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Calix[8]arene as new platform for Cobalt-Salen complexes immobilization and use in hydrolytic kinetic resolution of epoxides

Ibrahim Abdellah,[a] Cyril Martini,[a,b] Amandine Dos Santos,[a] Diana Dragoe,[a] Vincent Guérineau,[c] Vincent Huc*[a] and Emmanuelle Schulz*[a]

Abstract: Eight cobalt-salen complexes have been covalently attached to a calix[8]arene platform through a flexible linker by a procedure employing Click chemistry. The corresponding well-defined catalyst proved its efficiency in the hydrolytic kinetic resolution (HKR) of various epoxides through an operative bimetallic cooperative activation, demonstrating highly enhanced activity when compared to its monomeric analogue. As an insoluble complex, this multisite cobalt-salen catalyst could be easily recovered and reused in successive catalytic runs. Products were isolated by a simple filtration with virtually no cobalt traces and without requiring a prior purification by flash chromatography.

Introduction

Chiral enantiopure salen complexes are ubiquitous catalysts in asymmetric catalysis and resolution reactions. The reason behind is the readily availability and diversity of these complexes, which allowed their use in numerous asymmetric catalytic reactions, both under homogeneous[1] or heterogeneous conditions,[2] without forgetting to mention their applications on an industrial scale.[3] Regarding the asymmetric ring-opening reaction of epoxides, Jacobsen and his group discovered that a bimetallic cooperative activation of both the epoxide and the considered nucleophile was responsible for the high reactivity and selectivity observed with chromium- and cobalt-salen complexes.[4] In the case of the HKR of epoxides by salen-cobalt complexes, detailed mechanistic studies revealed the occurrence of a bimetallic pathway with the formation *in situ* of an Co(III)-OH intermediate by hydrolysis.[5] As a result, the transformation features a key transition state, in which one salen Co(III) complex acts as a Lewis acid to activate the epoxide and one Co(III)-OH species activates water through a well-defined geometry, delivering the products with high selectivity. Aiming at favoring the formation of these bimetallic intermediates, numerous studies have been directed towards the immobilization of salen complexes to bring the reactive sites in close proximity. For instance, different routes have been described, which involved the formation of linear oligomers and polymers by different methods, either by polymerization of complexed monomers or post-functionalization.[6] The association of two salen ligands by non-covalent interactions also resulted in enhanced efficiency.[7] The same applied to the formation of macrocyclic structures containing salen derivatives.[8] Other remarkable examples relied on the immobilization of those complexes onto insoluble supports, allowing their easy recovery by a simple filtration for a potential reuse in catalysis.[9] Of note, salen-based complexes proved to be also efficient when embedded in nanoporous metal organic frameworks.[10] In an original example, the group of Kleij anchored two chiral cobalt-salen complexes onto a calix[4]arene structure and reported an efficient intramolecular bimetallic activation with this hybrid structure in the HKR reaction.[11] A few examples can be found, in which calix[4]arene units are arranged by one or two salen complexes to perform asymmetric catalysis[12] and chirality transfer in host-guest systems.[13] Furthermore, the use of calixarene derivatives as ligands has also been reported to promote efficient metal-based catalysis of various reactions.[14]

In this context, our groups have recently described a simple, large-scale and practical route to benzyloxycalix[8]arene derivatives,[15] and we were able to immobilize eight NHC palladium complexes onto this molecular support to provide well-defined catalysts for efficient Suzuki-Miyaura couplings under heterogeneous conditions.[16] Following a similar strategy, we describe, herein, the synthesis of a chiral calixarene-supported Jacobsen-type ligand as a platform capable of immobilizing eight salen ligands in close proximity. Relying of this flexible benzyloxycalix[8]arene structure, our main goal was the preparation of a new efficient chiral supported catalyst, anticipating enhanced activity and enantioselectivity due to cooperative interactions between the metallic sites of the macrocyclic platform. Moreover, the efficiency of the corresponding cobalt complex **cat-1** was compared to the activity of the monomeric analogue **cat-2** in the HKR of epoxides (figure 1).

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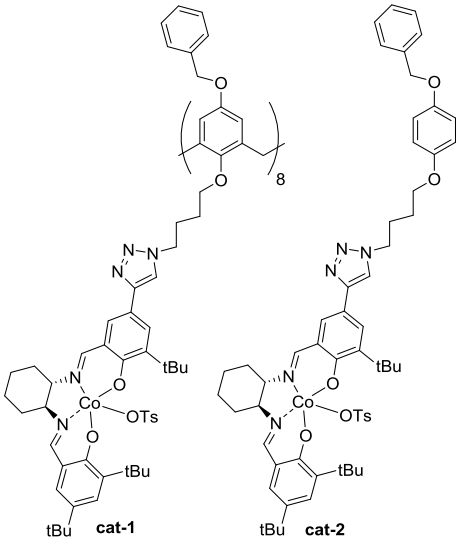
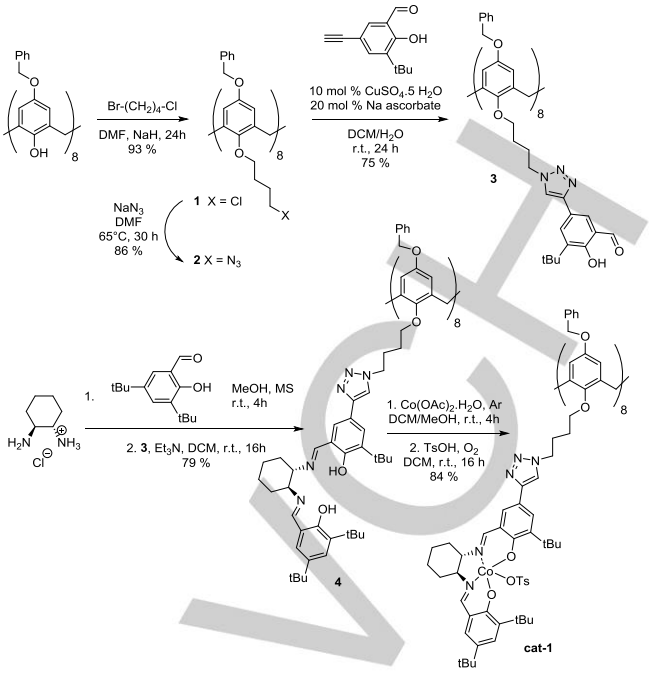


