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Editor's choice paper

# Highly active oligomeric Co(salen) catalysts for the asymmetric synthesis of α-aryloxy or α-alkoxy alcohols via kinetic resolution of terminal epoxides

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ABSTRACT

A mixture of Co(salen) macrocycles, prepared via the ring expansion metathesis oligomerization of salen-functionalized cyclooctene monomers, among the most active soluble catalysts for the hydrolytic kinetic resolution (HKR) of terminal epoxides, is exploited as the catalyst in the ring-opening of epoxides using aliphatic alcohols or phenols as nucleophiles, leading to the direct synthesis of optically active α-aryloxy alcohols or α-alkoxy alcohols. The catalyst is compared to other dimeric, oligomeric and monomeric Co(salen) complexes including a pimelate-linked macrocyclic Co(salen) catalyst and a dimeric Co(salen) catalyst referred to as a bisalen. The catalysts that contain multiple Co(salen) units within a single molecular framework allow for substantial decreases in catalyst loading compared with the monomeric catalyst. The cyclooctene-based Co(salen) macrocycle catalyst allows for good activity and enantioselectivity in the ring-opening of terminal epoxides with phenols as nucleophiles, giving enhanced turnover frequencies relative to many literature catalysts. The cyclooctene-based Co(salen) macrocycle catalyst and the bisalen catalysts are shown to be the most active in the asymmetric ring-opening of (±)1,2-epoxyhexane with methanol, out-performing the other catalysts tested. The Co(salen) macrocycle catalyst is recycled 3 times in this reaction with some loss in activity but no noteworthy change in selectivity.



## 1. Introduction

Studies on asymmetric reactions using optically active metallosalen complexes as catalysts [1–7] continue to increase, owing to the versatility of the salen ligand, being a "privileged catalyst," as designated by Jacobsen [8]. Salen complexes can be synthesized easily and exhibit distinctive catalytic performance in a wide array of enantioselective reactions [9–12]. Using chiral cobalt (salen) complexes as catalysts, Jacobsen and co-workers reported the hydrolytic kinetic resolution (HKR) of terminal epoxides using water as the nucleophile and proposed a dual activation pathway, namely, the activation of two substrates (e.g., an electrophile and a nucleophile) simultaneously by two catalytic species in the transition state of the rate-determining step [13–16]. Based on this mechanistic context, complexes that contain multiple metal centers in appropriate relative proximity and orientation can provide improved reactivity relative to monometallic catalysts [17–19]. Jacobsen and co-workers reported in 2001 the preparation of mixtures of cyclic oligomeric Co(salen) complexes that were designed to enforce the cooperative bimetallic mechanism common to many epoxide ring-opening reactions [20,21]. Our groups reported the preparation of mixtures of Co(salen) macrocycles (**1**) (Fig. 1) by the ring-expanding olefin metathesis of the Co(II) complex of a monocyclooct-4-en-1-yl-functionalized salen ligand, with the oligomeric catalysts exhibiting extremely high reactivity and selectivity (using the Co(III) complex) in the HKR of a variety of racemic terminal epoxides under neat conditions with very low catalyst loadings [22]. Recently a Co(bisalen) complex (**2**) (Fig. 1), with high reactivity and selectivity in the HKR of epoxides, was also reported by us [23]. Based on the hypothesis that strong performance in the HKR reaction may correlate with high activity in other epoxide ring-opening reactions such as aryloxylation [20,21,24–35] and alkoxylation [20,21], we extend here the scope of our Co(salen) macrocycle **1(OTs)** catalyzed reactions to the direct synthesis of optically active α-aryloxy alcohols and α-alkoxy alcohols that are valuable targets for asymmetric synthesis and key intermediates in a variety of pharmaceutically important compounds [36]. We report that **1**, upon aerobic oxidation under acidic conditions, exhibits excellent catalytic properties in the ring-opening of epoxides with phenols and aliphatic alcohols, allowing for substantial decreases in catalyst loading compared to reactions using the monomeric complex or dinuclear chiral (salen) Co-$MX_3$ (M = Al, Ga) [24–26], and excellent enantioselectivity.

