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A broadly applicable and practical oligomeric (salen)Co catalyst for enantioselective epoxide ring-opening reactions

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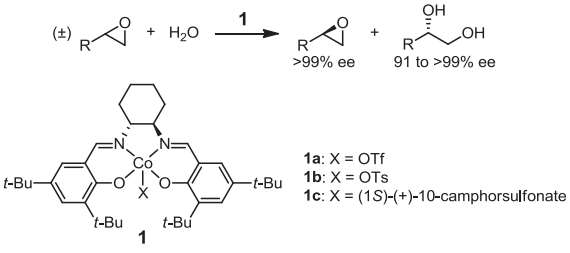
ABSTRACT

The (salen)Co catalyst (**4a**) can be prepared as a mixture of cyclic oligomers in a short, chromatography-free synthesis from inexpensive, commercially available precursors. This catalyst displays remarkable enhancements in reactivity and enantioselectivity relative to monomeric and other multimeric (salen)Co catalysts in a wide variety of enantioselective epoxide ring-opening reactions. The application of catalyst **4a** is illustrated in the kinetic resolution of terminal epoxides by nucleophilic ring-opening with water, phenols, and primary alcohols; the desymmetrization of meso epoxides by addition of water and carbamates; and the desymmetrization of oxetanes by intramolecular ring opening with alcohols and phenols. The favorable solubility properties of complex **4a** under the catalytic conditions facilitated mechanistic studies, allowing elucidation of the basis for the beneficial effect of oligomerization. Finally, a catalyst selection guide is provided to delineate the specific advantages of oligomeric catalyst **4a** relative to (salen)Co monomer **1** for each reaction class.

1. Introduction

Among the wide assortment of organic transformations catalyzed with high enantioselectivities by chiral (salen)metal complexes,[1] epoxide ring-opening reactions have arguably proven most impactful from a synthetic standpoint in both academic and industrial contexts. In particular, the hydrolytic kinetic resolution (HKR) catalyzed by monomeric (salen)Co complex **1** provides a general approach to the preparation of both enantiopure terminal epoxides and highly enantioenriched 1,2-diols (Scheme 1).[2–5] Monomeric complex **1** has also been applied with more limited success to the phenolytic kinetic resolution (PKR)[6] and the carbamolytic kinetic resolution (CKR)[7] of terminal epoxides to afford enantioenriched α-aryloxy alcohols and *N*-protected 1-amino-2-ols, respectively.[8,9] Other classes of nucleophiles and epoxides have generally remained beyond the scope of this system.[10,11] Moreover, although catalyst loadings required for HKR, PKR, and CKR reactions of most terminal epoxides are low (<5 mol % Co), additional improvements in catalytic reactivity are desirable in order to achieve highly efficient large-scale applications.[12]



Scheme 1. The HKR of terminal epoxides with monomeric (salen)Co complex **1**.

The recognition that the HKR[13] and related[14] epoxide ring-opening reactions proceed via cooperative bimetallic mechanisms, wherein both the epoxide electrophile and nucleophile are activated by separate (salen)Co complexes in the rate-limiting ring-opening event (Fig. 1),[15] has motivated the preparation and study of a wide variety of linked multi-(salen)metal complexes. The goal of these efforts has been to achieve higher catalytic activity by reducing the entropic cost of a second-order bimetallic pathway.[16,17] In several cases, these studies succeeded in uncovering catalyst systems with enhanced reactivity relative to monomer **1**, but that are also far more difficult to prepare and therefore less attractive

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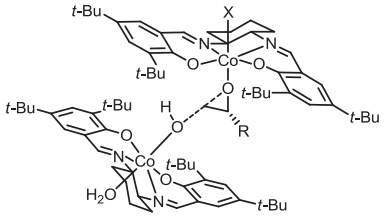


Fig. 1. Proposed rate-limiting transition structure in the hydrolytic kinetic resolution of terminal epoxides catalyzed by monomeric (salen)Co complex **1** (Ref. 15).

from a practical standpoint. This is due in large part to the need to synthesize unsymmetrical salen ligand frameworks to allow dimerization as in Fig. 2A.[18] As an alternative to these catalysts that possess local C_1 symmetry, multimeric (salen)Co complexes have been identified that are straightforward to prepare owing to the fact that they preserve the local C_2 symmetry of each salen unit. As such, they can be synthesized simply by condensation of appropriate linked bis(salicylaldehydes), or by linkage of preformed C_2-symmetric salen units (Fig. 2B).

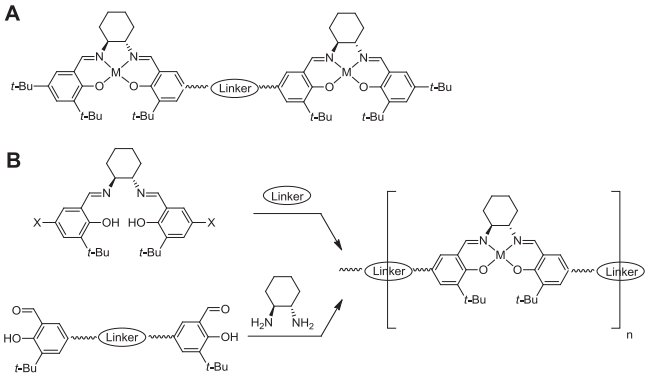
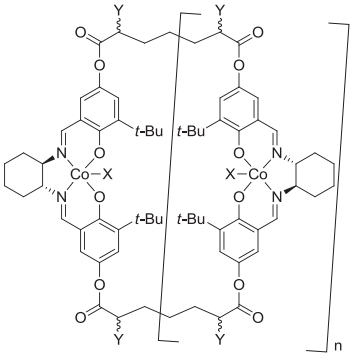


Fig. 2. (A) Linkage of metal salen complexes resulting in local C_1 symmetry in the individual salen units. (B) Strategies for the preparation of linked analogs of **1** with local C_2 symmetry in the individual salen units.

Linked complexes **2**[19] and **3**[20] represented the first reported examples of these more readily accessible catalysts (Fig. 3).[4h,8b,21] These mixtures of cyclic, oligomeric linked (salen)Co units displayed not only dramatic reactivity improvements in the HKR and PKR of terminal epoxides relative to monomer **1**, but also facilitated reactions that were impossible with monomeric catalyst such as the alcoholytic kinetic resolution (AKR) of terminal epoxides as well as the hydrolytic desymmetrization of cyclic meso epoxides. The basis for enhanced reactivity could be traced to cooperative reaction within the linked catalysts, as epoxide ring-opening reactions displayed a first-order kinetic dependence on catalyst concentration.[19]

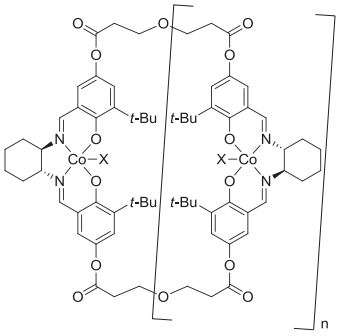


2: X = OTs, Y = Cl, n = 1-5

3a X = (1*S*)-(+)-10-camphorsulfonate, Y = H, n = 1–3
3b X = 3-NO_2-$C_6H_4SO_3$, Y = H, n = 1–3

Fig. 3. First- and second-generation cyclic oligomeric (salen)Co catalysts for epoxide ring-opening reactions.