Figure 1. Benzyloxycalix[8]arene-supported cobalt-salen catalyst and its monomer analogue.

Results and Discussion

The synthesis of the calixarene-based catalyst **cat-1** was accomplished in five steps from benzyloxycalix[8]arene in 40% overall yield (Scheme 1).[17] Chloroalkylation of phenol with 1-bromo-4-chlorobutane was achieved in an excellent yield (93%) using sodium hydride as a base in DMF to give calixarene **1**.[16] This compound was then readily transformed into the azido compound **2** with sodium azide. Huisgen cycloaddition with 5-ethynyl-3-*tert*-butyl-2-hydroxybenzaldehyde[18] in the presence of copper sulfate and sodium ascorbate[19] led to the formation of the calix[8]arene-derived salicylaldehyde **3**. A one-pot protocol, involving two consecutive condensations on HCl-protected (*S*,*S*)-cyclohexane-1,2-diamine, enabled the synthesis of the unsymmetrical salen derivative **4** in 79 % yield.[20] Finally, addition of $Co^{II}(OAc)_2.4H_2O$ and a subsequent oxidation in air of the Co^{II} complex in the presence of *para*-toluene sulfonic acid delivered **cat-1**, incorporating cobalt-tosylate active sites, in 84 % yield. All compounds were fully characterized by NMR and IR spectroscopy as well as mass spectrometry analyses. ^1H NMR analysis of compound **4** in $CDCl_3$ is particularly characteristic of a symmetrical calixarene-based structure, with additional signals corresponding to the formation of non-symmetrical salen derivatives. Two peaks were observed for the hydroxyl functions (at 14.1 and 13.6 ppm) and two for the imine groups (at 8.3 and 8.2 ppm, see SI, part V). MALDI analysis was also performed with calix-salen **4** (DCTB matrix), providing a molecular peak at 6724 ($[M+Cs]^+$) as a further evidence of the complete functionalization of each phenol site by a salen moiety. Characterization of **cat-1** could also be conducted by NMR studies, showing, among other features, disappearance of the hydroxyl groups.



Scheme 1. Synthetic procedure for **cat-1**.

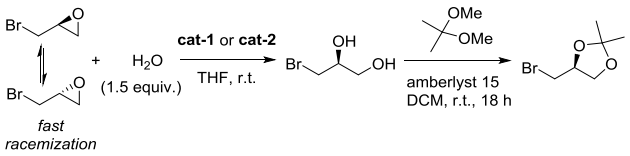
The symmetry of the spectra also showed that each salen ligand includes a cobalt atom. Additionally, the comparison of UV-Vis spectra between calix-salen derivative **4** and **cat-1** in DMF clearly demonstrated incorporation of cobalt salts in the salen ligand with the appearance of a new band at 400 nm, which was assigned to a new metal d-d transition in the complex.[21] In IR spectroscopy, we observed obvious differences regarding the imine stretching vibration *v*(C=N). This peak was observed at 1628 cm^{-1} for **4**, before shifting to 1623 cm^{-1} upon incorporation of cobalt salts.[6d,22] C,N,O elemental and XPS analyses were also performed to unambiguously prove the insertion of a cobalt atom in each of the eight salens and confirm the oxidation state of cobalt (III) (see SI, part VI-VII). One of the main advantages of this strategy is that this calixarene-supported, well-defined multisite chiral cobalt complex could be rapidly prepared through a short synthesis that did not require any purification by flash chromatography.

Following the same procedure, **cat-2** was isolated in 26 % overall yield starting from 4-(benzyloxy)phenol. Similarly, NMR, HRMS, IR, UV-Vis and elemental analyses allowed the complete characterization of this cobalt species as a soluble “monomeric” analogue of **cat-1**.

Catalysts **cat-1** and **cat-2** were then evaluated in the HKR of epoxides. Indeed cooperative bimetallic activation is of utmost importance for reaching both high activities and enantioselectivities in this transformation.

