexes **1** and **4** (Figure 4a). It became apparent that under these biphasic conditions, complex **4** became increasingly more effective than **1** as the concentration is increased (e.g. at 0.06 mol% catalyst loading, complex **4** is 5 times more effective than complex **1**, whereas at 0.10 mol%, complex **4** is 9.5 times more effective than complex **1**). Note that the ratio of reaction rates between complexes **4** and **1** was constant at different catalyst concentrations when performed under homogenous conditions.

As we were working in biphasic conditions, we rationalized that a possible reason for an increasingly more effective complex **4** at higher concentrations may be due to more efficient emulsion stabilization.

Table 1. Dimerization and association constants obtained by fitting chemical shifts in the ^{1}H NMR of compounds **5** and **6** into the monomer-dimer (MD) model and the equal K (EK) isodesmic model.

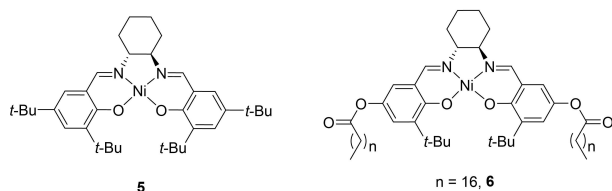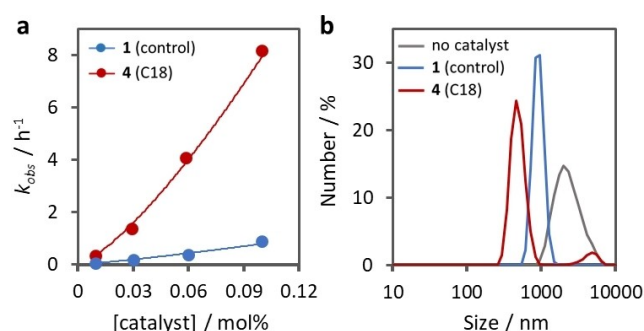| Complex	MD model	EK model
5	$K_2 = 0.36 \pm 0.20$	$K_{asso} = 0.68 \pm 0.57$
6	$K_2 = 1.43 \pm 0.75$	$K_{asso} = 2.82 \pm 2.19$

Figure 4. a) Initial rates of the HKR of epichlorohydrin (h^{-1}) vs [catalyst] with variable catalyst loadings under neat (biphasic) conditions. Experimental conditions: epichlorohydrin (1 equiv.), H_2O (0.6 equiv.), rt, stirring at 400 rpm, red = complex **4**, blue = complex **1**; b) Diameter of water droplets measured by dynamic light scattering. Experimental conditions: styrene oxide = 375 μL, milli-Q water = 36 μL, [catalyst] = 0.02 mol%. Grey line = no catalyst, blue line = complex **1**, red line = complex **4**. The samples were stirred for 2 minutes and left to rest for 10 minutes.

Reaction mixtures containing styrene oxide as the HKR substrate were examined using dynamic light scattering (DLS). The size of the water in oil (styrene oxide) emulsions in the absence of catalyst was observed to be 2–3 µm. The same mixture in the presence of complex **1** (0.02 mol%) showed droplet sizes of ~1 µm, suggesting that complex **1** has some effect in stabilizing the interface, resulting in a greater number of droplets of smaller size. The introduction of complex **4** resulted in a more pronounced effect, decreasing the size of the emulsions to the range of 400–600 nm. These results suggest that under neat conditions, complex **4** increases the rate of the reaction by stabilization of nanoemulsions, thereby increasing the interfacial area between the reagent water and the epoxide substrate.
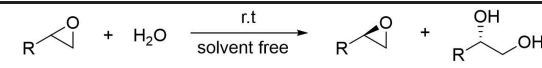
It is worth noting that for most previously described strategies for enhancing cooperative catalysis (covalent linkage, immobilization onto nanoparticles), the difference in catalytic activity between the newly designed catalyst and monomeric complex **1** can be expected to *decrease* at higher concentrations, as described by Kleij.[7b] This is because the advantage gained by preorganization is negated at higher concentrations due to the second order dependence of rate on catalyst concentration. In these examples, the kinetics can be described by a two-term equation involving both intramolecular and intermolecular components (equation 7).[7c]

$$\text{Rate} = k_{intra}\,[\text{catalyst}] + k_{inter}\,[\text{catalyst}]^2 \qquad (7)$$

Taking for example two (salen)Co(III) complexes joined covalently onto a molecular scaffold – the intramolecular component refers to catalysis by Co sites on the same molecule, while the intermolecular component refers to the reaction catalyzed by Co sites on different molecules. At low concentrations, the k_{intra} term is dominant due to preorganization of the Co sites within the same molecule which enhances cooperativity. However, at high catalyst concentrations, the k_{intra} term will not always compensate for a decrease in the k_{inter} term due to a halving in the total number of discrete catalysts because of preorganization. Thus, when comparing to complex **1** which has solely a k_{inter} term, the difference in rate between the two complexes will decrease at higher concentrations. In contrast to these previous examples, our current system does not rely on pre-formed dimers, and association between monomers is only expected to increase at higher catalyst concentrations and lead to enhanced activity.