Despite the very attractive properties of the cyclic oligomeric catalysts **2** and **3**, their practical utility and the ability to study them systematically was limited by their poor solubility. Poor reproducibility both between runs employing the same catalyst batch and between runs employing different catalyst batches was observed in several cases. For example, the conversion in the hydrolysis of *cis*-2-butene oxide using different batches of catalyst **3b** varied from 58 to 94% over 24 h. After systematic evaluation of various structural parameters, we discovered that the relatively minor perturbation of introducing an oxygen atom into the linker chain, as in **4** (Fig. 4), resulted in catalysts with substantially improved physical properties, including solubility in common organic solvents such as CH_2Cl_2 and CH_3CN.[22] Catalyst **4a** (X=OTf) was shown to be highly effective in a variety of HKR reactions, displaying both very high and reproducible activity and stereoselectivity with representative terminal epoxides. Tosylate derivative **4b** was found to be less reactive, but most effective for highly reactive terminal epoxides such as styrene oxide.[22,23] Catalyst **4a** has found application in several advanced synthetic applications[24] and new enantioselective ring-opening reactions.[25]



4a X = OTf
4b X = OTs

Fig. 4. Third-generation cyclic oligomeric (salen)Co catalysts for epoxide ring-opening reactions.

We provide here a full account of the scope of catalyst **4a** in enantioselective epoxide ring-opening reactions, thereby establishing **4a** as the most general and effective system for such reactions identified to date. We describe a practical, chromatography-free synthesis of catalyst **4a**, and document the application of this catalyst in the kinetic resolution of terminal epoxides by nucleophilic ring-opening with water, phenols, and primary alcohols, as well as the desymmetrization of meso epoxides by addition of water and carbamates, and the desymmetrization of oxetanes by intramolecular ring opening with alcohols and phenols. The favorable solubility properties of complex **4a** under the catalytic conditions were exploited in mechanistic studies, allowing elucidation of the basis for the beneficial effect of oligomerization. Finally, we provide a catalyst selection guide to delineate the specific advantages of oligomeric catalyst **4a** relative to (salen)Co monomer **1** for each reaction class.

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2. Results and discussion

2.1. Catalyst synthesis

A scalable, chromatography-free synthesis of catalyst **4a** starting from commercially available *tert*-butylhydroquinone (**6**) and 2-cyanoethyl ether (**8**) has been developed and is outlined in Scheme 2. Selective protection of the less hindered hydroxyl group of **6** was followed by Sn(IV)-mediated directed formylation and subsequent deprotection to provide aldehyde **7** according to the previously established route.[26] Acid-promoted hydrolysis of dinitrile **8** afforded diacid **9**,[27] which was coupled directly to salicylaldehyde **7** under carbodiimide-mediated conditions. Recrystallization from MeOH/H_2O then afforded pure bis(aldehyde) **10** in 77–82% overall yield from **8**. Following procedures analogous to those developed for the preparation of catalyst **3**,[20] bis(aldehyde) **10** was condensed with (1*R*,2*R*)-1,2-diaminocyclohexane generated in situ from its L-tartrate salt to yield the cyclic Schiff base ligand **5** as a mixture of oligomers (n=1,2) as determined by ESI MS and ^{1}H NMR analysis.[28] This material was then subjected directly to one-pot Co(II) insertion and subsequent air oxidation in the presence of triflic acid to provide complex **4a** in 100–102% yield based on the structure presented in Scheme 2. The catalyst thus obtained was thereby prepared in 60–66% yield from **6** on multigram scale. It was shown by ^{1}H NMR to contain varying amounts (up to 9% by weight) of residual toluene, but applied without further purification to all the asymmetric ring-opening reactions described herein.[29] Analyses of **4a** by MS and NMR revealed that the mixture of oligomers consisted primarily of dimer (**4a**$_{n=1}$) and smaller amounts of trimer (**4a**$_{n=2}$).[28] This material displayed excellent consistency across multiple batches, as illustrated in the PKR of 1,2-epoxyhexane with 2-bromophenol (Fig. 5).

2.2. Quantitative comparison of monomeric and oligomeric catalysts

The advantages of the third-generation oligomeric catalyst **4a** relative to both the second-generation oligomeric (**3b**) and monomeric (**1**) catalysts are illustrated in model epoxide ring-opening reactions (Fig. 6). The HKR of methyl glycidate (Fig. 6A) could be carried out with very low catalyst loadings (0.03 mol %) under solvent-free conditions with **4a**; in contrast, oligomer **3b** was poorly soluble under these conditions, thus reducing its already lower inherent reactivity. Catalyst **1b** was completely soluble under the same conditions, but displayed extremely low reactivity at such low concentrations.[30,31] In the PKR of 1,2-epoxyhexane with 2-bromophenol, catalyst **4a** induced both much faster rates and higher enantioselectivity than **3b** in the formation of the ring-opened addition product (Fig. 6B). The monomeric catalyst **1c** that is optimal for PKR reaction was almost completely unreactive under the same conditions.[32] A significant improvement in both reactivity and enantioselectivity of **4a** relative to oligomer **3b** and monomer **1a** was also observed in the hydrolysis of cyclohexene oxide (Fig. 6D).

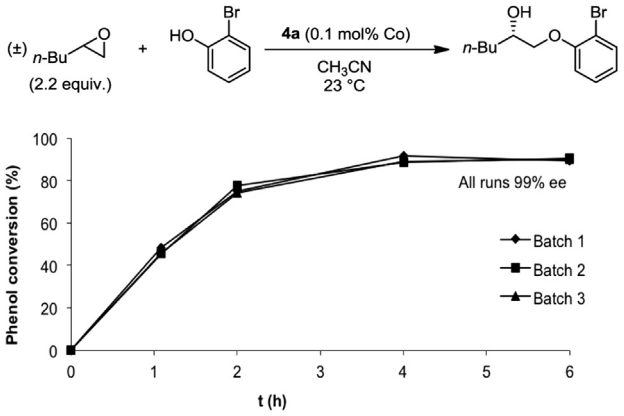
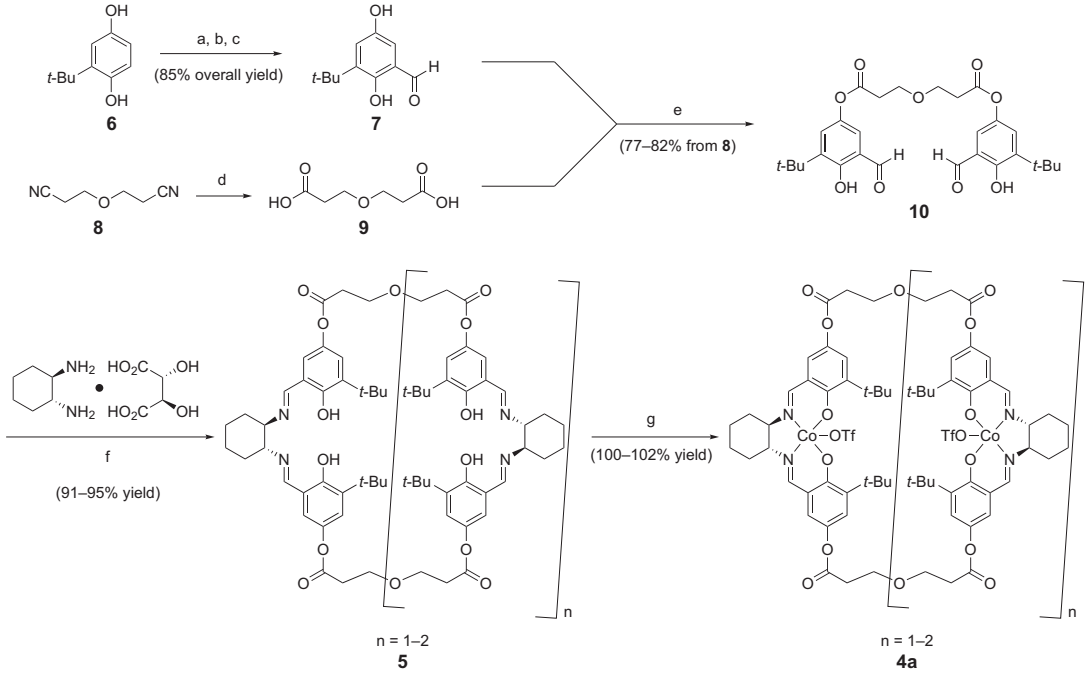