In particular, dynamic kinetic resolution (DKR) of epibromohydrin was chosen as a benchmark reaction. It allows complete conversion to optically active 3-bromopropane-1,2-diol, as the starting material undergoes a fast epimerization under the DKR conditions.[23] The reaction was performed in THF at room temperature in the presence of water (1.5 equiv) and the

conversion of the reaction was determined by GC analyses, using chlorobenzene as an internal standard. Upon complete conversion, the resulting diol was protected by 2,2-dimethoxypropane to determine the enantiomeric excess by chiral GC analyses. As a comparison, Jacobsen and his group reported that 3-bromopropane-1,2-diol was isolated in 93 % yield and 96 % ee in the presence of 2 mol% of the classical chiral bis-*tert*-butyl-cyclohexyl-salen Co(III)-OAc catalyst.[24]



Scheme 2. Dynamic HKR of epibromohydrin catalyzed by **cat-1** and **cat-2**

Our first attempt to utilize insoluble **cat-1** in an amount that matches a total cobalt content of 1 mol% delivered promising results with a complete conversion within 4 h and the corresponding acetonide was obtained in 94% ee. After dilution of the highly concentrated reaction mixture with diethylether to facilitate the product recovery, the determination of residual cobalt traces was evaluated by ICP-MS analyses of the diol after a simple paper filtration. Almost no leaching was observed (1.2 ppm), providing, thus, an easy procedure to recover enantioenriched valuable synthons without virtually any metallic traces.

Then, kinetic studies were performed for a comparative evaluation of **cat-1** and **cat-2** activity in this transformation by varying the introduced cobalt amount (between 0.06 and 1.5 mol%). Conversion *vs* time plots obtained in these conditions were reported in figure 2. At an equal cobalt loading, the initial reaction rates are significantly affected by the use of either **cat-1** or **cat-2**. Thus, almost no conversion was observed with **cat-2** when the lowest cobalt amount was used in this study (0.06 mol%). On the other hand, **cat-1** promoted the transformation with an initial rate of 0.007 mmol.min^{-1} under the same reaction conditions. Furthermore, almost complete conversion could be reached with **cat-1** after 4 h reaction with a cobalt amount of 1.5 mol%, whereas **cat-2** afforded the diol in only 86% conversion under the same conditions. Nevertheless, the structure of the catalysts did not influence the enantioselectivity of the transformation since the acetonide was isolated with 94 % ee in each case. Additionally, at a higher catalyst loading, larger rate values were obtained for **cat-1** (0.033 mmol.min^{-1} for 1.5 mol% Co-active sites) when compared to **cat-2** at the same catalyst loading (0.025 mmol.min^{-1}). Such a difference was not observed for the bis-cobalt(III)salen-calix[4]arene used by Kleij *et al.* for the HKR of racemic 1,2-epoxyhexane.[11] Although a cooperative and intramolecular mode of activation could be proven in this last case, an overall gain in activity was not observed when compared to the monometallic analogue, which might be explained by a probable decrease in the reaction rate, arising from intermolecular bimetallic activation.

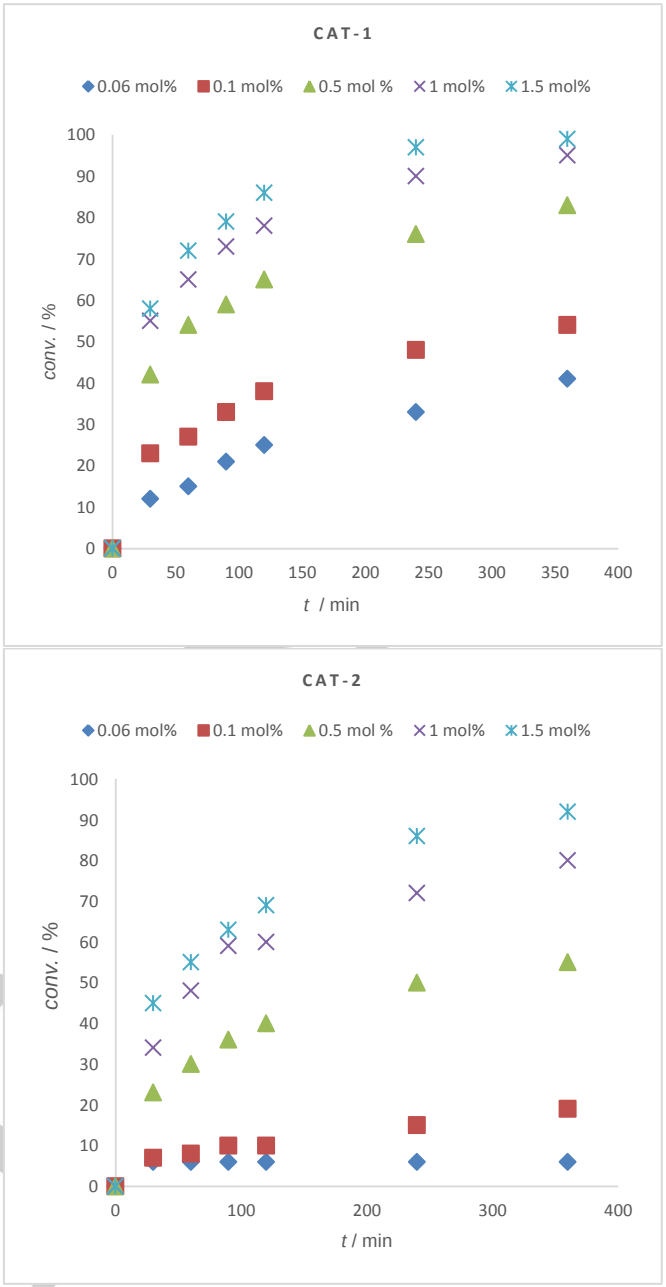


Figure 2. Conversion/time plots for the dynamic HKR of epibromohydrin catalysed by **cat-1** (above) or **cat-2** (below) (0.06 – 1.5 mol %).