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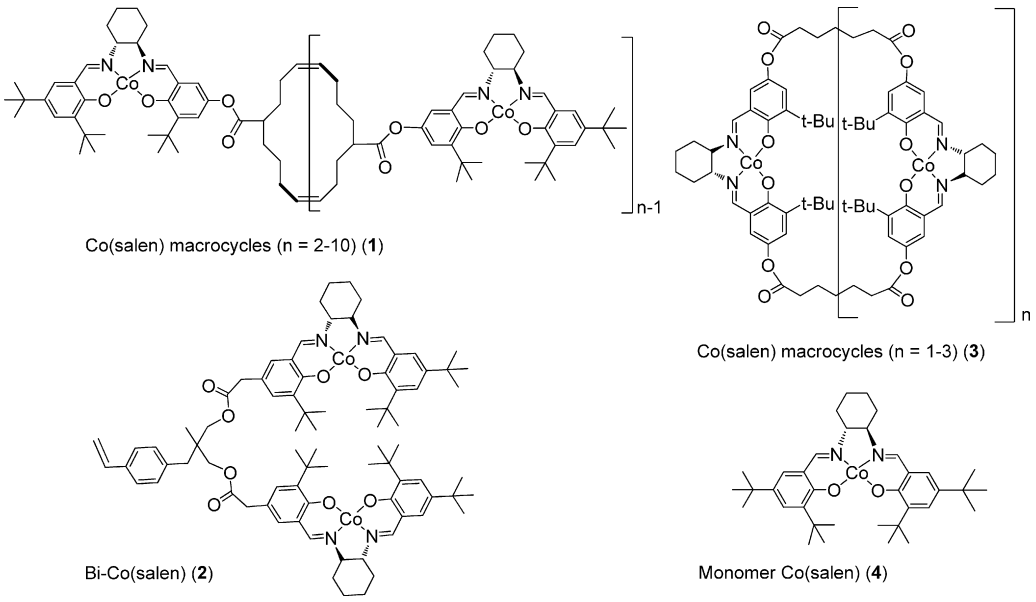



**Fig. 1.** Structures of Co(salen) macrocycles (**1**), bi-Co(salen) (**2**), oligomeric Co(salen) (**3**) and monomeric Co(salen) (**4**).

## 2. Results and discussion

### 2.1. Preparation of catalysts

A mixture of the Co(salen) macrocycles (**1**) was prepared via the ring expansion olefin metathesis reaction of salen-functionalized cyclooctene monomers. The mixture of oligomeric salen species obtained had a stoichiometric cobalt content after metallation based on elemental analysis (EA) (calcd: 8.42%, found: 8.25%) and exhibited a mass spectrum essentially identical to that reported previously [22]. For comparison, two additional cooperative catalysts were prepared, following literature reports. These included the bisalen monomer (**2**) previously reported by us [23] and the pimelate-linked macrocyclic catalyst (**3**) described by Jacobsen [21]. The elemental analyses show that **2** had a stoichiometric cobalt content (calcd: 8.53%, found: 8.56%) after metallation while **3** gave a somewhat lower metalation efficiency (calcd: 9.10%, found: 8.00%).

All catalysts were oxidized prior to use by stirring in THF under air in the presence of toluene sulfonic acid (HOTs), to provide the corresponding activated catalysts in Co(III) form with $TsO^-$ as the counter ion.