Fig. 5. Batch consistency of catalyst **4a** prepared under optimized synthetic conditions in the PKR of 1,2-epoxyhexane with 2-bromophenol. Conversions were determined by GC analysis relative to an internal standard. Enantiomeric excesses were determined by chiral HPLC analysis and are provided for the last data point of each curve.



Scheme 2. Optimized synthesis of catalyst **4a**. Conditions: (a) *t*-BuCOCl, DMAP (0.15 equiv), imidazole, CH_2Cl_2, 0→4 °C, 97%; (b) $SnCl_4$ (0.5 equiv), 2,6-lutidine, 0 °C, then $(CH_2O)_n$, toluene, 90 °C, 93%; (c) KOH, H_2O/EtOH, 23 °C, 94%; (d) concd HCl 50–55 °C; (e) EDC, DMAP (0.4 equiv), CH_2Cl_2/DMF, 0 °C→23 °C, recrystallized from MeOH/H_2O; (f) K_2CO_3, THF/H_2O, reflux; (g) $Co(OAc)_2 \cdot 4H_2O$, toluene/MeOH, N_2, 23 °C, then TfOH, air, CH_2Cl_2, 23 °C.

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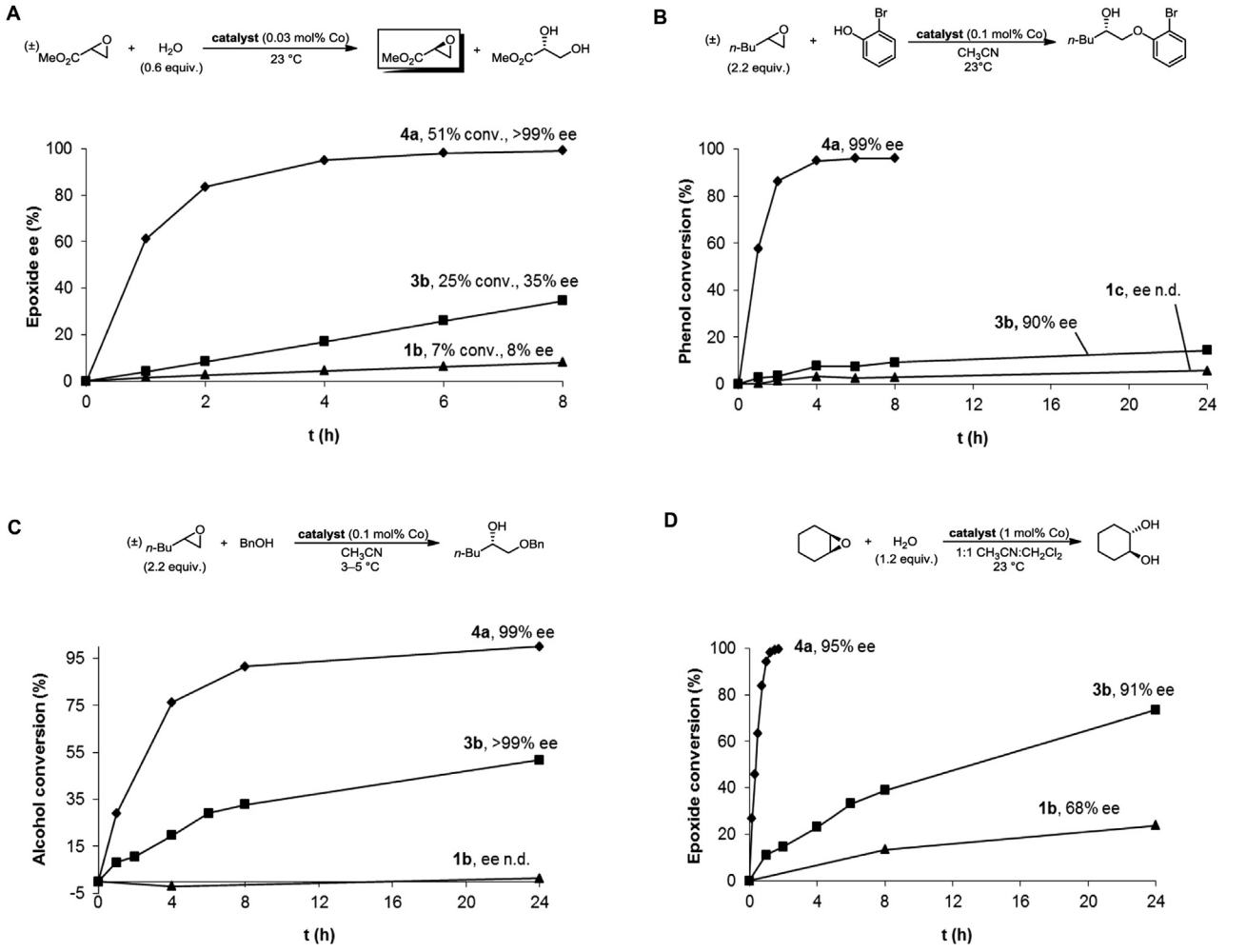


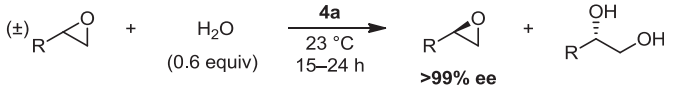
Fig. 6. Comparison of previous generations of (salen)Co(III) catalysts with oligomeric (salen)Co complex **4a**. Conversions were determined by GC analysis relative to an internal standard or by ^{1}H NMR analysis. Enantiomeric excesses were determined by chiral GC or HPLC analysis. Numerical conversion and ee values are provided for the last data point of each curve.

