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Mixing and matching chiral cobalt- and manganese-based calix-salen catalysts for the asymmetric hydrolytic ring opening of epoxides

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ABSTRACT

Homochiral oligomeric salen macrocycles possessing aromatic spacers have been prepared as new calix-salen derivatives. The corresponding cobalt and manganese complexes were synthesized and characterized, and their catalytic activities have been studied in the challenging hydrolysis of *meso* epoxides. While manganese calix-salen complexes were not active in the studied reactions, the dual heterobimetallic system, using an equimolar combination of cobalt and manganese calix-salen derivatives proved to be more enantioselective than the sole cobalt system. Furthermore, as heterogeneous complexes, the catalytic mixture could be easily recovered by simple filtration and successfully reengaged in subsequent catalytic runs. Interestingly, no need for cobalt reactivation was noticed to maintain maximum efficiency of this dual system. The matched Co/Mn dual catalyst was also used to promote the dynamic hydrolytic kinetic resolution of epibromohydrin.

1. Introduction

The high efficiency in terms of both the activity and enantioselectivity of salen-derived complexes to achieve the formation of new bonds is well-established, for the synthesis of valuable enantioenriched synthons,[1] even on a large industrial scale.[2] Consequently, numerous research teams have already described different methods to heterogenize and, thus, recycle these catalysts.[3] Moreover, they have been proven to be particularly efficient for promoting epoxide ring-opening.[4] Precisely in this context, Jacobsen et al. demonstrated that catalysis occurred through cooperative bimetallic activation.[5] Numerous efforts have since been devoted to the specific preparation of such catalysts for efficient dual activation. Some of them are based on the formation of bimetallic complexes arising from the association of two ligands by non-covalent interactions.[6] Other research teams have proposed the immobilization of various salen-complexes on insoluble supports, with the aim of enhancing cooperativity by specific spatial arrangement while also promoting easy recovery.[7] Some valuable examples also imply the formation of soluble or insoluble salen-type linear oligomers or polymers.[8] Macrocyclic structures have also been described to show undeniable activity enhancement.[9] These examples have in common the use of polysalen complexes, in which the same metal is used to promote the bimetallic activation.

We have recently developed a heterobimetallic dual-catalyst system based on the preparation and use of various salen complexes, for the hydrolytic kinetic resolution of terminal epoxides.[10] A combination of cobalt-salen and manganese-salen complexes, generated from ligands possessing the same stereochemical configuration, produced highly enantioselective catalysts for the hydrolysis of epibromohydrin, or other terminal epoxides and also for the more challenging ring opening of cyclohexene oxide. Furthermore, we have reported the efficient synthesis of new macrocyclic salen complexes (calix-salen complexes), containing either chromium, cobalt or copper salts, and their use as catalysts to promote various enantioselective reactions, such as Diels–Alder and Henry reactions, the additions of dimethylzinc to aldehydes, nucleophilic ring-openings of epoxides and hydrolytic kinetic resolution reactions.[11] Efficient reactivities were recorded, leading in some specific cases to enhanced isolated yields and enantioselectivities, especially for those transformations in which cooperative catalysis was already reported to be operative. Furthermore, all macrocyclic catalysts were easily recovered by simple filtration at the end of

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the reactions and could be reused in renewed runs, thus proving their recyclability and following, at best, the principles of green chemistry.

Herein we report our investigations toward the use of such macrocyclic complexes containing different metals and their efficiency in their dual use for the ring opening of epoxides. Special attention will also be drawn for evaluating their recovery and reuse in these transformations.

2. Results and discussion

We have previously reported a straightforward synthesis of calix-salen ligands, based on the condensation of the chiral, enantiopure (*S*,*S*)-cyclohexane-1,2-diamine with a disalicylaldehyde compound linked by a phenyl group. The judicious choice of the concentration of the reaction mixture allowed us to control the macrocycle size; a concentrated solution led to the formation of large rings, whereas dilution led to the main formation of dimeric structures.[12] Other macrocycles, possessing aromatic spacers with various structures, have also been prepared, following the same procedure. The synthesis of the targeted dialdehydes is depicted in Scheme 1. The boronic ester (3-*tert*-butyl-2-hydroxy-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzaldehyde) was synthesized in three steps, starting from 2-*tert*-butyl-phenol, by *para*-bromination, *ortho*-carbonylation and the final introduction of the boron ester, in 63% overall yield, as previously reported. Subsequent Suzuki–Miyaura type coupling with 1,4-dibromobenzene, 2,7-dibromofluorene or 4,7-dibromobenzo[*c*]-1,2,5-thiadiazole gave the targeted triaromatic structures **1**, **2,** and **3** in good yields.

With the aim of preparing macrocycles with a large ring size, dilute conditions used for the condensation reactions were chosen in accordance with those used for the preferential synthesis of the tetrameric benzene containing structures.[12] The reactions occurred for all compounds in THF in which an equimolar mixture of the chosen dialdehyde **1** to **3** was engaged with the enantiopure (*S*, *S*)-cyclohexane-1,2-diamine (each compound 0.112 M), at 70 °C in the presence of molecular sieves for 24 h. The corresponding macrocycles were recovered by precipitation in methanol and subsequent filtration, to give the expected compounds in quantitative yields for the three calix-salen derivatives **4** to **6** (Scheme 2). These ligands have been characterized by ^{1}H NMR spectroscopy (DOSY experiments), following a characterization method we developed for analyzing the parent macrocycle with the phenyl spacer. The chemical shift of the imine protons in these structures and comparison with the values obtained in the previous case (see Supporting information) indicated that the tetrameric species was indeed that mainly formed. According to these NMR studies, the macrocycle **5** produced from **2** did not contain any dimeric species and was only the tetramer (76%) and the pentamer (24%). The same trend as observed for the calix-salen **6** from **3**, although in this specific case, a small amount of the trimer could be detected (10%) along with the pentamer (8%), with the tetramer being formed as the major species (82%).