### 2.2. Catalytic activity in the hydrolytic kinetic resolution

The pre catalysts **1**–**4** have previously been used in the HKR of terminal epoxides [8,20,22,23], but they have been run under different conditions. To set the stage for our epoxide ring-opening studies using aliphatic alcohols and phenols as nucleophiles, we first compared the catalytic activity of catalysts **1**–**4** in the HKR of racemic epichlorohydrin under identical conditions. The reactions were completed in 20, 30 and 120 min at ambient temperature (RT) with 0.1 mol% cobalt loading of catalysts **1(OTs)**, **3(OTs)** and **2(OTs)**, respectively, affording the (R)-enantiomer of the epoxide in >99% ee. In comparison, the standard monometallic Co(salen) catalyst **4(OTs)** required a prolonged reaction time (15 h) to reach >99% ee in this reaction. The aforementioned data clearly demonstrate that **1(OTs)** and **3(OTs)** possess similar outstanding catalytic activities in the HKR of epoxides (Fig. 2). Compared with **4(OTs)**, the enhanced reactivity with **1(OTs)**, **2(OTs)** and **3(OTs)** at the same metal loading indicates that the HKR of terminal epoxides takes place via the intramolecular cooperative action of two cobalt sites present in a single catalyst framework, which has been described in previous reports [6].

### 2.3. Catalytic activity in the alcoholic and phenolic kinetic resolutions

Based on the results of the HKR studies, we selected the most active catalyst **1(OTs)**, for use in the ring-opening of epoxides with phenols as well as aliphatic alcohols. The kinetic resolution of terminal epoxides with phenols has been widely studied recently with supported and unsupported bimetallic Co(salen)-$MX_3$ catalysts [25–35], following initial studies using supported and unsupported cooperative Co(salen) catalysts by Jacobsen [20,21,24]. Here, the asymmetric ring-opening of racemic terminal epoxides with phenol and its derivatives was selected to evaluate the reactivity and enantioselectivity of **1(OTs)**. The addition of 0.45 equivalents of phenol derivative to racemic epichlorohydrin or 1,2-epoxyhexane in *tert*-butyl methyl ether (TBME) solution was examined with catalyst loadings as low as 0.02% on a per cobalt basis relative

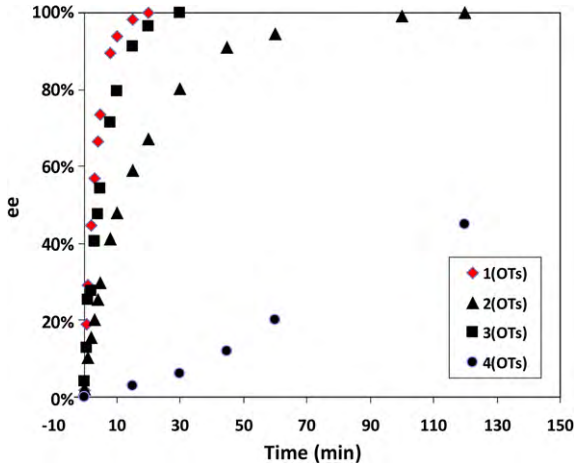
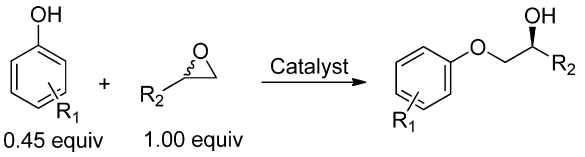



**Fig. 2.** HKR of racemic epichlorohydrin catalyzed by **1(OTs)**, **2(OTs)**, **3(OTs)** and **4(OTs)** at ambient temperature with 0.1 mol% cobalt catalyst loading.

**Table 1**
Preparation of α-aryloxy alcohols by ring-opening of epoxides with phenol catalyzed by **1(OTs)**.

| Entry | $R_1$ | $R_2$[a] | Co (mol%)[b] | $T$ (°C) | Reaction time (h) | Yield (%)[c] | ee (%)[d] |
|---|---|---|---|---|---|---|---|
| 1 | H | $CH_2Cl$ | 0.02 | RT | 9 | 91 | 97 |
| 2 | 3-$CH_3$ | $CH_2Cl$ | 0.02 | RT/4 | 21/48 | 89/85 | 92/99 |
| 3 | 3-Cl | $CH_2Cl$ | 0.02 | RT | 24 | 96 | 95 |
| 4 | H | *n*-Butyl | 0.02 | RT/4 | 12/24 | 95/97 | 94/99 |
| 5 | 3-$CH_3$ | *n*-Butyl | 0.02 | RT | 19 | 91 | 97 |
| 6 | 3-Cl | *n*-Butyl | 0.05 | 4 | 24 | 87 | 99 |

[a] Reactions were carried out with $[epoxide]_0 = 5$ M in TBME.
[b] Catalyst loading on a per Co basis relative to epoxides.
[c] Isolated yields based on phenol.
[d] *ee* of product, as determined by chiral GC or HPLC analysis.