2.3. Applications of oligomeric catalyst 4a

2.3.1. HKR of terminal epoxides. The extraordinary effectiveness of oligomeric (salen)Co catalyst **4a** in HKR reactions of terminal epoxides is illustrated in the representative examples in Table 1. All reactions were carried out under solvent-free conditions at ambient temperature. Extremely low catalyst loadings can be employed with several important classes of terminal epoxides including aliphatic epoxides (entry 1), epichlorohydrin (entry 2), glycidol derivatives (entry 3), glycidic esters (entry 4), vinyl epoxides (entry 5), and styrene derivatives (entry 6). The efficiency of this catalyst system is highlighted by considering the amounts of **4a** required to effect HKR reactions: 1.5 mol of racemic propylene oxide was resolved within 24 h using only 3.6 mg (41 ppm by mass, 3 ppm on a molar basis) of **4a** to yield 35 g (40%) of recovered epoxide in >99% ee (entry 1); similarly, only 18 mg of **4a** are required to obtain 1 mol (93 g) of resolved epichlorohydrin. In addition, the HKR of epichlorohydrin can now be carried out at room temperature with **4a** without any detectable signs of a secondary racemization pathway that is observed with monomeric catalyst **1**.[17b] In certain cases, trace impurities present in the racemic epoxides may have a deleterious effect on catalyst efficiency. However, this problem may be circumvented by purification of the epoxide by standard protocols.[33]

As noted above, the HKR of certain sensitive conjugated epoxides such as styrene oxide are best carried out with tosylate catalyst **4b** (entry 6).[23] Phenylacetaldehyde is present in variable amounts in commercially available racemic styrene oxide and is very difficult to remove completely. Because of the inhibitory effect of this impurity, the catalyst loading required to achieve >99% ee within 24 h was found to be somewhat variable (0.025–0.04 mol % Co).

Table 1
The HKR of terminal epoxides catalyzed by oligomeric (salen)Co complex **4a**[a,b]



Entry	R	Co[c] (mol %)	Epoxide yield[d] (%)
1[e]	Me	0.0003	40
2	CH_2Cl	0.001	44
3	$CH_2OCH_2CH{=}CH_2$	0.0025	43
4	CO_2Me	0.015	44
5[e,f]	$CH{=}CH_2$	0.025	35
6[g]	Ph	0.04	40

[a] Entry 1 was carried out on a 1.5 mol scale. Entries 2–7 were carried out on 80–130 mmol scale.
[b] Enantiomeric excesses were determined by chiral GC or HPLC analysis.
[c] Catalyst loading relative to racemic epoxide.
[d] Isolated yield based on racemic epoxide (theoretical maximum=50%).
[e] Enantiomeric excess was determined by chiral HPLC analysis of the terminal addition product of 2-naphthalenethiol.
[f] Employed 0.7 equiv H_2O.
[g] Employed catalyst **4b**.

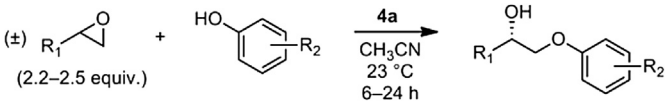
The protocol for the HKR of terminal epoxides with catalyst **4a** or **4b** is operationally very simple. Water is added to a mixture of catalyst and epoxide,[34] and the resulting reaction mixture is stirred at room temperature while the epoxide ee is monitored by chromatographic analysis of small aliquots. Once >99% ee has been attained, the epoxide is isolated by vacuum transfer and dried over an appropriate desiccant.[35] In cases where the physical properties of the epoxide prevent resolution under solvent-free conditions (e.g., viscous or solid substrates), HKR reactions can be accomplished successfully by adding small amounts of CH_3CN.[36]

2.3.2. Phenolytic kinetic resolution (PKR) of terminal epoxides. The efficiency and scope of the PKR of terminal epoxides are expanded greatly relative to monomer **1** or oligomer **3** using catalyst **4a** (Fig. 6B). The ring-opening of epoxides with phenols bearing a broad range of electron-withdrawing and donating substituents at the *ortho*, *meta*, and *para* positions was accomplished in good yields and ≥97% ee at ambient temperatures with catalyst loadings under 0.1 mol % Co in nearly all cases (Table 2).[37] Sterically hindered *ortho*-substituted phenols generally required higher catalyst loadings than their *meta*- or *para*-substituted counterparts (e.g., entries 4 vs 6), but the desired α-aryloxy alcohols could be obtained nonetheless in excellent yields and very high ees. With sufficiently elevated catalyst loadings, even highly sterically hindered 2,6-disubstituted phenols could be engaged in the PKR of relatively unreactive epoxides such as methyl glycidate (entry 16). Epichlorohydrin is an excellent reaction partner in PKR reactions catalyzed by **4a** (entries 10–13), providing practical access to a wide range of aryl glycidyl ethers. The PKR of styrene oxide with *p*-cresol (entry 15) provided a 25:1 ratio of desired terminally to undesired internally opened products.[38] In contrast to the HKR of styrene oxide (vide supra),[23] no advantage in regioselectivity was obtained by employing tosylate **4b** in the PKR reaction.[39]

As with the HKR, the experimental protocol for the PKR of terminal epoxides is straightforward. Reactions are carried out at ambient temperature with no special precautions to exclude air or moisture. Use of 2.2 equiv of racemic epoxide relative to phenol is sufficient for hydrophobic epoxides such as 1,2-epoxyhexane, while more hygroscopic epoxides require the use of 2.5 equiv to compensate for competitive HKR due to small amounts of adventitious water. Introduction of powdered 3 Å molecular sieves led to significant decreases in reaction rate, and is therefore not recommended.

2.3.3. Alcoholytic kinetic resolution (AKR) of terminal epoxides. Oligomeric complex **4a** is an excellent catalyst for the kinetic resolution of terminal epoxides with primary alcohols, providing a variety of monoprotected 1,2-diols in good yields and ≥97% ee (Table 3).[40] This methodology provides access to protected 1,2-diols, including benzyl, allyl, and 2-(trimethylsilyl)ethyl ethers (entries 1–3, 5–10), as well as methyl ethers (entry 4). Orthogonally protected chiral glycerol derivatives are prepared readily from racemic protected glycidols (entries 3 and 4), and enantioenriched glycidyl ethers can be accessed in two steps from epichlorohydrin after ring closure (entries 7–10).[41] Activated epoxides again displayed excellent regioselectivity in ring opening, with styrene

Table 2
The PKR of terminal epoxides catalyzed by oligomeric (salen)Co complex **4a**[a]