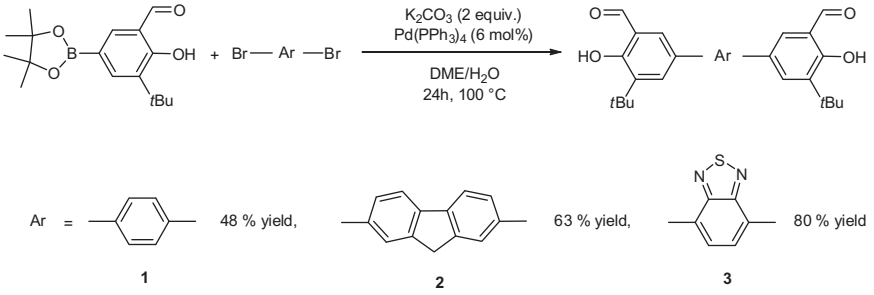
The macrocycles were further characterized by Maldi-TOF analyses, proving that the condensation occurred together with the loss of two water molecules, and thus confirming the formation of cyclic structures. As for compound **4** a repetitive unit of *m*/*z* 508.31 was observed; this value was *m*/*z* 596.34, which is characteristic for the targeted structure of **5**. For this fluorene containing compound, the dimer, the trimer, and the tetramer could be detected but the presence of the corresponding pentamer was not noticed (see SI). Accordingly for the calix-salen **6**, the cyclic oligomers were observed with a repetitive mass unit of 566.27. Although this spectroscopic technique is not quantitative, it demonstrates that the production of cyclic structures can be efficiently extended to the use of structurally varied disalicylaldehydes, possessing rigid linkers (see Scheme 2).

Finally, cobalt salts were incorporated into these cyclic salen ligands (used as mixtures of differently sized macrocycles) following classical procedures,[13] with the aim of forming active catalytic sites in each coordinating salen. The cobalt complexes **7**, **8,** and **9** were easily recovered in quantitative yields as brown powders by filtration and subsequent washing with methanol. Accordingly, the corresponding manganese complexes were also prepared from manganese acetate tetrahydrated in an ethanol/toluene mixture under an argon atmosphere. Subsequent aerobic oxidation occurred in the presence of brine to give the targeted manganese complexes **10**, **11,** and **12** in up to quantitative yield as brown powders (see Scheme 3).[14]

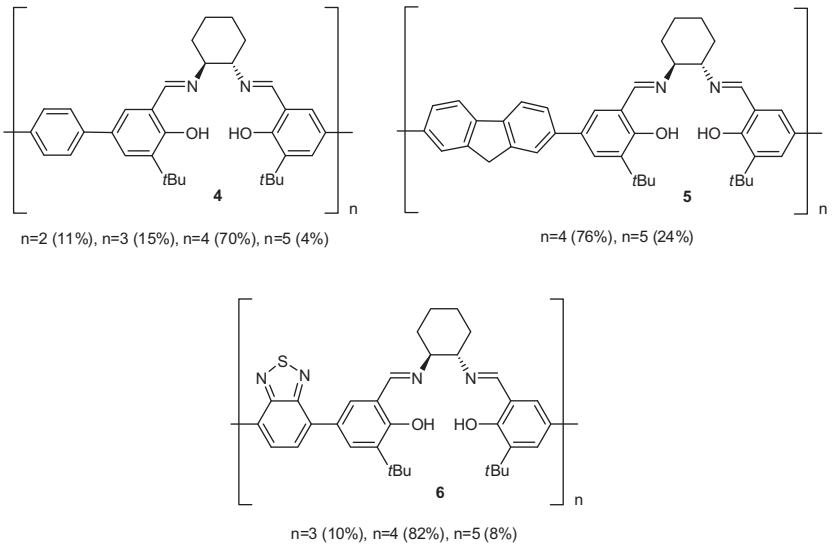
Characterization of the obtained complexes was mainly performed via ATR–IR spectroscopy of the insoluble species. Before complexation of any metals, the vibrational elongation wavelength of the imine function was observable at ca. 1628 cm^{-1}. The coordination steps, leading to the formation of Co(III) complexes were accompanied with a shift of the wavelength and a splitting of two bands at approximately 1604 cm^{-1} and 1637 cm^{-1} in each case. For the manganese complexes this imine vibration is visible at approximately 1606–1611 cm^{-1} (see SI for more information).

The nucleophilic ring opening of *meso*-epoxides is a valuable synthetic transformation, leading to the formation of two stereogenic centers.[15] The control of the enantioselectivity, for instance in the case of the hydrolysis, is not so straightforward and typical homogeneous enantiopure cobalt-salen complexes struggle to provide high enantioselectivities. In this context, Jacobsen et al. prepared salen-based macrocycles with Co-OTs active sites, and demonstrated their ability to perform this transformation efficiently.[9a,f] The hydrolytic enantioselective opening of cyclohexene oxide was thus chosen as a benchmark reaction to evaluate the catalytic efficiency of the new cobalt- and manganese-based calix-salen complexes.