**Scheme 1.** Preparation of α-aryloxy alcohols by the ring-opening of epoxides with phenol catalyzed by **1(OTs)**.

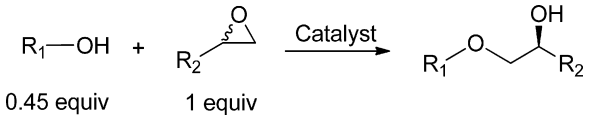
to epoxide (Scheme 1). The results are summarized in Table 1. At a catalyst loading of 0.02–0.05 mol%, both electron-poor and electron-rich phenols reacted at room temperature with a small series of epoxides to provide the corresponding chiral α-aryloxy alcohols in good to excellent yields and high ee's. The kinetic resolutions were accomplished with only 0.02 mol% of catalyst **1(OTs)** in less than 12 h using phenol, whereas more than 24 h were required when using the bulkier molecules 3-chlorophenol or 3-cresol as nucleophiles. Use of these nucleophiles also resulted in lower enantioselectivities compared to the phenol case. For comparison, with 3-chlorophenol as the nucleophile in the kinetic resolution of epichlorohydrin (ECH), the α-aryloxy alcohol was synthesized in high yield and optical purity after 24 h using only 0.05 mol% of **1(OTs)**. In contrast, under otherwise identical conditions, 12 h were required to obtain a similar result using 0.8 mol% of catalyst **3(OTs)** [21]. Higher enantioselectivities could be obtained at lower reaction temperatures and with longer reaction times using catalyst **1(OTs)**. For example, when the reaction was carried out at 4 °C, improved enantioselectivities (99%) were obtained (entry 2, 4 and 6, Table 1) in 24–48 h. Overall, it is evident that **1(OTs)** exhibits excellent activity and selectivity in the kinetic resolutions of racemic epichlorohydrin and 1,2-epoxyhexane with a variety of phenol derivatives.

The data in Table 1 give times required to fully resolve epoxides using different phenols as nucleophiles, an important parameter needed by synthetic chemists. For catalysis scientists, comparing the reactivity of various catalysts is more easily achieved by comparing initial reaction rates. To this end, the data in Table 2 give the initial TOFs of catalyst **1(OTs)** for the reactions with various epoxides and phenols. Using **1(OTs)** as catalyst, the initial TOF for the reactions between epoxides and phenols is much higher

**Table 2**
The initial TOF in asymmetric ring-opening of racemic epoxides with phenols catalyzed by **1(OTs)**.

| Entry | Reactants | Co loading (%) | Initial TOF ($min^{-1}$) |
|---|---|---|---|
| 1 | ECH, phenol | 0.02 | 31 |
| 2 | ECH, 3-cresol | 0.02 | 10 |
| 3 | ECH, 3-chlorophenol | 0.02 | 8.3 |
| 4 | EH, 3-cresol | 0.02 | 2.5 |

*Note*: ECH = epichlorohydrin; EH = 1,2-epoxyhexane.




**Scheme 2.** Preparation of α-alkoxy alcohols by ring-opening of epoxides with alcohols catalyzed by **1(OTs)**.

than the estimated initial TOF with several previously reported unsupported or supported Co(salen) catalysts, which ranged from ~0.05–1 $min^{-1}$ [25,29,31,32,34].