We assumed that the benzyloxycalix[8]arene platform bearing eight cobalt-salen active sites through a very flexible linker favored the probability that two of these catalysts can be ideally positioned to create a cooperative bimetallic transition state geometry, allowing both high rate and high selectivity. The conformational flexibility of the calix[8]arene scaffold associated with its large cavity were additional elements supporting this cooperativity, which would be less the case with the use of more common calix[4]arene platforms. Such rate acceleration has already been observed with other catalytic systems, in which cobalt-salen active sites have been immobilized to be close to each other or loaded onto the same scaffold.[9b,25]

Hydrolysis of cyclohexene oxide was then selected as a more challenging reaction, attempting to illustrate the better efficiency of our macromolecular catalyst (table 1). Indeed, this transformation is known to be difficult to achieve by monomeric salen-cobalt complexes. Jacobsen and his group described highly enhanced reactivity and enantioselectivity by employing cyclic multimeric cobalt-salen complexes. While using their monomeric Co(OTs)-complex at 4 °C, 80 % conversion could be reached after three days and the diol was isolated with 64 % ee; the oligomeric species allowed increasing both the activity (>99 % conversion after 11h) and the selectivity (96 % ee).[8a,b,e] In our case, an adjustment of the reaction conditions was necessary to obtain a complete conversion into (1*R*,2*R*)-cyclohexane-1,2-diol. When the reaction was conducted without any solvent, a complete conversion could not be reached, even in the presence of 2 mol% of **cat-1** after a prolonged reaction time (entries 1-2). Using the reaction conditions developed by Jacobsen's group with acetonitrile as a solvent resulted in no conversion in our case.[8e] Therefore, other solvents were tested (entries 3-5) and toluene delivered the best results in both conversion (>99 % after 6 days) and enantioselectivity (76 % ee with (*R*,*R*)-configuration for the major enantiomer) at room temperature. Lowering the substrate concentration or increasing the water amount did not improve these results (entries 5-7). Increasing the reaction temperature was detrimental to the enantioselectivity (55 % ee) without improving noticeably the conversion. In the optimized conditions for **cat-1**, the monomeric complex **cat-2** gave the product in a significantly lesser amount, clearly demonstrating its reduced activity when compared to the multisite complex **cat-1**.

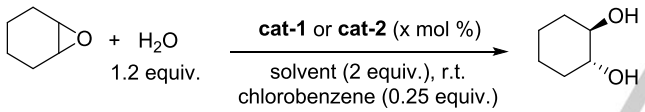


Table 1. Hydrolysis of cyclohexene oxide with **cat-1** or **cat-2**

entry	catalyst	[Co] (mol %)	solvent	t (d)	conv. (%)[a]	ee (%)[a]
1	**cat-1**	1	neat	4	50	64
2	**cat-1**	2	neat	3	55	68
				5	85	68
3	**cat-1**	2	DMF	6	75	12
4	**cat-1**	2	chlorobenzene	2	45	72
				6	69	72
5	**cat-1**	2	Toluene	1	44	76
				6	**>99**	**76**
6	**cat-1**	2	Toluene[b]	6	54	74
7	**cat-1**	2	Toluene[c]	6	97	76
8	**cat-2**	2	Toluene	1	26	74
				6	60	74

[a] determined by chiral GC analysis, with internal standard; [b] toluene (10 equiv.); [c] H_2O (4 equiv.)

The activity of both catalytic systems was also evaluated for the HKR of other terminal epoxides to widen the scope of their application (table 2). 2-Phenoxymethyl oxirane, 2-allyloxymethyl oxirane and 2-phenyloxirane were subjected to hydrolysis in the presence of **cat-1** and **cat-2**. To our delight, **cat-1** promoted, in each case, the HKR of these representing terminal epoxides with higher selectivity factors.[26] The differentiation is obvious for 2-phenoxymethyl oxirane (entries 1-2), whereas same results in terms of selectivity were obtained for the resolution of 2-allyloxymethyl oxirane; in this case, however, the transformation was complete in only 6 h with **cat-1**, whereas 16 h were necessary in the presence of **cat-2** (entries 3-4). The performances are lower for the hydrolysis of 2-phenyloxirane as a demanding substrate; nevertheless, in this case, the structure of the macrocyclic support in **cat-1** seemed again to be a major factor to reach better results from cooperative catalysis than those obtained with **cat-2** as a homogeneous monocatalytic species.