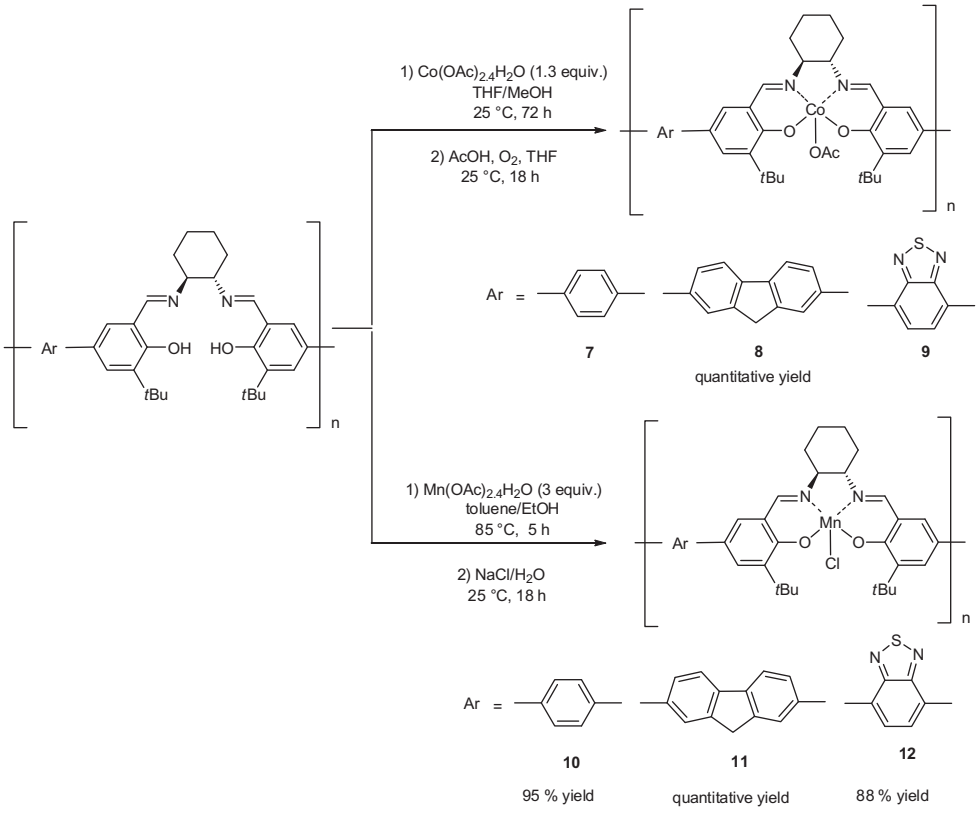
The hydrolysis of cyclohexene oxide was performed in a small amount of THF (0.33 M) with 1.3 equiv of water and the reaction



Scheme 1. Synthesis of dialdehydes **1**, **2,** and **3** by a Suzuki cross-coupling.



Scheme 2. Synthesis of calix-salen derivatives.

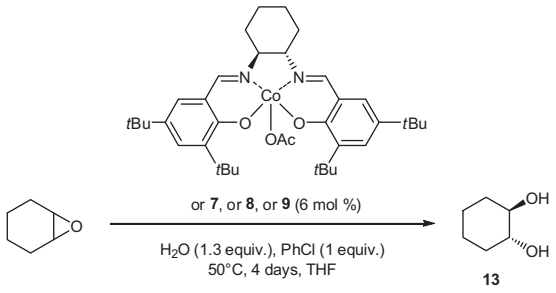


Scheme 3. Synthesis of calix-salen cobalt and manganese complexes.

was run at 50 °C for four days, in the presence of chlorobenzene as the internal standard. Under these conditions, the Jacobsen salen cobalt–acetate complex prepared from (*S*,*S*)-cyclohexane-1,2-diamine (6 mol %), gave the expected diol with an (*R*,*R*)-configuration in 80% isolated yield and with 18% ee (see Scheme 4).

Complexes **7**, **8,** and **9** were tested to evaluate their ability to perform this transformation, and all species proved active to produce the targeted diol, albeit with low conversions and selectivities (see Table 1). The recorded enantioselectivities remained modest, but in each case better selectivities were observed compared to those obtained with the Jacobsen monomeric counterpart, specifically by using catalyst **9** which gave diol **13** with up to 58% ee. The configuration of **13** was also assigned as (*R*,*R*) according to co-elution tests performed by chiral gas chromatography analyses.

Catalysts **7**, **8,** and **9**, as insoluble species, were easily recovered by filtration after the first reaction run. They were subsequently washed with a THF/pentane mixture, vacuum dried and then reused in the same transformation to evaluate their stability and their catalytic activities. Unfortunately, these macrocyclic complexes proved to be poorly recyclable since the second use of **7** or **8** in the hydrolysis of cyclohexene oxide was accompanied with a substantial loss of activity, thus preventing the possibility to



Scheme 4. Hydrolysis of cyclohexene oxide by salen-based cobalt complexes.

Table 1
Cyclohexene oxide hydrolysis promoted by cobalt (*S*,*S*)-calix-salen complexes **7**, **8,** and **9**[a]

Run	7		8		9	
	Conv.[b] (%)	ee[c] (%)	Conv.[b] (%)	ee[c] (%)	Conv.[b] (%)	ee[c] (%)
1	33	28	41	26	66	58
2	15	21	17	4	40	46
3					16	30

[a] Substrate 0.4 mmol, 6 mol % cobalt (*S*,*S*)-calix-salen, 1.3 equiv H_2O, 4 days, THF, 50 °C.
[b] Determined by GC analysis, with chlorobenzene as internal standard.
[c] Determined by chiral GC analysis (see SI).

realize a third run; in the case of **8**, diol **13** was recovered in its nearly racemic form. The use of the benzothiadiazole-containing calix-salen **9** improved these results since three runs could be performed, albeit with a decrease in both the conversion and selectivity of the reaction.

Accordingly, manganese derivatives **10**, **11,** and **12** were also evaluated as presumed non-catalysts in these hydrolytic ring-opening reactions,[16] and as expected under the same reaction conditions, no reaction occurred even after prolonged reaction times.

The cooperativity of cobalt and manganese species was then explored and both cyclic catalysts containing cobalt and manganese metals, respectively, were thus mixed, in an equimolar ratio, to evaluate any potential beneficial effect of their dual use on the course of the transformation.