The catalytic asymmetric ring-opening of epoxides using aliphatic alcohols as nucleophiles is a related reaction that has proven particularly difficult to promote, with few effective catalysts reported to date [20,21]. In the context of kinetic resolution of terminal epoxides, alcoholic ring-opening provides an attractive strategy for the direct preparation of optically active α-alkoxy alcohols. A variety of alcohols were found to effectively ring-open epoxides when using **1(OTs)** (Table 3). In all cases, α-alkoxy alcohols were synthesized in high yields and enantioselectivities. The ring-opening reaction of racemic epichlorohydrin or 1,2-epoxyhexane with methanol was chosen as a model reaction with a Co loading of 0.1% (Scheme 2 and entries 1 and 3 in Table 3). Catalyst **1(OTs)** promoted the kinetic resolution of terminal epoxides effectively to afford 1-chloro-3-methoxy-2-propanol and 1-methoxy-2-hexanol, respectively, in highly enantioenriched form (entry1 and 3, Table 3). As for the less nucleophilic reagent 1-hexanol or the bulky 2-bromobenzyl alcohol, the reaction was completed effectively at room temperature in less than 12 h in these cases using a higher Co loading (1% Co), while low temperatures

**Table 3**
Preparation of α-alkoxy alcohols by ring-opening of epoxides with alcohol catalyzed by **1(OTs)**.

| Entry | $R_1$ | $R_2$[a] | Co (mol%)[b] | $T$ (°C) | Reaction time (h) | Yield (%)[c] | ee (%)[d] |
|---|---|---|---|---|---|---|---|
| 1 | $CH_3$ | $CH_2Cl$ | 0.1 | RT | 2 | 97 | 99 |
| 2 | *n*-Hexyl | *n*-Butyl | 1 | RT | 4 | 99 | 99 |
| 3 | $CH_3$ | *n*-Butyl | 0.1 | RT | 3 | 96 | 99 |
| 4 | 2-$BrPhCH_2$ | $CH_2Cl$ | 1 | RT | 8 | 99 | 98 |
| 5 | 2-$BrPhCH_2$ | *n*-Butyl | 1 | 4 | 24 | 97 | 99 |

[a] Reactions were carried out with $[epoxide]_0 = 5$ M in $CH_3CN$ for 2-24 h unless indicated otherwise.
[b] Catalyst loading on a per Co basis relative to epoxides.
[c] Isolated yields based on alcohol.
[d] *ee* of product, as determined by chiral GC or HPLC analysis.

**Table 4**
The initial TOF in asymmetric ring-opening of racemic 1,2-epoxyhexane with methanol catalyzed by **1(OTs)**, **2(OTs)**, **3(OTs)** and **4(OTs)** with 0.1 mol% Co loading.

| Entry | Initial rate ($min^{-1}$) |
|---|---|
| **1(OTs)** | 6.7 |
| **2(OTs)** | 3.3 |
| **3(OTs)** | 2.5 |
| **4(OTs)** | 0.7 |

were required to produce optically pure 1-(2-bromobenzyloxy)-2-hexanol.

The catalytic results support the hypothesis that strong performance in the HKR reaction can correlate with efficient reactivity in other epoxide ring-opening reactions such as aryloxylation and alkoxylation. In the case of **1(OTs)**, it is suggested that the same cooperative macrocyclic structure that allowed for extremely efficient HKR catalysis also allows for conversion of more demanding substrates such as alcohols and phenols.

As noted above, the literature contains very few examples of effective catalysts for ring-opening of epoxides with aliphatic alcohols as nucleophiles. The best example is Jacobsen's work using **3(OTs)** [21]. In that system, the reactions were conducted under different conditions than those used here. To better compare the catalytic activity of catalysts **1(OTs)**–**4(OTs)** in the kinetic resolution of terminal epoxides with alcohols, the ring-opening of 1,2-epoxyhexane with 0.6 equivalents of methanol was examined under identical conditions with all four catalysts, using $CH_3CN$ as the solvent at 0.1 mol% catalyst loading relative to epoxide. While complexes **1(OTs)** and **3(OTs)** displayed similar activities in the HKR (vide supra), in our hands, **1(OTs)** proved to be superior for the kinetic resolution of terminal epoxides with alcohols. The initial TOFs using the four catalysts are given in Table 4, again showing that **1(OTs)** is the most active catalyst. In this case, **2(OTs)**, which was inferior to **1(OTs)** and **3(OTs)** in the HKR, unexpectedly showed similar activities to **1(OTs)**, completing the reaction within 3 h, affording the (R)-enantiomer of the epoxide in >99% ee (50–53% GC conversion) at low catalyst loadings (Fig. 3). The cause of this different behavior using the two nucleophiles (water vs. methanol) is not yet clear. It should be noted that the somewhat lower metalation efficiency of **3** might be one reason for the lower reactivity of **3(OTs)** compared with **1(OTs)**. Although the reactions were compared at the same cobalt loading, lower metalation efficiency means a larger fraction of the available salen ligands are not metalated in **3(OTs)** compared to **1(OTs)**, which may affect the intramolecular site pairing probabilities.