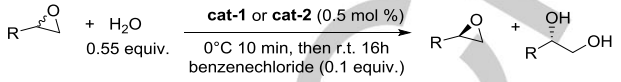
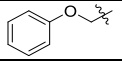
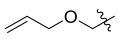


Table 2. HKR of other epoxides with either **cat-1** or **cat-2**

entry	R	cat-x	conv (%)[a]	ee (%)[b]	ee (%)[c]	K_{rel}[d]
1		**cat-1**	52	>99	63	116
2		**cat-2**	51	95	81	81
3[e]		**cat-1**	50	>99	nd	1057
4		**cat-2**	50	>99	nd	1057
5[f]		**cat-1**	52	88	94	28
6[f]		**cat-2**	42	47	96	7

[a] determined by chiral GC analysis, with internal standard; [b] ee of the epoxides determined by chiral GC or HPLC analyses (see SI, part IV); [c] ee of the diols determined by chiral GC or HPLC analyses (see SI, part IV); [d] calculated by equation: $k_{rel} = \ln[(1 - c)(1 - ee)]/\ln[(1 - c)(1 + ee)]$, with c=conversion , and ee of the epoxide; [e] only 6 h reaction time; [f] reaction performed in THF (1.2 equiv.)

Finally, as **cat-1** proved to be insoluble under the highly concentrated reaction conditions, its recyclability was evaluated in the DKR of epibromohydrin. The reaction was performed in THF in the presence of 1.5 equiv. of water and 1.5 mol% of **cat-1** was introduced for the first run of the reaction. To easily recover the catalyst by filtration, diethyl ether was added to the reaction mixture after complete conversion of the substrate in order to both dilute the sample and ensure thorough precipitation of the catalyst. **Cat-1** was rinsed with diethyl ether, dried, and reused in three other similar catalytic runs. After 7h, the first cycle allowed recovery of the targeted product with high yield and enantioselectivity, and the first recycling took gratifyingly place in the same way (table 3). A third run could also be performed, albeit showing some loss of activity, since a prolonged reaction time was necessary to allow complete conversion affording the product in 92 % ee. The last fourth utilization of the catalyst has been achieved with still a good efficiency, delivering continuously the product with high selectivity.

Table 3. DKR of epibromohydrin with **cat-1** with catalysts recycling

run	conv (7 h) (%)[a]	conv (24 h) (%)[a]	ee (%)[b]
1	99	-	94
2	97	-	94
3	89	99	92
4	78	96	90

[a] determined by chiral GC analysis, with internal standard; [b] ee determined by chiral GC (see SI, part IV).

Conclusion

The easily prepared benzyloxy[8]calixarene platform bearing eight enantiopure cobalt-salen complexes has been efficiently used to perform catalytic hydrolysis of various terminal and *meso* epoxides. It is worth mentioning that higher activity was

recorded with this multisite catalyst than with its homogeneous monomer analogue in all the cases studied. The location of the various cobalt sites, connected to the conformationally floppy support by a flexible link, is clearly favorable for their optimal arrangement to achieve a bimetallic cooperativity. Furthermore, and due to its insolubility in the reaction conditions, the catalyst was easily recovered by simple filtration and successfully recycled in subsequent catalytic runs, proving the stability of the cobalt sites in these conditions. We also demonstrated that the targeted enantioenriched products were recovered almost rid of any cobalt traces, without requiring a prior purification by flash column chromatography. This characteristic, which is due to the particular structure of our support, is of major importance for the development of new catalytic processes dedicated to the preparation of enantioenriched synthons towards biological applications. The functionalization of these calix[8]arene by ligands of various structures can also be envisioned by generalizing our simple Click reaction approach. It should make it possible to easily perform a large range of asymmetric catalysis reactions with these insoluble catalysts, notably those for which the notion of cooperativity is essential.

Experimental Section

General. Complete synthetic procedures, description of catalytic tests, characterization details and copy of NMR, IR, UV and XPS spectra and GC chromatograms are given in the supporting information. All reactions were carried out under argon atmosphere and all glassware was flamed before use. Dichloromethane (CH_2Cl_2) was distilled over CaH_2 and Methanol (MeOH) was distilled over magnesium. Extra dry Dimethyformamide (DMF) and Toluene were purchased from ACROS and Alfa Aesar. Sodium hydride (NaH) was purchased from Aldrich. All commercially available reagents were used as received. 5-Ethynyl-2-hydroxybenzaldehyde and (1*S*, 2*S*)-diaminocyclohexane mono-(hydrogen chloride) were prepared by previously reported procedures. ^{1}H NMR and ^{13}C NMR spectra were recorded on either a Bruker DPX 250, Brucker 300 MHz, Bruker Avance 360 MHz, Bruker 400 (400 MHz) or Bruker DRX 400 (400 MHz) instrument and data are reported in ppm with the solvent signal as reference. The HRMS analyses were performed with a MicroTOFq (quadrupole coupled with TOF analyzer). Gas chromatography (GC) analyses were performed on a Varian 430-GC gas chromatograph. Elemental analyses and MALDI were performed by the microanalysis service and Mass Spectrometry group of the Institut de Chimie des Substances Naturelles in Gif-Sur-Yvette (France). ICP-MS analyses were performed by IRAMIS (CEA-Saclay).