Accordingly, each cobalt calix-salen complex **7**–**9** was again employed in the hydrolytic kinetic resolution of cyclohexene oxide with its corresponding manganese analogue, possessing the same configuration at the stereogenic centers. Although no major improvement could be detected concerning the activity of the implied catalysts, in each case however, an important increase in the selectivity of the reaction could be observed. The use of additional manganese (*S*,*S*)-calix-salen, gave diol **13** with 52% ee instead of 28% in the case of the cobalt calix-salen **7**, and with 50% ee, instead of 26% for the transformation in the presence of **8**. The best system was obtained for the catalyst combination **9** and **12**, resulting in a large enantioselectivity enhancement. The importance of the configuration of the additional cyclic manganese complex was checked by carrying out the synthesis and characterization of *ent*-**6** and its corresponding Mn complex *ent*-**12** (see SI). As can be deduced from Table 2, the combination of (*S*,*S*)-cobalt calix-salen together with an (*R*,*R*)-manganese calix-salen led to poorer results. We already observed such cooperative positive or negative effects by studying homogeneous salen-type complexes,[10] confirming the involvement of the manganese additive in the selectivity-determining transition state and the importance of its configuration. We proposed, by using our previously described monomeric salen complexes species that a matched combination of the cobalt and the manganese complexes resulted exclusively from the arrangement of species with ligands possessing the same configuration leading

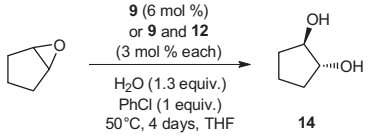
Table 2
Cyclohexene oxide hydrolysis promoted by cobalt (*S*,*S*)-calix-salen complexes **7**, **8** and **9** together with manganese calix-salen complexes **10**, **11**, **12** and ***ent*-12**[a]

Run	7 and 10		8 and 11		9 and 12		9 and *ent*-12	
	Conv.[b] (%)	ee[c] (%)	Conv.[b] (%)	ee[c] (%)	Conv.[b] (%)	ee[c] (%)	Conv.[b] (%)	ee[c] (%)
1	16	52	88	50	53	70	37	48
2	19	42	5	34	39	75	24	26
3					12	71		

[a] Substrate 0.4 mmol, 3 mol % cobalt (*S*,*S*)-calix-salen and 3 mol % manganese (*S*,*S*)-calix-salen (or (*R*,*R*)-calix-salen), 1.3 equiv H_2O, 4 days, THF, 50 °C.
[b] Determined by GC analysis, with chlorobenzene as internal standard.
[c] Determined by chiral GC analysis (see SI).

to an optimized spatial shape necessary for obtaining high enantioselectivities. We propose that in the case of the macrocyclic calix-salen involved herein, the manganese species is used as an epoxide activator, whereas the cobalt complex activates the water. This heterobimetallic activation leads thus to the reduction of the alternative less enantioselective monometallic pathway and allows selectivity enhancement.[5a] Furthermore, each mixture of catalysts could be recovered by simple filtration and used in a new run with fresh substrates; the combination **9** and **12** could be reused up to three times.

These cooperative effects were successfully applied to the transformation of other substrates, to study the scope of their application. Since the combination **9** and **12** led to the best results for the hydrolysis of cyclohexene oxide, it seemed important to verify this effect with the analogous substrate, cyclopentene oxide (see Scheme 5).



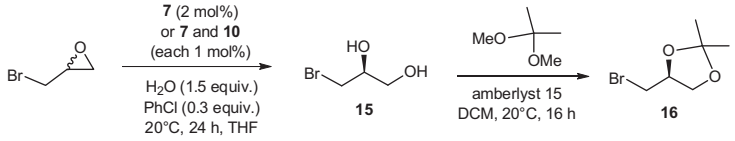
Scheme 5. Hydrolysis of cyclopentene-oxide by salen-based cobalt complexes.

(*S*,*S*)-Cobalt calix salen **9** was first used to promote this transformation to provide diol **14** with 38% ee and 39% conversion of the epoxide. This macrocyclic catalyst could be recovered by precipitation and filtration and its reuse gave the targeted product albeit with a decreased yield and enantioselectivity (see Table 3). Analogously to the transformation of cyclohexene oxide, the dual use of an equimolecular mixture of (*S*,*S*)-cobalt calix salen **9** and (*S*,*S*)-manganese calix salen **12** drastically improved the course of the reaction, leading in this case again to a matched effect and produced **14** both in high conversion (90%) and with an increased ee of 58%. The catalyst was recovered and reused three times, still supplying **14** with 52% ee in the third run.

Table 3
Cyclopentene-oxide hydrolysis promoted by **9**, or **9** and **12**[a]

Run	9		9 and 12	
	Conv.[b] (%)	ee (%)[c]	Conv.[b] (%)	ee (%)[c]
1	39	38	90	58
2	19	18	66	60
3			49	52

[a] Substrate 0.4 mmol, 6 mol % **9** or 3 mol % **9** and 3 mol % **12**, 1.3 equiv H_2O, 4 days, THF, 50 °C.
[b] Determined by GC analysis, with chlorobenzene as internal standard.
[c] Determined by chiral GC analysis (see SI).



Scheme 6. Dynamic hydrolytic kinetic resolution of epibromohydrin.