To demonstrate that our catalyst is practically useful, the reactivity of (salen)Co(III) complex **4** with a range of different substrates was examined under neat conditions (Table 2). Reaction of terminal epoxides containing an aliphatic chain proceeded quickly using complex **4**, with the HKR of 1,2-epoxyhexane

Table 2. Substrate scope for the hydrolytic kinetic resolution of terminal epoxides using complex **4**. The reactions were conducted in solvent free conditions.

Entry	R	Catalyst / mol %	H$_2$O / equiv.	Time	$e.e_{epoxide}$ [a]
1	(CH$_2$)$_3$CH$_3$	**1** 0.1	0.6	60 min	66%
2	(CH$_2$)$_3$CH$_3$	**4** 0.1	0.6	60 min	>99%
3	CH$_2$Cl	**1** 0.1	0.6	70 min	37%
4	CH$_2$Cl	**4** 0.1	0.6	70 min	>99%
5	Ph	**1** 0.5	0.6	3h	73%
6	Ph	**4** 0.5	0.6	3h	>99%
7	CH$_2$O(CH$_2$)$_3$CH$_3$	**1** 0.1	0.6	25 min	67%
8	CH$_2$O(CH$_2$)$_3$CH$_3$	**4** 0.1	0.6	25 min	>99%
9	CH=CH$_2$	**1** 0.1	1.2	5 h	40.5%
10	CH=CH$_2$	**4** 0.1	1.2	5 h	>99%
11	CH$_2$OPh	**1** 0.1	0.6	80 min	78%
12	CH$_2$OPh	**4** 0.1	0.6	80 min	98.5%
13	t-Bu	**1** 0.1	0.6	4 days	49%
14	t-Bu	**4** 0.1	0.6	4 days	>99%

[a] The enantiomeric excess was determined by either chiral GC or chiral HPLC and the yield of the product is inferred from the *ee* (see SI).

complete (>99% *e.e.*) after 1 hour (entry 2), while in the same time period, 66% *e.e.* was obtained using complex **1** (entry 1). 2-Vinyloxirane required a higher equivalence of water to obtain high enantioselectivity, and complete chiral resolution was achieved in 5 hours with complex **4** (entry 10). Epoxides containing ether side chains were also good substrates, with the HKR of butyl glycidyl ether complete within 25 min (entry 8) while the HKR of benzyl glycidyl ether was complete within 80 min using 0.1 mol% of complex **4** (entry 12). Within in the same time period, catalysis with complex **1** arrived to 67% and 78% *e.e.* respectively (entries 7 and 11). Styrene oxide, known to be a slow reacting substrate,[4a] was conducted using 0.5 mol% of catalyst. Complete resolution was achieved using complex **4** within three hours (entry 4), while 73% *e.e.* was reached with complex **1** (entry 3). HKR of the sterically demanding 3,3-dimethyl-1,2-epoxybutane required 4 days to reach completion (entry 14). The control conditions reach 49% *e.e.* after this time (entry 13), which clearly demonstrates the advantage to be had with a more active catalyst. Unlike many previously reported examples,[7b,8e,11a] this catalyst is efficient under solvent free conditions and does not

require the addition of an organic solvent to homogenize the reaction mixture.

In conclusion, this work demonstrates that hydrophobic interactions can be used to enhance the efficiency of a practically useful cooperative catalyst. The results from kinetic studies reveal that under homogenous conditions, this rate acceleration is due to an increase in the association constant, leading to enhanced cooperativity. Under neat biphasic conditions, the amphiphilic nature of the catalyst acts to increase the interfacial area between the two immiscible reactants, resulting in an almost 10 times increase in reaction rate over catalysts from commercially available sources. It is worth noting that Jacobs has previously shown that the addition of external surfactants does *not* result in rate enhancement in the HKR reaction.[24] This is likely because any added surfactants will dilute the concentration of (salen)Co complexes at the interface, preventing the required cooperativity for effective catalysis. In the current example, by incorporating amphiphilicity into the catalyst itself, significant rate enhancement was observed under industrially relevant, neat conditions, without the need for added solvent. We believe that this concept will become increasing valuable for the design of green chemical methods that accelerate reactions occurring 'on-water' and at the oil-water interface. The reversible nature of these hydrophobic interactions also provides modularity and the potential to readily mix and match different monomeric catalysts for the development of novel cooperative systems.

Experimental Section

A specific volume of a solution of complex **4** in chloroform was introduced to a vial and the chloroform evaporated. Milli-Q water (0.6 eq.) was added followed by racemic epichlorohydrin (1.0 eq., 1 volume). For experiments under homogenous conditions, THF (2 volumes) was also added. The reaction mixtures were stirred at 400 rpm and aliquots of the reaction mixture were taken at specific time intervals to monitor the reaction progress. The aliquots were filtered through a plug of silica and eluted with Et_2O before chiral GC or HPLC analysis.

Acknowledgements

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[16] It is important to note that the mechanism of rate acceleration in these examples is distinctly different to conventional micellar catalysis. In the above systems, rate enhancement is due to an increase in cooperativity between catalytic units, whereas micellar catalysis relies on an increase in reactant concentration in the hydrophobic core of the micellar structures.

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