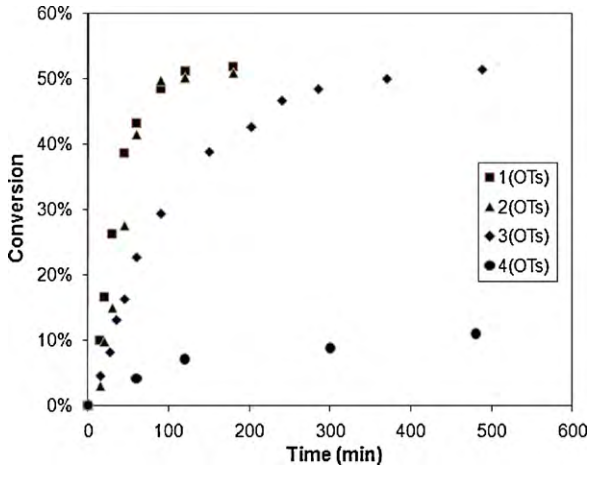



**Fig. 3.** Asymmetric ring-opening of racemic 1,2-epoxyhexane with methanol catalyzed by **1(OTs)**, **2(OTs)**, **3(OTs)** and **4(OTs)** with 0.1 mol% Co loading.

Compared with the monomeric Co(salen) **4(OTs)**, the enhanced reactivity with all the multi-center catalysts **1(OTs)**, **2(OTs)** and **3(OTs)** indicates that the kinetic resolution of terminal epoxides with alcohols also takes place via the intramolecular cooperative action of two cobalt sites present in a single catalyst framework, when using these cooperative catalysts.

To further demonstrate the cooperativity of the catalysts, we assessed the order of the reactions with respect to catalyst concentration during the kinetic resolution of racemic epichlorohydrin with phenol using activated **1(OTs)**. The plot of initial rate vs. [catalyst] gives insight into the catalyst reaction order. In this case, the plot is linear within the reported range of catalyst loadings, consistent with a first-order kinetic dependence on catalyst concentration (Fig. 4) [13]. This stands in contrast to the second-order dependence observed with monomeric catalysts [15,16,20] and indicates that epoxide ring-opening with activated **1(OTs)** takes place via the cooperative reactivity of two (or possibly more) metal sites within a single cyclic framework under the diluted conditions used here. As noted in Table 4, the initial TOF using **1(OTs)** for ring-opening of epoxide with methanol as well as phenol is about ten times higher than using monomeric Co(salen) **4(OTs)**. Thus, active, bimetallic transition states are more effectively created intramolecularly with cooperative catalysts at high dilution, whereas conversion arising from inter-molecular cooperativity contributes very little to the observed rate under the conditions used here.

### 2.4. Catalyst recovery and recycle

The recovery and reuse of the catalyst was assessed. For these studies, the ring-opening reactions of (±)-1,2-epoxyhexane using 0.6 equivalents of methanol in the presence of **1(OTs)** (0.2 mol% Co) was chosen. After each cycle, the catalyst was recovered via removal of the product, residual reactant, and solvent under vacuum, followed by washing with a mixture of water and ethanol (1:1, v/v) to further clean the liquid residue, followed by drying under vacuum prior to reuse. The recycle studies show that the selectivity of the recycled catalyst remained about the same after three runs, but the reactivity clearly decreased (Fig. 5). The time required to achieve ≥99% *ee* of the epoxide increased from 45 to 90 min over three runs. It should be noted that no regeneration of the catalyst with *p*-toluenesulfonic acid was carried out between individual runs. Future studies may focus on elucidating the mechanisms that lead to loss of activity upon recycle, with past work on HKR reactions suggesting that ligand hydrolysis, decomposition, metal leaching, metal reduction, and counter ion exchange may be important [37–40].