The last benchmark transformation used to evaluate this heterobimetallic enhancement effect, was the hydrolytic kinetic resolution of epibromohydrin (see Scheme 6). This substrate undergoes fast racemization under the hydrolytic kinetic resolution conditions and the resulting diol **15** was obtained with complete conversion since, in this case, kinetic hydrolytic resolution proceeded in dynamic mode. The product was recovered and analyzed as acetonide derivative **16** for a straightforward determination of the transformation selectivity. Jacobsen et al. reported that 3-bromopropane-1,2-diol was isolated in 93% yield and 96% ee, with 1.5 equiv of H_2O in THF, in the presence of 2 mol % of the classical chiral bis-*tert*-butyl-cyclohexyl-salen Co(III)-OAc catalyst.[17]

Cobalt catalyst **7** (2 mol %) was used in the hydrolytic kinetic resolution of epibromohydrin, and complete conversion toward the formation of the expected diol was observed after 24 h reaction time, with compound **16** being isolated with 88% ee. The macrocyclic insoluble catalyst was easily recovered and reused in subsequent runs while showing no loss in selectivity after each reuse. The catalytic activity could be maintained for three runs, but a significant decrease was observed after the fourth use of the catalyst (see Table 4). Such a deactivation is well described in the bibliography, due to the transformation of essential Co(III)-OAc sites into Co(III)-OH species, due to the nucleophilicity of the acetate counteranion. Treatment is then necessary for reactivation,[5a,18] and catalyst **7** was thus triturated with acetic acid before its reuse for a fifth run and provided high activity for this last transformation. On the other hand, the combination of **7** and **10** was tested for the same transformation by using an equimolar mixture (1 mol % each) of both cyclic complexes. An important match effect could again be observed since an almost complete conversion gave compound **16** with 92% ee at the first run. More interestingly, this mixture of catalyst was recovered and reused up to eight times with only a slight decrease in its efficiency. Notably in this case, no reactivation step was needed; we assume this indicates the heterobimetallic activation, the Mn-complex probably substituting the through time disappearing cobalt–acetate complex, for activating the epoxide.

Table 4
Hydrolytic kinetic resolution of epibromohydrin hydrolysis promoted by **7**, or **7** and **10**[a]

Run	**7**		**7** and **10**	
	Conv.[b] (%)	ee[c] (%)	Conv.[b] (%)	ee[c] (%)
1	>99	88	97	92
2	88	89	97	90
3	83	93	97	90
4	68	91	97	90
5	85[d]	89[d]	97	90
6			82	90
7			83	86
8			83	82

[a] Substrate 1.7 mmol, 2 mol % **7** or 1 mol % **7** and 1 mol % **10**, 1.5 equiv H_2O, 24 h, THF, 20 °C.
[b] Determined by GC analysis, with chlorobenzene as internal standard.
[c] Determined by chiral GC analysis (see SI).
[d] The catalyst has been reactivated in the presence of AcOH before reuse.

Since chiral catalysts stability issues in recovery studies are often caused by small-scale handling difficulties, the best optimized system **9** and **12** was used to hydrolyze cyclohexene oxide at a ten times larger scale (see Table 5).

Table 5
Cyclohexene oxide hydrolysis promoted by cobalt (*S,S*)-calix-salen complex **9** together with manganese (*S,S*)-calix-salen complex **12**[a]

Run	**9** and **12**	
	Conv.[b] (%)	ee[c] (%)
1	38	78
2	38	78
3	39	78
4	38	78
5	10	47
6	8	46

[a] 4 mmol cyclohexene oxide, 3 mol % **9** and 3 mol % **12**, 1.3 equiv H_2O, 4 days, THF, 50 °C.
[b] Determined by GC analysis, with chlorobenzene as internal standard.
[c] Determined by chiral GC analysis (see SI).

The preceding experiment (see Table 2) could only be performed for three runs with concomitant loss of activity. In this case, the catalysts mixture performed better, since six runs could be achieved, four of them with no loss of selectivity or activity.

3. Conclusion

We have thus demonstrated that the use of heterogeneous heterobimetallic catalytic systems was particularly effective to promote the hydrolytic kinetic resolution of cyclohexene oxide, cyclopentene oxide and epibromohydrin. A matched effect was obtained using an equivalent catalytic mixture of cobalt and manganese-based calix-salen derivatives generated from macrocycles possessing the same structural configuration. This approach allowed for better enantioselectivities than the ones obtained with the use of the homometallic cobalt-based calix-salen catalyst, for each targeted products. In addition, this mixture of catalyst could be easily recovered by filtration and reused in subsequent runs with reasonable stability in terms of activity and selectivity. In these cases, the known cobalt reactivation step, unavoidable in many procedures involving such catalyst recovery, was not necessary here to maintain high catalytic activity along with the reuse. Although manganese-based calix-salen proved to be inactive in the studied reactions when used alone, we suggest that their use together with the cobalt-based calixsalen analogues inhibits the competitive monometallic, less enantioselective, reaction pathway. We propose in this case that the manganese-based calix-salen serves as a Lewis activator for the epoxides, and catalyzes the hydrolytic kinetic resolution together with the Co-OH species generated from cobalt acetate-based calix-salen, by hydrolysis.

4. Experimental

4.1. General

Reactions (except catalytic transformations) were carried out under argon in oven-dried glassware with magnetic stirring. THF was distilled from sodium/benzophenone and DCM was distilled from CaH_2 before use. ^1H NMR spectra and ^{13}C NMR spectra were