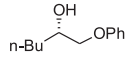
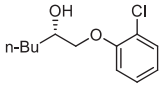
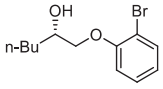
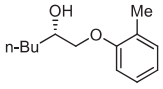
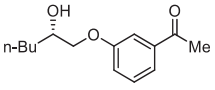
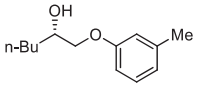
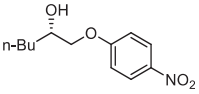
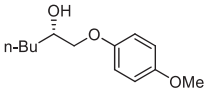
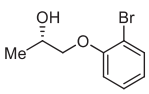
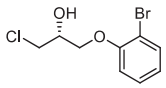
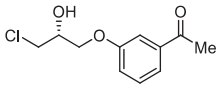
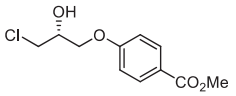
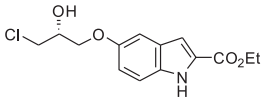
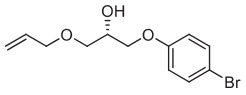
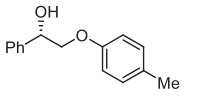
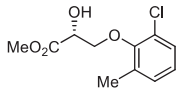
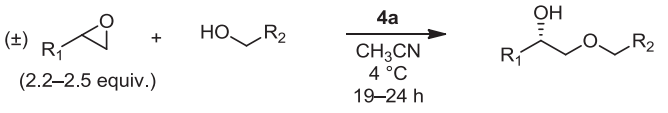
Entry	Product	Co[b] (mol %)	Yield[c] (%)	ee[d] (%)
1		0.0075	92	99
2		0.05	97	>99
3		0.075	96	99
4		0.5	89	98
5		0.05	95	>99
6		0.0075	95	99
7		0.15	87	97
8		0.05	87	99
9		0.05	96	>99

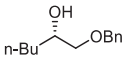
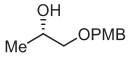
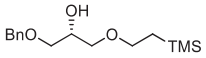
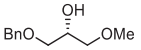
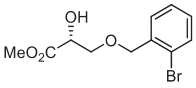
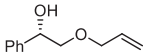
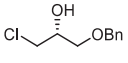
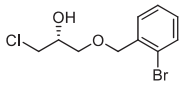
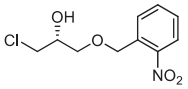
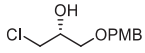
Table 2 (*continued*)

Entry	Product	Co[b] (mol %)	Yield[c] (%)	ee[d] (%)
10		0.05	>99	98
11		0.005	90	>99
12		0.0075	92	>99
13		0.2	92	98
14		0.05	87	98
15		0.075	79	98
16		2.5	80	98

[a] All entries were carried out on a 2.5 mmol scale relative to nucleophile.
[b] Catalyst loadings calculated relative to the limiting reagent (phenol).
[c] Isolated yield based on nucleophile.
[d] Enantiomeric excesses were determined by chiral HPLC analysis.

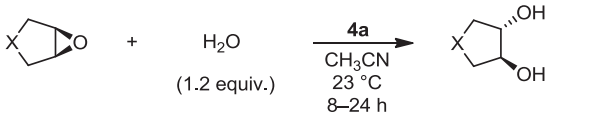
Table 3
The AKR of terminal epoxides catalyzed by oligomeric (salen)Co complex **4a**[a]

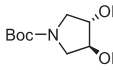
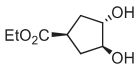
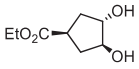


Entry	Product	Co[b] (mol %)	Yield[b] (%)	ee[c] (%)
1		0.1	92	>99
2		0.2	91	>99
3[d,e]		0.1	>99	98
4[f]		0.01	92	97
5		0.1	94	>99
6		0.5	80	>99
7		0.1	98	>99
8		0.02	94	>99
9		0.1	94	>99
10		0.5	91	98

[a] All entries carried out on a 2.5 mmol scale relative to nucleophile.
[b] Catalyst loadings and yields calculated relative to the limiting reagent (alcohol).
[c] Enantiomeric excesses were determined by chiral HPLC analysis.
[d] Enantiomeric excess was determined by chiral SFC analysis of the diol obtained from selective deprotection of the SEM ether.
[e] R_1=CH_2OBn, R_2=$(TMS)CH_2$.
[f] R_1=CH_2OBn, R_2=H.

Table 4
The hydrolytic desymmetrization of meso epoxides catalyzed by oligomeric (salen)Co complex **4a**[a]



Entry	Product	Co[b] (mol %)	Yield[b] (%)	ee[c] (%)
1		1	85	96
2[d]		1	77	96
3[e,f]		2.5	>99% Conv.	72
4[g]		2.5	<5% Conv.	—
5		2.5	87	80
6		2.5	76	99
7		2.5	91	99
8		1	98	99
from trans epoxyester				
9		1	92	98
from cis epoxyester				
10		1	89	97

[a] Entries 1 and 2 carried out on a 101 and 99 mmol scale, respectively. Entries 3–10 were carried out on a 1 mmol scale.
[b] Catalyst loadings and isolated product yields calculated relative to the limiting reagent (epoxide).
[c] Enantiomeric excesses were determined by chiral GC analysis of the corresponding bis(trifluoroacetate) derivatives.
[d] Yield: 93%, ee: 93% prior to recrystallization from hexanes/EtOAc. The crude product was suitable for most uses, containing only solvent and minor baseline impurities.
[e] Reaction time: 72 h.
[f] Conversion determined by GC analysis of the reaction mixture.
[g] Reaction time: 48 h.

oxide affording a 24:1 ratio of terminally to internally opened products in reactions with allyl alcohol (entry 6). Tosylate catalyst **4b** afforded an even higher ratio of regioisomers (>100:1 terminal to internal opening) in this reaction, although the selectivity obtained with **4a** was sufficient to allow isolation of pure product in 80% yield.

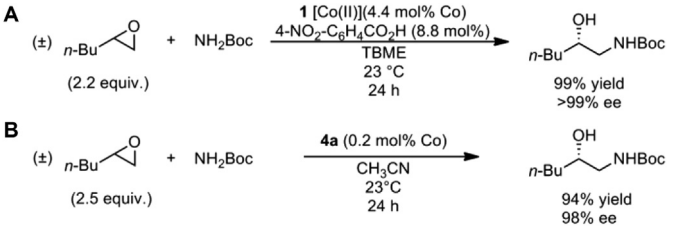
The basic experimental procedure for AKR of terminal epoxides is analogous to that employed in PKR reactions, except that AKR reactions are best carried out at reduced temperature. At ambient temperature, the active Co(III) catalyst is reduced by primary alcohols to the inactive Co(II) complex, presumably by one-electron transfer oxidation of the bound nucleophile. Lowering the temperature to 4 °C minimizes this catalyst deactivation pathway and allows efficient resolution to take place.

2.3.4. Hydrolytic desymmetrization of meso epoxides. Hydrolysis of meso epoxides derived from cyclic alkenes (Table 4) represents an attractive approach to chiral diols that are not accessible via asymmetric alkene dihydroxylation. To our knowledge, **3** is the only non-enzymatic catalyst system that has been reported to date that promotes meso epoxide hydrolysis with high enantioselectivity.[5,19,20,42,43] Oligomeric catalyst **4a** confers significant improvements in both reactivity and enatioselectivity over monomeric catalyst **1** and oligomeric catalyst **3** in this reaction manifold (see Fig. 6D, above). meso Epoxides derived from five- and six-membered ring cyclic alkenes undergo hydrolysis to provide the corresponding *trans* 1,2-diols in good yield and excellent ee (Table 4, entries 1, 2, 6–10).[44] Seven- and eight-membered endocyclic epoxides are also reactive, although with decreased enantioselectivity (entries 3 and 5). Cycloheptene oxide underwent ring-opening in 72% ee, but the diol could not be isolated cleanly from the crude reaction mixture (entry 3). Cyclooctene oxide was unreactive, presumably due to well known deactivating conformational effects (entry 4).[45] In contrast, 1,5-cyclooctadiene mono epoxide underwent ring-opening in 80% ee (entry 5). Access to

highly enantioenriched tetrahydrofuran and pyrrolidine derivatives from readily available precursors is illustrated in entries 6 and 7, while the stereoconvergent synthesis of 4-carboethoxy-1,2-cyclopentanol from diastereomeric epoxides is illustrated in entries 8 and 9. Similar enantioselectivity was observed in the hydrolysis of both the *trans* and *cis* epoxide isomers to yield the same enantiomer of diol in high ee.