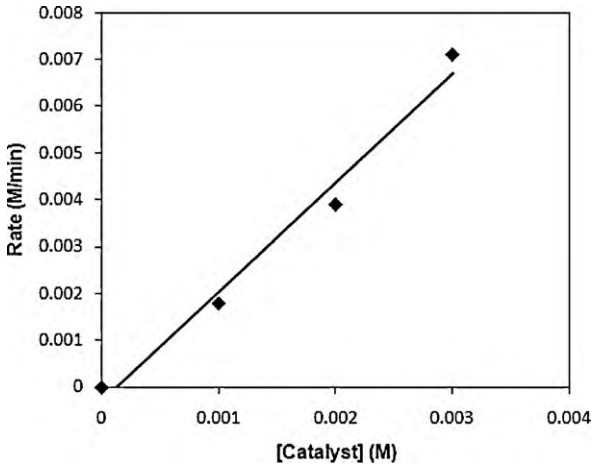



**Fig. 4.** Initial reaction rates of the phenolic ring-opening of ECH catalyzed by **1(OTs)**.

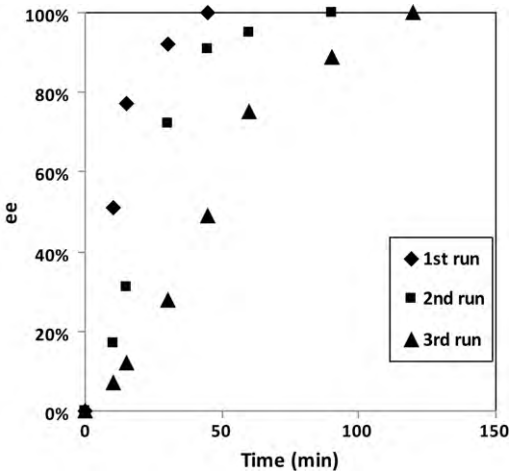



**Fig. 5.** Asymmetric ring-opening of racemic 1,2-epoxyhexane with methanol catalyzed by **1(OTs)** with 0.2 mol% Co loading.

## 3. Conclusions

Upon aerobic oxidation under acidic conditions, the mixture of Co(salen) macrocycles **1(OTs)** exhibited excellent catalytic properties in the ring-opening of epoxides with phenols and alcohols, showing substantial decreases in catalyst loading compared to the monomeric salen catalyst **4(OTs)**, and displaying excellent enantioselectivity. The high reactivity and enantioselectivity of **1(OTs)** may be associated with the incorporation of salen units into an extremely flexible cyclic framework allowing for improved bimetallic cooperativity. Kinetic studies indicated that epoxide ring-opening with **1(OTs)** followed a first-order kinetic dependence on catalyst, which was consistent with an intramolecular bimetallic cooperative reaction of multiple centers within the cyclic oligomeric framework. While macrocycles **1(OTs)** and **3(OTs)** displayed similar activity in the HKR reaction, complex **1(OTs)** proved superior for the kinetic resolution of terminal epoxides with aliphatic alcohols under the conditions used. Catalyst **1(OTs)** also proved to be substantially more active than other cooperative Co(salen) catalysts reported in the literature for epoxide ring-opening with phenols. Catalyst **2(OTs)**, which was inferior in the HKR, unexpectedly showed similar activity to **1(OTs)** in ring-opening of 1,2-epoxyhexane with methanol. The recycle studies showed that over three runs in the ring-opening of 1,2-epoxyhexane with methanol, the activity of **1(OTs)** clearly decreased but that catalytic selectivity remained excellent.