recorded on either a Bruker AM 360 (360 MHz), AM 300 (300 MHz) or AM 250 (250 MHz) instrument with samples dissolved in $CDCl_3$ and data are reported in ppm with the solvent signal as reference (7.24 ppm for ^1H NMR and 77 ppm for ^{13}C NMR). MALDI-TOF analyses were performed by the service of mass spectrometry of the Institut de Chimie des Substances Naturelles, Gif sur Yvette, on a Voyager DE-SFR spectrometer with a solution of dithranol in THF (10 g/L) as matrix. High resolution mass spectra were recorded on a Bruker MicrOTOF-Q spectrometer using electrospray ionization (ESI) and tandem quadrupole coupled with a time-of-flight mass analyzer. FTIR spectra were measured on a Vertex 70 Bruker spectrometer with a germanium gate ATR accessory. Optical rotations were determined on a Perkin–Elmer 241 digital polarimeter with a sodium lamp (489 nm, D line). Achiral gas chromatography analyses were performed on a Varian 430-GC chromatograph using helium as a carrier gas. Chiral gas chromatography analyses were performed on a GC Shimadzu 2010-Plus, FID, SSL using hydrogen as a carrier gas. For the hydrolysis of cyclohexene oxide, the conversion was determined by using the column VF1-MS 15 m × 0.25 mm × 0.25 μm (50 °C, 5 min, 10 °C/min, 250 °C, 2 min). The enantioselectivity of the reactions were determined with a Chiraldex column B-PM 50 m × 0.25 mm × 0.12 μm, isotherm, 130 °C. For the hydrolysis of cyclopentene oxide, the conversion was determined by using the column UB-624 30 m × 0.32 mm × 1.8 μm (50 °C, 1 min, 10 °C/min, 250 °C, 20 min). The enantioselectivity of the reactions were determined with a Chiraldex column B-PM 50 m × 0.25 mm × 0.12 μm, isotherm, 90 °C. For the hydrolytic kinetic resolution of epibromohydrin, the conversion was determined by using the column VF1-MS 15 m × 0.25 mm × 0.25 μm (110 °C, 10 min to 250 °C, 2 min). The enantioselectivity of the reactions were determined with a Chiraldex column B-PM 50 m × 0.25 mm × 0.12 μm, isotherm, 110 °C.

4.2. Suzuki cross-coupling

A Schlenk tube was charged with boronic ester (2 equiv, 40.8 mmol, 12.4 g), dibromoaryl (1 equiv, 20.4 mmol), $Pd(PPh_3)_4$ (0.06 equiv, 1.2 mmol, 1.4 g) and K_2CO_3 (2 equiv, 40.8 mmol, 5.6 g) and kept under argon by successive vacuum-argon cycles. Degassed DME (73 ml) and degassed water (30 ml) were transferred via cannula into the Schlenk flask. The reaction mixture was further heated at 100 °C, with stirring for 24 h. Water (200 ml) was then added and the aqueous layer was extracted with DCM. The organic layer was dried over magnesium sulfate and filtered. The solvent was removed by rotary evaporation. The crude product was filtered through a silica plug and washed with DCM and acetone. The filtrate was concentrated by rotary evaporation. The product was then precipitated with Et_2O and filtered.

Phenyl dialdehyde **1** was prepared from 1,4-dibromobenzene (20.4 mmol, 4.8 g). The residue was collected to afford 4.22 g of dialdehyde **1** as a yellow solid (9.8 mmol, 48% yield). R_f (pentane/Et_2O: 95/5) = 0.46. ^1H NMR (360 MHz, $CDCl_3$) δ (TMS, ppm): 11.82 (s, 2H, OH), 9.99 (s, 2H, CHO), 7.81 (d, J_{meta} = 2.3 Hz, 2H), 7.65 (d, J_{meta} = 2.3 Hz, 2H), 7.64 (s, 4H), 1.49 (s, 18H). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ (TMS, ppm): 197.4 (2COH), 160.9 (2Cq arom-OH), 139.1 (2Cq arom), 133.2 (2CH arom), 132.1 (2Cq arom), 131.5 (2Cq arom), 130.1 (2CH arom), 128.4 (4CH arom), 120.9 (2Cq arom), 35.3 (2Cq-*t*Bu), 29.5 (2*t*Bu).

Fluorene dialdehyde **2** was prepared from 2,7-dibromofluorene (20.4 mmol, 6.6 g). Purification by silica-gel column chromatography (pentane/Et_2O: 94/6) afforded 6.7 g of dialdehyde **2** as an orange solid (12.9 mmol, 63% yield). R_f (pentane/Et_2O: 94/6) = 0.13. ^1H NMR (250 MHz, $CDCl_3$) δ (TMS, ppm): 11.81 (s, 2H, OH), 9.99 (s, 2H, CHO), 7.88 (d, 2H, J_{ortho} = 7.8 Hz), 7.85 (d, 2H, J_{meta} = 2.0 Hz), 7.76 (br s, 2H), 7.67 (d, 2H, J_{meta} = 2.2 Hz), 7.60 (dd, 2H, J_{ortho} = 7.8 Hz, J_{meta} = 2.0 Hz), 4.05 (s, 2H), 1.50 (s, 18H). ^{13}C NMR (91 MHz, $CDCl_3$) δ (TMS, ppm): 197.3 (2COH), 160.7 (2Cq arom-OH), 144.4 (2Cq arom), 140.6 (2Cq arom), 139.0 (4Cq arom), 133.3 (2CH arom), 132.9 (2Cq arom), 130.2 (2CH arom), 125.9 (2CH arom), 123.5 (2CH arom), 121.0 (2Cq arom), 120.5 (2CH arom), 37.3 (CH_2), 35.3 (2Cq-*t*Bu), 29.5 (2*t*Bu).

Benzothiadiazole dialdehyde **3** was prepared from 4,7-dibromobenzo[*c*]-1,2,5-thiadiazole (20.4 mmol, 6.0 g). The residue was collected to afford 8.0 g of dialdehyde **3** as a yellow solid (16.3 mmol, 80% yield). R_f (pentane/Et_2O: 94/6) = 0.31. ^1H NMR (250 MHz, $CDCl_3$) δ (TMS, ppm): 12.00 (s, 2H, OH), 10.04 (s, 2H, CHO), 8.14 (s, 4H), 7.79 (s, 2H), 1.52 (s, 18H). ^{13}C NMR (63 MHz, $CDCl_3$) δ (TMS, ppm): 197.4 (2COH), 161.5 (2Cq arom-OH), 154.2 (2Cq arom), 138.9 (2Cq arom), 135.1 (2CH arom), 132.9 (2CH arom), 132.1 (2Cq arom), 128.5 (2Cq arom), 127.5 (2CH arom), 120.9 (2Cq arom), 35.3 (2Cq-*t*Bu), 29.4 (2*t*Bu).