The hydrolytic desymmetrization reactions are conducted under ambient atmosphere at room temperature with epoxides used as received from commercial sources.[46] Cyclopentene and cyclohexene oxide were hydrolyzed on a 101 and 99 mmol scale, respectively, to provide in each case 8.8 g (85% and 77% yields, respectively) of isolated product after purification. It should be noted that an exotherm was observed at larger scales (>1 mmol), resulting in slightly decreased enantioselectivity. Slow addition of epoxide to a solution of catalyst and water in CH_3CN was therefore necessary in order to minimize this effect.

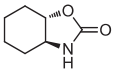
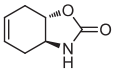
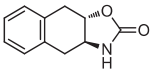
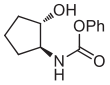
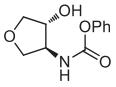
2.3.5. Carbamolytic kinetic resolution (CKR) of terminal epoxides and carbamolytic desymmetrization of meso epoxides. Bartoli and coworkers discovered that (salen)Co monomer **1** is a highly stereoselective catalyst for the kinetic resolution of terminal epoxides with carbamates, providing *N*-protected 1-amino-2-ols in good yields and excellent stereoselectivities (e.g., Scheme 3A).[7] Oligomeric complex **4a** displays similar stereoselectivity and significantly enhanced reactivity in the same transformation, allowing a greater than 20-fold reduction in catalyst loading (Scheme 3B).



Scheme 3. The CKR of terminal epoxides catalyzed by monomeric (salen)Co complex **1** (Ref. 7a) and oligomeric (salen)Co complex **4a**. (a) The reaction with catalyst **1** was carried out on a 0.5 mmol scale relative to nucleophile; the reaction with catalyst **4a** was carried out on a 2.5 mmol scale. (b) Catalyst loadings are relative to limiting reagent ($BocNH_2$). (c) Co(II) is converted in situ to Co(III)($O_2CC_6H_4NO_2$) in the presence of 4-NO_2-$C_6H_4CO_2H$ and air. (d) Isolated yields are based on nucleophile. (e) Enantiomeric excesses were determined by chiral HPLC analysis of the *O*-benzyl derivative.

An even more significant advantage of the oligomeric catalyst relative to monomer **1** was seen in the ring opening of meso epoxides with phenyl carbamate.[25b,47] Whereas monomer **1a** (5 mol %) catalyzes addition to cyclohexene oxide to generate the corresponding cyclic carbamate in 33% yield and 21% ee at 5 mol % catalyst loading, oligomeric catalyst **4a** (1 mol % Co) promotes the same transformation in high yield and 96% ee (Table 5). This methodology provides practical access to a variety of cyclic, protected *trans*-1,2-amino alcohols in high yield and enantioselectivity as demonstrated in the addition of phenyl carbamate to a variety of meso epoxides. Six-membered ring epoxides underwent clean addition with subsequent intramolecular cyclization to afford *trans*-4,5-disubstituted oxazolidinone products (entries 1–3). Phenyl carbamate addition to five-membered ring epoxides also proceeded with excellent enantioselectivity (entries 4 and 5), providing a mixture of the monomeric addition product together with carbamate-bridged oligomers. Here intramolecular cyclization appears to be impeded, presumably due to the unfavorable strain in trans-fused 5–5 ring systems.[48] The free *trans*-1,2-amino alcohol product could subsequently be liberated in high overall yield through hydrolysis of the product mixture with base. This reaction

Table 5
The carbamolytic desymmetrization of endocyclic meso epoxides catalyzed by oligomeric (salen)Co complex **4a**[a]

Entry	Product	Co[b] (mol %)	Yield[b] (%)	ee[c] (%)
1		1	94	96
2		2	84	96
3		2	63	95
4		1	66	>99
5		1	49	>99

[a] All reactions were carried out on a 1 mmol scale.
[b] Catalyst loadings and isolated yields calculated relative to the limiting reagent (phenyl carbamate).
[c] Enantiomeric excesses were determined by chiral GC or HPLC analysis.

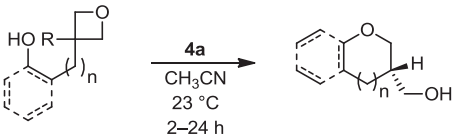
is readily conducted under ambient atmosphere and has been used to prepare multigram quantities of *trans*-1,2-amino alcohol hydrochlorides.[25b]

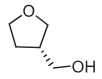
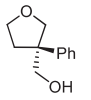
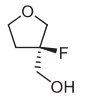
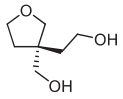
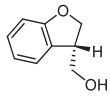
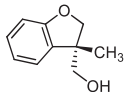
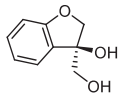
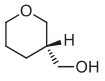
2.3.6. Intramolecular alcoholytic and phenolytic desymmetrization of oxetanes. In efforts to broaden the scope of electrophiles activated by (salen)Co(III) catalysts beyond epoxides, we demonstrated that the intramolecular alcoholytic and phenolytic desymmetrization of oxetanes could be catalyzed by oligomeric complex **4a** to provide a variety of tetrahydrofuran, dihydrobenzofuran, and tetrahydropyran products in high enantioselectivity (Table 6).[25a,49] Alkyl (entries 2, 4, and 6) and phenyl (entry 3) substitution at the 3-position of the oxetane was tolerated, affording products bearing quaternary stereocenters. Incorporation of a fluorine substituent yielded a tetrahydrofuran containing a fully substituted fluorine-bearing stereocenter (entry 5). Ring opening of phenolic substrates (entries 7–9) generated enantioenriched dihyrobenzofurans; however, higher catalyst loadings were required to attain high levels of enantioselectivity. Consistent with the cooperative bimetallic mechanism established for epoxide openings,[13] use of oligomeric complex **4a** lowered the required catalyst loading by 10–500-fold compared to (salen)Co monomer **1** (X=OTf) in all cases studied. Enantioselectivities were comparable with monomeric and oligomeric catalyst in oxetane ring-opening reactions, with the exception of the tetrahydropyran-forming reaction (entry 10) wherein the oligomeric catalyst **4a** afforded much higher product ee.[50]