Compound 4. In a Schlenk flask equipped with a magnetic stirring bar and flushed with argon, (*1S*, *2S*)-diaminocyclohexane mono-(hydrogen chloride) (0.336 g, 2.43 mmol), 3,5-di-*tert*-butyl-2-hydroxybenzaldehyde (0.569 g, 2.43 mmol) and 4 Å molecular sieves (1g) were introduced and dry and degassed methanol (20 mL) was added under argon. The reaction mixture was stirred at r.t. under argon for 4 hours. Dry Et_3N (0.965 mL, 7.02 mmol) was added under argon, and the compound **3** was dissolved in CH_2Cl_2 (30 mL) and added to the methanol mixture. The reaction was stirred over night at r.t. under argon. The mixture was filtered on Celite, the filtrate was evaporated under reduced pressure. The solid residue was washed with methanol (30 mL) and ethanol (30 mL). The yellow solid was dissolved in Et_2O, precipitated with ethanol and filtered, affording a yellow solid after drying under vacuum (1.4 g, 79 %). **^{1}H NMR** (400 MHz, $CDCl_3$): δ=14.12 (s, 8 H), 13.58 (s, 8 H), 8.28 (s, 8 H), 8.19 (s, 8 H), 7.68 (s, 8 H), 7.61 (s, 8 H), 7.43 (s, 8 H), 6.95-7.03 (m, 40 H), 6.46 (s, 16 H), 4.55 (bs, 16 H), 4.13 (bs, 16 H), 3.86 (bs, 16 H), 3.54 (bs, 16 H), 3.24 (bs, 16 H), 1.79-1.88 (m, 48H), 1.53-1.69 (m, 48 H), 1.36-1.38 (m, 144 H), 1.20 (s, 72 H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$): δ=166.0, 165.3, 160.7, 158.0, 154.9, 149.0, 147.6, 140.1, 137.9, 136.9, 136.5, 134.9, 128.4, 127.8, 127.6, 127.1, 127.0, 126.1, 120.7, 119.0, 118.8, 117.9, 115.2, 72.9, 72.6, 71.9, 69.9, 50.1, 35.1, 35.0, 34.1, 33.2, 33.1, 31.5, 30.3, 29.5, 29.4, 27.3, 27.2, 24.3. **MALDI** (DCTB matrix): calcd (m/z) for $C_{416}H_{520}N_{40}O_{32}Cs$ $[M+Cs]^+$ 6723.9. Found 6724. **Elemental analysis.** Calcd for $C_{416}H_{520}N_{40}O_{32}.2\ CH_2Cl_2$. C, 74.24; H, 7.81; N, 8.28; O, 7.57. Found: C, 74.46; H, 7.95; N, 8.34; O, 7.95. **IR** (KBr, cm^{-1}) ν 3135, 2950, 2862, 2094, 1628, 1599, 1462, 1439, 1389, 1361, 1306, 1272, 1202, 1172, 1045, 1027, 980, 876, 860, 827, 802, 772, 731, 696. **UV-Vis** (DMF) λ_{max} 334 nm, ε 10430 $L.mol^{-1}.cm^{-1}$. **$[\alpha]^{20}$** + 105.34 (c 0.002 $CHCl_3$).

Complex Cat-1. In a Schlenk flask equipped with a magnetic stirring bar and flushed with argon, compound **4** (0.5 g, 0.075 mmol) was dissolved in dry CH_2Cl_2 (10 mL). Solution of $Co(OAc)_2.3H_2O$ (0.187 g, 0.75 mmol) in dry methanol (6 mL) was added to the resulting CH_2Cl_2 solution under argon. The reaction mixture was stirred at r.t. for 4 hours. The mixture was cooled at 0°C, *p*-toluenesolfonic acid monohydrate (0.143 g, 0.75 mmol) in CH_2Cl_2 (5 mL) was added under air; the mixture was further stirred under 1 atm of oxygen for 16 hours. The mixture was then evaporated under reduced pressure and the solid was washed with methanol, affording a green solid after drying under vacuum (0.534 g, 84 %). **^{1}H NMR** (400 MHz, DMSO-d_6): δ=8.37 (s, 8 H), 8.03 (s, 8 H), 7.91 (s, 8 H), 7.81-7.83 (m, 16 H), 7.46-7.48 (m, 32 H), 7.03-7.08 (m, 56 H), 6.54 (bs, 16 H), 4.64 (bs, 16 H), 4.32 (bs, 16 H), 3.92 (bs, 8 H), 3.61 (s, 24 H), 3.05 (s, 16H), 2.25 (s, 24 H), 1.56-1.96 (m, 24 H), 1.30 (s, 72 H). **^{13}C{^{1}H} NMR** (100 MHz, DMSO-d_6): δ=164.8, 164.3, 164.2, 161.9, 154.1, 148.5, 146.7, 142.9, 141.8, 137.5, 136.8, 136.2, 134.8, 130.4, 129.3, 129.0, 128.6, 128.0, 127.4, 125.5, 119.6, 119.3, 118.5, 117.3, 114.5, 72.6, 69.4, 69.0, 49.3, 35.8, 35.7, 33.6, 31.5, 30.5, 30.2, 29.6, 29.4, 26.8, 24.3, 20.8. **Elemental analysis.** Calcd for $C_{472}H_{560}N_{40}O_{56}S_8Co_8.5\ CH_2Cl_2$. C, 64.79; H, 6.50; N, 6.34; S, 2.90. Found: C, 64.34; H, 6.57; N, 6.67; S, 2.40. **IR** (KBr, cm^{-1}) ν 2946, 2864, 2094, 1623, 1529, 1467, 1435, 1385, 1320, 1254, 1201, 1168, 1121, 1033, 1010, 813, 782, 743, 681, 567. **UV-Vis** (DMF) λ_{max} 400 nm, ε 7263 $L.mol^{-1}.cm^{-1}$. **$[\alpha]^{20}$** + 1020.4 (c 8.10^{-6} DMF). **XPS quantification** calcd for. $C_{472}N_{40}O_{56}S_8Co_8$. C, 80.8; N, 6.8; O, 9.6; S, 1.4; Co, 1.4. Found: C, 81.3; N, 5.7; O, 10.7; S, 1.3; Co, 1.