4.3. Synthesis of calix-salen derivatives

A 100 mL, two-necked, round-bottomed flask equipped with a reflux condenser was charged with a solution of dialdehyde (0.9 mmol, 400 mg) in THF (8 mL). Molecular sieves (4 Å) and (*R*,*R*)- or (*S*,*S*)-cyclohexane-1,2-diamine (1 equiv, 0.9 mmol, 106.1 mg) were added under argon with continuous stirring. The reaction mixture was further stirred for 24 h at 70 °C. After cooling to room temperature and filtration to remove the molecular sieves, the filtrate was concentrated by rotary evaporation. The crude product was then precipitated with methanol, filtered and washed with cold methanol.

(*S*,*S*)-Calix-salen **4** was prepared from phenyl dialdehyde **1** (0.9 mmol, 400 mg). The residue was collected to afford 472 mg of a mixture of macrocyclic compounds as a yellow powder (0.9 mmol, quantitative crude yield). Macrocyclic oligomers distribution δ (ppm) (%): 8.56 pentamer (4%), 8.35 tetramer (70%), 8.23 trimer (15%), 7.88 dimer (11%). Maldi-Tof (*m*/*z*): 1017.36 (*n* = 2), 1526.49 (*n* = 3), 2034.50 (*n* = 4), 2542.59 (*n* = 5). IR (ATR, ν cm^{-1}) 2953, 2932, 2864, 1628, 1441. $[\alpha]_D^{20}$ = −242.8 (*c* 0.01, DCM).

(*S*,*S*)-Calix-salen **5** was prepared from fluorene dialdehyde **2** (0.9 mmol, 481.9 mg). The residue was collected to afford 554.5 mg of a mixture of macrocyclic compounds as a yellow powder (0.9 mmol, quantitative crude yield). Macrocyclic oligomers distribution δ (ppm) (%): 8.52 pentamer (24%), 8.39 tetramer (76%). Maldi-Tof (*m*/*z*): 1193.58 (*n* = 2), 1789.97 (*n* = 3), 2386.27 (*n* = 4). IR (ATR, ν cm^{-1}) 2932, 2863, 1628, 1441. $[\alpha]_D^{20}$ = −423.9 (*c* 0.01, DCM).

(*S*,*S*)-Calix-salen **6** was prepared from benzothiadiazole dialdehyde **3** (0.9 mmol, 454 mg). The residue was collected to afford 526.6 mg of a mixture of macrocyclic compounds as a red powder (0.9 mmol, quantitative crude yield). Macrocyclic oligomers distribution δ (ppm) (%): 8.57 pentamer (8%), 8.45 tetramer (82%), 8.35 trimer (10%). Maldi-Tof (*m*/*z*): 1133.46 (*n* = 2), 1699.85 (*n* = 3), 2266.12 (*n* = 4), 2833.35 (*n* = 5). IR (ATR, ν cm^{-1}) 2945, 2863, 1626, 1441. $[\alpha]_D^{20}$ = −467.6 (*c* 0.0025, DCM).

(*R*,*R*)-Calix-salen *ent*-**6** was prepared from benzothiadiazole dialdehyde **3** (0.9 mmol, 454 mg). The residue was collected to afford 437.1 mg of a mixture of macrocyclic compounds as an orange powder (0.8 mmol, 83% yield). Macrocyclic oligomers distribution δ (ppm) (%): 8.45 tetramer (100%). HRMS (ESI+): calcd for $C_{68}H_{76}N_8NaO_4S_2$: 1155.5323; found: 1155.5341, calcd for $C_{136}H_{152}N_{16}NaO_8S_4$: 2288.0746; found: 2289.0802. IR (ATR, ν cm^{-1}) 2951, 2864, 1626, 1441. $[\alpha]_D^{20}$ = +603.0 (*c* 0.005, DCM).

4.4. Synthesis of (*S*,*S*)-calix-salen cobalt(III) complexes

A Schlenk tube thoroughly maintained under a dry argon atmosphere was charged with a solution of calix-salen (0.7 mmol) in degassed THF (16 mL). A solution of $Co(OAc)_2{\cdot}4H_2O$ (1.3 equiv,

0.9 mmol, 226.7 mg) in degassed methanol (8 mL) was then transferred via cannula into the Schlenk flask. The reaction mixture was further stirred for 72 h at 25 °C. Acetic acid (3.5 mL) was added to the reaction medium. The reaction mixture was further stirred under an oxygen atmosphere for 18 h at 25 °C with the formation of a precipitate. The product was filtered and the residue was washed with methanol.

(*S*,*S*)-Calix-salen cobalt(III) **7** was prepared from (*S*,*S*)-calix-salen **4** (0.7 mmol, 356.1 mg). The residue was collected to afford 437.3 mg of the catalyst mixture **7** as a dark brown solid (0.7 mmol, quantitative yield). IR (ATR, ν cm^{-1}) 2945, 2866, 1715, 1638, 1605, 1534, 1435.

(*S*,*S*)-Calix-salen cobalt(III) **8** was prepared from (*S*,*S*)-calix-salen **5** (0.7 mmol, 417.8 mg). The residue was collected to afford 498.9 mg of the catalyst mixture **8** as a dark brown solid (0.7 mmol, quantitative yield). IR (ATR, ν cm^{-1}) 2949, 2864, 1638, 1607, 1532, 1435.