2.4. Mechanistic studies

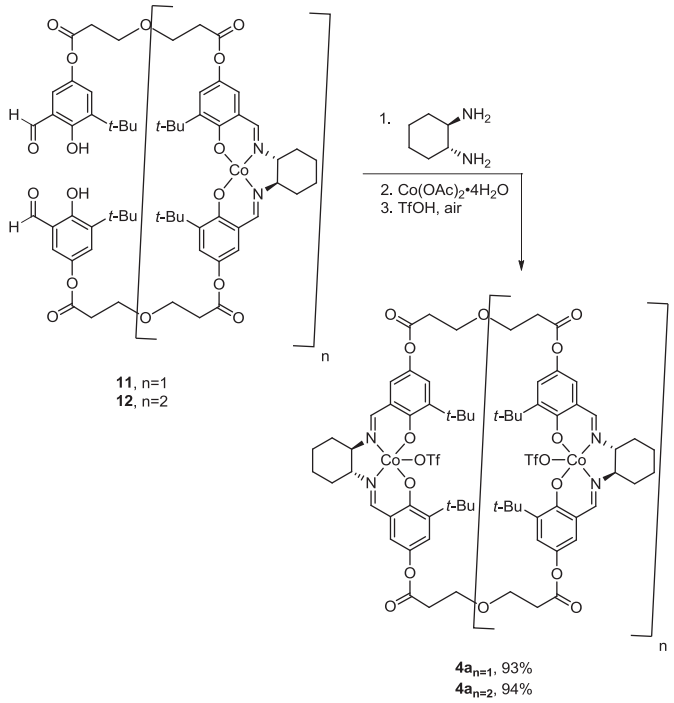
2.4.1. Effects of ring size and oligomeric distribution. As noted, the (salen)Co complex **4a** is prepared and used as a mixture of cyclic dimer and trimer. Extensive efforts to effect separation of these complexes were unsuccessful, so an independent synthesis of the two macrocycles, $\mathbf{4a}_{n=1}$ and $\mathbf{4a}_{n=2}$ was carried out in order to assess

Table 6
The intramolecular alcoholytic and phenolytic desymmetrization of oxetanes catalyzed by oligomeric (salen)Co complex **4a**[a]



Entry	Product	Co (mol %)	Yield[b] (%)	ee[c] (%)
1[d]		0.01	93	96
2		0.01	88	96
3		0.01	98	99
4		0.01	97	99
5[d]		0.01	76	98
6		0.01	98	99
7		0.01	89	98
8		1	95	98
9		1	94	88
10[e]		0.1	89	96

[a] All entries were carried out on a 0.15–0.5 mmol scale.
[b] Isolated yield.
[c] Enantiomeric excesses were determined by chiral HPLC analysis of the corresponding benzoylated derivative unless noted otherwise.
[d] Enantiomeric excess was determined by chiral GC analysis of the corresponding trifluoroacetylated derivative.
[e] Reaction time: 96 h.



Scheme 4. Synthesis of the individual components of oligomeric mixture **4a**.

their relative contributions to the overall performance of the oligomeric catalyst. It proved possible to synthesize each macrocycle in pure form by condensation of the appropriate dialdehydes with diaminocyclohexane (Scheme 4).[28]

The pure dimeric and trimeric catalysts were analyzed in a series of model epoxide ring-opening reactions and compared to the mixture **4a** that was prepared as described in Scheme 2. All reactions were conducted at the same loading of (salen)Co units to allow the most direct comparison between the mixture and its components. This resulted in the actual loading of catalyst molecules in runs with the cyclic trimer (**4a**$_{n=2}$) being two-thirds of that in runs with the cyclic dimer (**4a**$_{n=1}$). As illustrated in Fig. 7, the cyclic trimer **4a**$_{n=2}$ was more reactive than dimer **4a**$_{n=1}$ in all cases. These differences were relatively small in the HKR and PKR reactions (Fig. 7A and B), but quite significant in the more challenging reactions such as the AKR of terminal epoxides and the hydrolytic desymmetrization of meso epoxides (Fig. 7C and D). As expected based on the characterization data discussed above that demonstrated the oligomer mixture **4a** to be a mixture of mostly dimer and a small amount of trimer,[28] **4a** displayed intermediate reactivity between **4a**$_{n=1}$ and the more reactive **4a**$_{n=2}$. It is particularly noteworthy, and perhaps somewhat unexpected that catalyst stereoselectivity differed very little with ring size. Indeed, only in the hydrolytic desymmetrization of cyclohexene oxide could a measurable change in enantioselectivity be detected: 92% ee for cyclic dimer **4a**$_{n=1}$ and 94% ee for cyclic trimer **4a**$_{n=2}$. The mixture **4a** exhibited intermediate behavior (93% ee), once again consistent with its composition being mostly dimer.

While the trimer **4a**$_{n=2}$ displays measurable advantages in reactivity relative to the mixture **4a**, it can only be accessed by a substantially more complicated synthesis (nine steps and two purifications by preparative HPLC for **4a**$_{n=2}$ versus four steps and no chromatographic purifications for **4a**). As such, there is no practical advantage to the pure trimeric catalyst, particularly since the stereoselectivities are so similar with the two catalyst compositions. While efforts to bias the synthesis of **4a** toward the selective formation of cyclic trimer appear worthwhile, these have not yet been undertaken.

*2.4.2. Structural basis for the enhanced reactivity of **4a**: effect of substituents, tethering, and cyclization.* As illustrated in several contexts in Section 2.2, oligomeric catalyst **4a** displays consistently superior reactivity and often higher stereoselectivity relative to monomer **1** in a variety of epoxide ring-opening and related reactions. While **4a** was designed to be essentially a covalently linked, multimeric version of **1**, it in fact possesses three potentially important differences with the original monomeric catalyst: the replacement of *tert*-butyl for carboxylate ligand substituents,