Compound 9. In a Schlenk flask equipped with a magnetic stirring bar and flushed with argon, (*1S*, *2S*)-diaminocyclohexane mono-(hydrogen chloride) **C** (0.081 g, 0.54 mmol), 3,5-di-*tert*-butyl-2-hydroxybenzaldehyde (0.126 g, 0.54 mmol) and 4 Å molecular sieves (1g) were introduced and dry and degassed methanol (5 mL) was added under argon. The reaction mixture was stirred at r.t. under argon for 4 hours. Dry Et_3N (0.205 mL, 1.47 mmol) was added under argon, and compound **8,** dissolved in CH_2Cl_2 (6 mL), was then added to the methanol mixture. The reaction was stirred overnight at r.t. under argon. The mixture was filtered on Celite, the filtrate was evaporated under reduced pressure. The solid residue was purified by silica gel column chromatography with pentane/AcOEt (7/3) as eluent, to afford a yellow solid (0.241 g, 61 %). **^{1}H NMR** (400 MHz, $CDCl_3$): δ=14.09 (s, 1 H), 13.62 (s, 1 H), 8.32 (s, 1 H), 8.29 (s, 1 H), 7.72 (d, *J* = 1.6Hz, 1 H), 7.59 (s, 1 H), 7.28-7.43 (m, 7 H), 6.96 (d, *J* = 6.9 Hz, 1 H), 6.89 (d, *J* = 9.0 Hz, 2 H), 6.80 (d, *J* = 9.0 Hz, 2 H), 5.00 (s, 2 H), 4.45 (t, *J* = 6.9 Hz, 2 H), 3.94 (t, *J* = 5.8 Hz, 2 H), 3.29-3.38 (m, 2 H), 2.14 (quint, *J* = 7.2 Hz, 2 H), 1.74-2.04 (m, 10H), 1.45 (s, 9 H), 1.39 (m, 9 H), 1.21 (s, 9 H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$): δ=166.1, 165.4, 160.8, 158.1, 153.2, 148.0, 140.1, 137.9, 137.4, 136.5, 128.7, 128.0, 127.6, 127.2, 127.1, 126.9, 126.1, 120.6, 118.8, 118.5, 116.0, 115.5, 72.5, 72.4, 70.8, 67.6, 50.1, 35.1, 35.0, 34.1, 33.2, 33.1, 31.5, 30.3, 29.6, 29.5, 27.4, 26.4, 24.4. **HRMS** (ESI, positive mode): calcd (m/z) for $C_{51}H_{65}N_5NaO_4$ $[M+Na]^+$ 834.4929. Found 834.4905. **Elemental analysis.** Calcd for $C_{51}H_{65}N_5O_4$. C, 75.43; H, 8.07; N, 8.62; O, 7.88. Found: C, 75.00; H, 8.28; N, 8.19; O, 7.70. **IR** (KBr, cm^{-}

^{1}) ν 2952, 2862, 1628, 1598, 1507, 1469, 1454, 1439, 1389, 1361, 1272, 1227, 1202, 1173, 1044, 1026, 824, 802, 773, 732, 696. **UV-Vis** ($CHCl_3$) λ_{max} 336 nm, ε 1765 $L.mol^{-1}.cm^{-1}$. $[\alpha]^{20}$ + 140 (c 0.002 $CHCl_3$).