(*S*,*S*)-Calix-salen cobalt(III) **9** was prepared from (*S*,*S*)-calix-salen **6** (0.7 mmol, 396.7 mg). The residue was collected to afford 477.9 mg of the catalyst mixture **9** as a dark brown solid (0.7 mmol, quantitative yield). IR (ATR, ν cm^{-1}) 2951, 2866, 1634, 1603, 1528, 1437.

4.5. Synthesis of calixsalen manganese(III) complexes

A Schlenk tube thoroughly maintained under a dry argon atmosphere was charged with a solution of calix-salen (0.5 mmol) in degassed toluene (4 mL). A solution of $Mn(OAc)_2{\cdot}4H_2O$ (3 equiv, 1.5 mmol, 367.6 mg) in degassed ethanol (8 mL) was then transferred via cannula into the Schlenk flask. The reaction mixture was further stirred for 5 h at 85 °C. A saturated aqueous sodium chloride solution (5 mL) was added to the reaction medium. The reaction mixture was further stirred under an air atmosphere for 18 h at 25 °C with the formation of a precipitate. The product was filtered and the residue was washed with ethanol.

(*S*,*S*)-Calix-salen manganese(III) **10** was prepared from (*S*,*S*)-calix-salen **4** (0.5 mmol, 254.3 mg). The residue was collected to afford 283.6 mg of the catalyst mixture **10** as a dark brown solid (0.47 mmol, 95% yield). IR (ATR, ν cm^{-1}) 3387, 2945, 2864, 1611, 1539, 1429.

(*S*,*S*)-Calix-salen manganese(III) **11** was prepared from (*S*,*S*)-calix-salen **5** (0.5 mmol, 298.4 mg). The residue was collected to afford 342.6 mg of the catalyst mixture **11** as a dark brown solid (0.5 mmol, quantitative yield). IR (ATR, ν cm^{-1}) 3416, 2955, 2866, 1611, 1539, 1427.

(*S*,*S*)-Calix-salen manganese(III) **12** was prepared from (*S*,*S*)-calix-salen **6** (0.5 mmol, 283.4 mg). The residue was collected to afford 288.3 mg of the catalyst mixture **12** as a dark brown solid (0.4 mmol, 88% yield). IR (ATR, ν cm^{-1}) 3414, 2949, 2864, 1607, 1533, 1431.

(*R*,*R*)-Calix-salen manganese(III) *ent*-**12** was prepared from (*R*,*R*)-calix-salen *ent*-**6** (0.5 mmol, 283.4 mg). The residue was collected to afford 271.9 mg of the catalyst mixture *ent*-**12** as a dark brown solid (0.41 mmol, 83% yield). IR (ATR, ν cm^{-1}) 2945, 2863, 1609, 1535, 1441.

4.6. Catalytic tests—hydrolytic kinetic resolution of *meso*-epoxides

meso-Epoxide (1 equiv), chlorobenzene (internal standard—1 equiv) and THF were introduced into a screw-capped vial. A reference sample was prepared by adding a small drop of the solution to THF. On the other hand, the solution was introduced in a tube containing calix-salen catalyst(s) (0.06 equiv), and then H_2O (1.3 equiv) was added. The reaction mixture was further stirred for approximately 4 days at 50 °C. At the end of the reaction, THF (1.5 mL) and pentane (5 mL) were added and the catalyst was precipitated for 2 h. A drop of the supernatant was dissolved in THF (0.5 mL) and analyzed by GC analysis. The supernatant was then removed using a micro immersion filter for reverse filtration, filtered through a plug of Celite and washed with EtOAc. The recovered filtrate was gently concentrated by removing the solvent by slow rotary evaporation without heating the water bath. The catalyst was washed with THF/pentane 1.5 mL/5 mL (4 times), dried under vacuum and then reused for the next cycle.

Cyclohexane-1,2-diol **13** was prepared from cyclohexene oxide (0.4 mmol, 40 μL), chlorobenzene (0.4 mmol, 40.2 μL) in THF (1.2 mL) and H_2O (0.5 mmol, 9.3 μL) or for the test at a larger scale from cyclohexene oxide (4.0 mmol, 0.4 mL), chlorobenzene (4.0 mmol, 0.4 mL) in THF (9.7 mL) and H_2O (5.1 mmol, 93 μL).

Cyclopentane-1,2-diol **14** was prepared from cyclopentene oxide (0.5 mmol, 40 μL), chlorobenzene (0.5 mmol, 46.6 μL) in THF (1.2 mL) and H_2O (0.6 mmol, 10.7 μL).

4.7. Catalytic test—hydrolytic kinetic resolution of epibromohydrin

Epibromohydrin (1.7 mmol, 141 μL), chlorobenzene (internal standard—0.3 equiv, 0.5 mmol, 50 μL) and THF (197.5 μL) were introduced into a screw-capped vial. A reference sample was prepared by adding a small drop of the solution to THF. On the other hand, the solution was introduced in a tube containing calix-salen catalyst(s) (0.02 equiv, 0.03 mmol, 20 mg), and then H_2O (1.5 equiv, 2.5 mmol, 44.5 μL) was added. The reaction mixture was further stirred for approximately 24 h at room temperature. At the end of the reaction, the catalyst was filtered off, washed with THF, dried under vacuum and then reused for the next cycle. The recovered filtrate was concentrated by removing the solvent by rotary evaporation. Dimethoxypropane (3.3 equiv, 5.5 mmol, 677.4 μL), DCM (7.3 mL) and 27 mg of Amberlyst 15 were added to the crude product. The reaction mixture was further stirred for 16 h at room temperature. The solution was filtered through a plug of Celite and then analyzed by chiral GC analysis.

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Supplementary data

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