## 4. Experimental section

Reagents were used as received unless otherwise noted. Dichloromethane (DCM) was dried by passing through columns of activated alumina. Toluene and tetrahydrofuran (THF) were dried by passing through columns of activated copper oxide and alumina successively. $^{1}H$ and $^{13}C$ NMR spectra were acquired with a Varian Mercury 400 MHz spectrometer, and chemical shifts are reported in ppm with reference to the corresponding residual nuclei of the deuterated solvents. Mass spectra were analyzed using a VG 7070 EQ-HF hybrid tandem mass spectrometer. Gel permeation chromatography (GPC) analyses were performed on American Polymer Standards columns equipped with a Waters 510 pump and UV detector, using poly(styrene) standards for calibration and THF as the mobile phase at a flow rate of 1.0 mL/min. Enantiomeric excesses were determined by capillary gas-phase chromatography (GC) analysis on a Shimadzu GC 14A instrument equipped with a FID detector and a Chiraldex γ-TA column (40 m × 25 mm × 0.25 μm). An Shimadzu HPLC with a UV detector and a CHIRALCEL OD (4.6 × 250 mm, 10 mic) column for separation was also utilized. Elemental analyses were performed by Desert Analytics Lab (Tucson, AZ, USA).

### 4.1. Preparation of catalysts

The Co(salen) macrocycle (**1**) and the bi-Co(salen) (**2**) complexes were prepared according to published literature methods [22,23]. The $^{1}H$ NMR spectra and matrix assisted laser desorption ionization time-of-flight (MALDI-TOF) mass spectra obtained for **1** as well as **2** were similar to literature reports.

Elemental analysis for Co(salen) macrocycles (**1**): calcd (%) C 70.37, H 8.07, N 4.00, Co 8.42; found: C 70.63, H 8.04, N 3,56, Co 8.25. Elemental analysis for bi-Co(salen) (**2**): calcd (%) C 70.42, H 7.73, N 4.06, Co 8.53; found: C 69.70, H 7.61, N 3.92, Co 8.56. The monomeric Co(salen) (**4**) was used as received from Sigma–Aldrich.

The pimelate-linked oligomeric Co(salen) (**3**) catalyst was prepared in close analogy to the method reported by Jacobsen and co-workers [21]. A solution of (1R,2R)-1,2-diaminocyclohexane mono-(+)-tartrate salt (1.75 g, 6.59 mmol) in THF was mixed with $K_2CO_3$ in $H_2O$ (8.2 mL) and the resulting solution was refluxed for 30 min. Next, 0.5 equivalent of dialdehyde, which was prepared by condensation of 3-tert-butyl-2,5-dihydroxy benzaldehyde and pimelic acid, was added as a solution in THF (22 mL). The reaction was stirred at reflux for 2 h, cooled to room temperature and diluted with ethyl acetate (100 mL). After separation, a yellow solid was obtained quantitatively, and characterized by $^{1}H$ NMR and $^{13}C$ NMR spectroscopies and MS, with the results consistent with the literature. Metalation using cobalt(II) actetate tetrahydrate with the (salen) macrocycles in a dichloromethane/methanol mixture afforded the oligomeric Co(salen) (**3**) pre-catalyst. Elemental analysis for Co(salen) macrocycles (**3**): calcd (%) C 64.91, H 6.85, N 4.33, Co 9.10; found: C 64.49, H 6.78, N 4.55, Co 8.00.

### 4.2. General procedure for the catalytic synthesis of α-alkoxy alcohols or α-aryloxy alcohols

The alcohol or phenol of choice (45 mmol), epoxide (10.00 mmol), internal standard chlorobenzene (100 μL) and $CH_3CN$ or tert-butyl methyl ether (TBME) (0.2 mL) were mixed with activated 1 (7.2 mg, 0.01 mmol Co containing for Table 2 entry 3) at room temperature or 4 °C, and the solution was stirred until GC analysis indicated complete conversion of the alcohol. The reaction was then diluted with 5 mL $Et_2O$ and filtered through a plug of silica gel to remove the catalyst. The plug was washed with 20 mL $Et_2O$. The filtrates were combined and concentrated under reduced pressure to provide the crude product. Further purification included flushing through a silica gel column and distillation under vacuum for recovery of individual compounds. The ee of the product was determined by chiral GC or HPLC.

## Acknowledgement

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