Complex Cat-2. In a Schlenk flask equipped with a magnetic stirring bar and flushed with argon, compound **9** (0.25 g, 0.31 mmol) was dissolved in dry CH_2Cl_2 (10 mL). A solution of $Co(OAc)_2.3H_2O$ (0.085 g, 0.34 mmol) in dry methanol (6 mL) was added to a CH_2Cl_2 solution under argon. The reaction mixture was stirred at r.t. under argon for 4 hours. The mixture was cooled at 0°C, *p*-toluenesulfonic acid monohydrate (0.066 g, 0.34 mmol) in CH_2Cl_2 (8 mL) was added under air, and the mixture was stirred under 1 atm of oxygen for 16 hours. The mixture was evaporated under reduced pressure. The solid was dissolved in CH_2Cl_2 filtered, dissolved in minimum of CH_2Cl_2, precipitated with Et_2O and washed with Et_2O, affording a dark green powder after drying under vacuum (0.272 g, 84 %). **^{1}H NMR** (360 MHz, DMSO-d_6): δ=8.43 (s, 1 H), 8.03 (s, 1 H), 7.95 (s, 1 H), 7.84 (d, *J* = 8.9 Hz, 2 H), 7.31-7.47 (m, 9 H), 7.10 (d, *J* = 7.7 Hz, 2H), 6.92 (d, *J* = 8.9 Hz, 2 H), 6.85 (d, *J* = 8.9 Hz, 2 H), 5.02 (s, 2 H), 4.46 (t, *J* = 6.6 Hz, 2 H), 3.93 (t, *J* = 6.0 Hz, 2 H), 3.61 (bs, 2 H), 3.08 (bs, 2 H), 2.28 (s, 3 H), 1.8959-2.02 (m, 28 H), 1.30 (s, 9 H). **^{13}C{^{1}H} NMR** (100 MHz, DMSO-d_6): δ=164.7, 164.5, 164.2, 161.9, 152.6, 152.3, 146.6, 145.9, 142.9, 141.7, 137.5, 137.3, 135.9, 130.3, 129.3, 128.9, 128.6, 128.3, 127.9, 127.7, 127.5, 125.4, 119.5, 119.2, 118.4, 117.2, 115.6, 115.2, 69.5, 69.3, 55.9, 49.1, 35.8, 35.7, 33.5, 31.4, 30.3, 30.2, 29.5, 29.3, 26.5, 25.7, 24.2, 20.7, 18.5. **HRMS** (ESI, positive mode): calcd (m/z) for $C_{51}H_{63}CoN_5NaO_4$ $[M\text{-}OTs]^+$ 868.4207. Found 868.4158. **HRMS** (ESI, negative mode): calcd (m/z) for $C_7H_7O_3S$ $[M]^-$ 171.0116. Found 171.0109. **Elemental analysis.** Calcd for $C_{58}H_{70}N_5O_7SCo.2$ MeOH. C, 65.26; H, 7.12; N, 6.34; S, 2.90. Found: C, 65.47; H, 6.88; N, 6.54; S, 2.89. **IR** (KBr, cm^{-1}) ν 2944, 2864, 1623, 1527, 1506, 1455, 1435, 1385, 1323, 1256, 1229, 1207, 1168, 1119, 1034, 1011, 814, 782, 746, 680, 567. **UV-Vis** ($CHCl_3$) λ_{max} 398 nm, ε 700 $L.mol^{-1}.cm^{-1}$. $[\alpha]^{20}$ + 2267(c 8.610^{-4} $CHCl_3$).

Dynamic HKR of epibromohydrin catalyzed by cat-1 or cat-2. To a salen Co^{III} (**cat-1**) or (**cat-2**) (x mol% [Co]) epibromohydrin (141 µL, 1.7 mmol), chlorobenzene (50 µL, 0.5 mmol) and THF (200 µL) were added; water (44.5 µL, 2.55 mmol) was then added slowly at r.t. under continuous stirring. The resulting solution was stirred at r.t. for 24 h before the addition of CH_2Cl_2 (5 mL), Amberlyst 15 (16 mg) and 2,2-dimethoxypropane (418 µL, 3.4 mmol). The mixture was stirred at room temperature for another 18 h and then filtered on Celite. The yield of resoluted epoxide was determined by achiral GC analysis (column VF-1ms) with chlorobenzene as an internal standard. The ee of the resulted acetal was determined by chiral GC analysis (column chiraldex β-PM, 110°C, isothermal, tmaj =6.68 min, tmin = 6.84 min). The absolute stereochemistry of the main product was consequently assigned as (*S*).

Hydrolysis of cyclohexene oxide catalyzed by complex cat-1 or cat-2. Water (21 µL, 1.2 mmol) was added dropwise at r.t under continuous stirring to a solution of the salen Co(III) complex **cat-1** or **cat-2** (1 or 2 mol%) in cyclohexene oxide (100 µl, 0.99 mmol), chlorobenzene (25 µL, 0.25 mmol) and solvent (2 equiv.). The resulting solution was stirred at room temperature for 6 days before addition of THF (5 mL) and subsequent filtration on celite. The yield of resoluted epoxide was determined by achiral GC analysis (column VF-1ms) with chlorobenzene as an internal standard. The ee of the diol was determined by chiral GC analysis (column chiraldex B-PM, 130 °C, 30 min, tmaj = 10.36 min, tmin = 10.17 min).

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Keywords: Calixarenes • Cobalt • Epoxides • Kinetic resolution • Salen ligands

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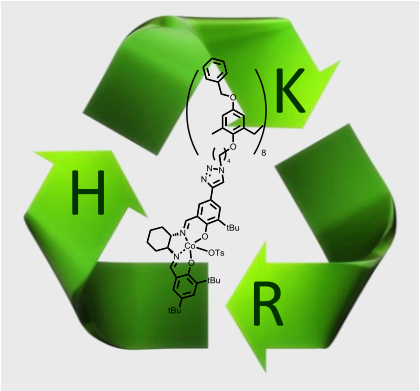
A calix[8]arene supported cobalt-salen complex has been straightforwardly prepared as multisite catalyst, efficient for the hydrolytic kinetic resolution of various epoxides, demonstrating highly enhanced activity compared to its monomeric analogue. It was recovered and reengaged in successive catalytic runs demonstrating its high stability. Products were isolated almost rid of any cobalt traces by simple filtration.



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Calix[8]arene as new platform for Cobalt-Salen complexes immobilization and use in hydrolytic kinetic resolution of epoxides