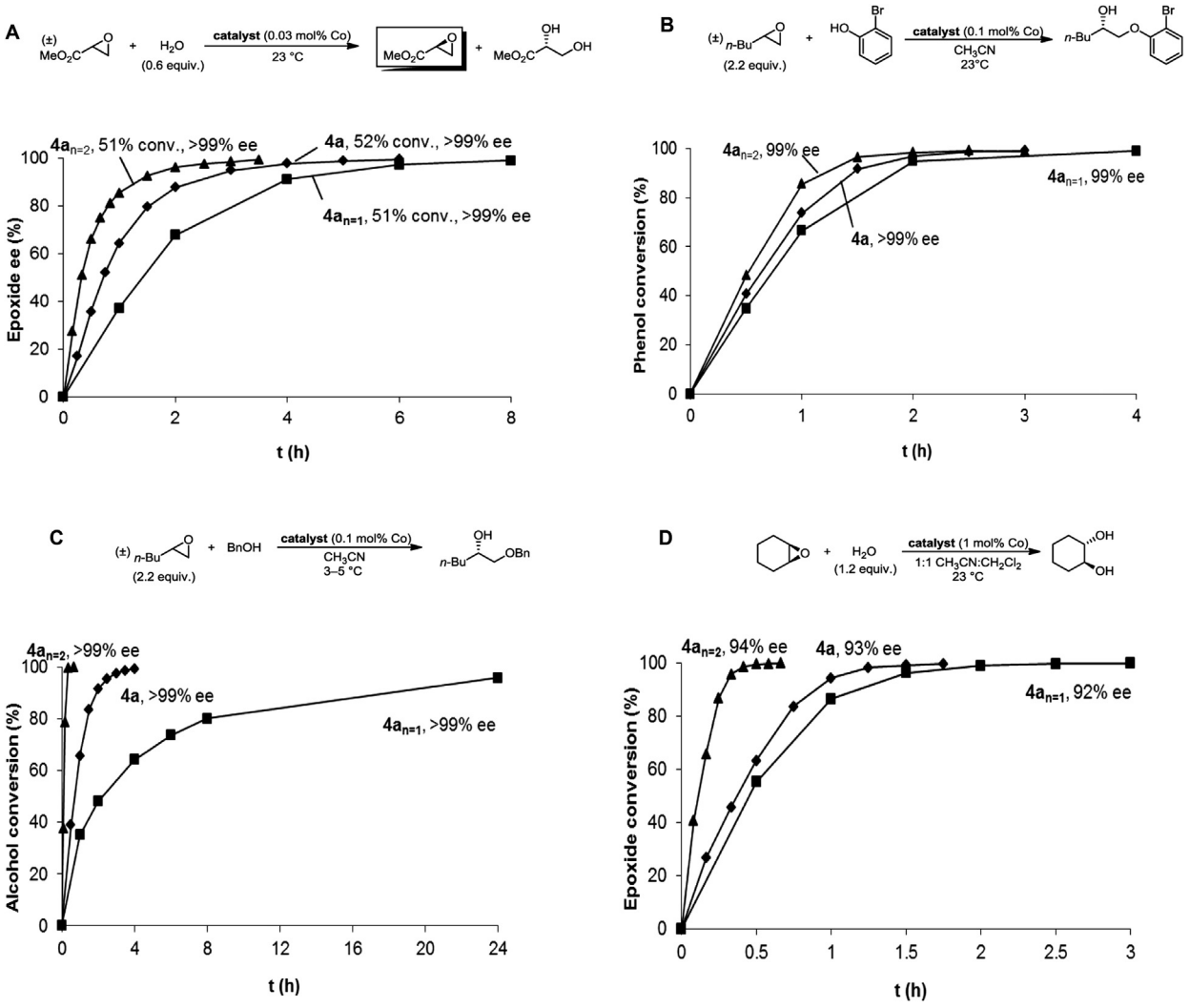


Fig. 7. Comparison of the cyclic dimer (**4a**$_{n=1}$) and the cyclic trimer (**4a**$_{n=2}$) with the oligomeric mixture **4a** in representative epoxide ring-opening reactions. Conversions were determined by GC analysis relative to an internal standard or by ^{1}H NMR analysis. Enantiomeric excesses were determined by chiral GC analysis or HPLC analysis. Numerical conversion and ee values are provided for the last data point of each curve.

the covalent linkage of the salen units, and the macrocyclic structure.

In order to assess how each of these differences is related to the enhanced catalytic properties of oligomeric complex **4a**, we carried out a systematic study of closely related model systems **13**–**15** (Fig. 9). Monomeric complex **13** was prepared and compared to **1a** to evaluate the effect of the change in substituent. A significant effect was indeed observed in the HKR of 1,2-epoxyhexane (Fig. 8), with catalyst **13** promoting complete resolution within 2 h under conditions where monomer **1a** required ca. 10 h.

However, the substituent effect was relatively small compared to the benefit of linking two (salen)Co units covalently as in dimer **14** (Fig. 10). At catalyst loadings where monomer **13** was virtually unreactive, linear dimer **14** proved to be highly active and stereoselective in representative epoxide ring-opening reactions (Fig. 10A–C). Similar to what was observed in comparisons of monomer **1b** with oligomer **4a** (Fig. 6D), monomer **13** catalyzed hydrolysis of cyclohexene oxide with poor enantioselectivity (19% ee), while dimer **14** was highly effective in the same reaction (94% ee, Fig. 10D).

2.4.3. Effect of cyclization. The effect of constraining the tethered salen units in a macrocycle was next analyzed by comparison of the

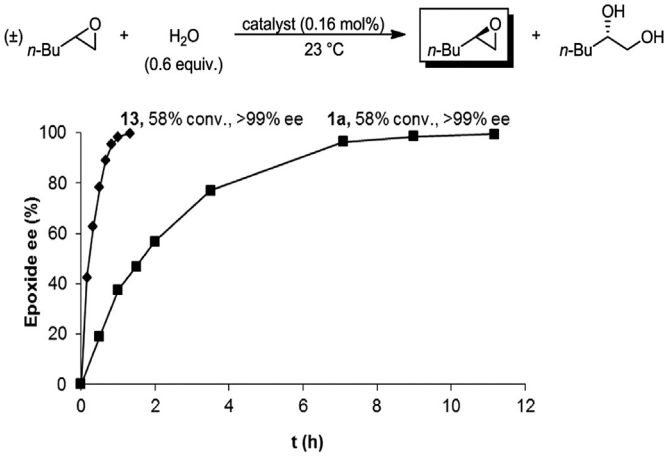


Fig. 8. Comparison of monomer **13** to monomer catalyst **1a** in the HKR of 1,2-epoxyhexane. Numerical conversion and ee values are provided for the last data point of each curve.

cyclic oligomers **4a**$_{n=1}$ and **4a**$_{n=2}$ to linear dimer **14** and linear trimer **15**. As illustrated in Fig. 11, the differences in reactivity between the four catalysts vary considerably depending on the type of epoxide ring-opening reaction, but interesting patterns emerge. The

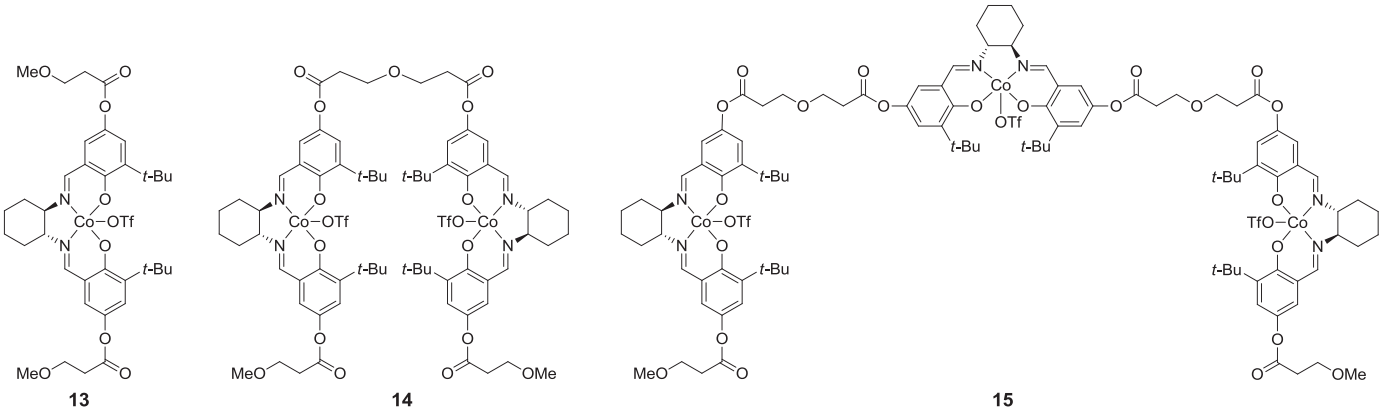


Fig. 9. Mono-, di-, and trimeric acyclic analogs of oligomeric complex **4a**.

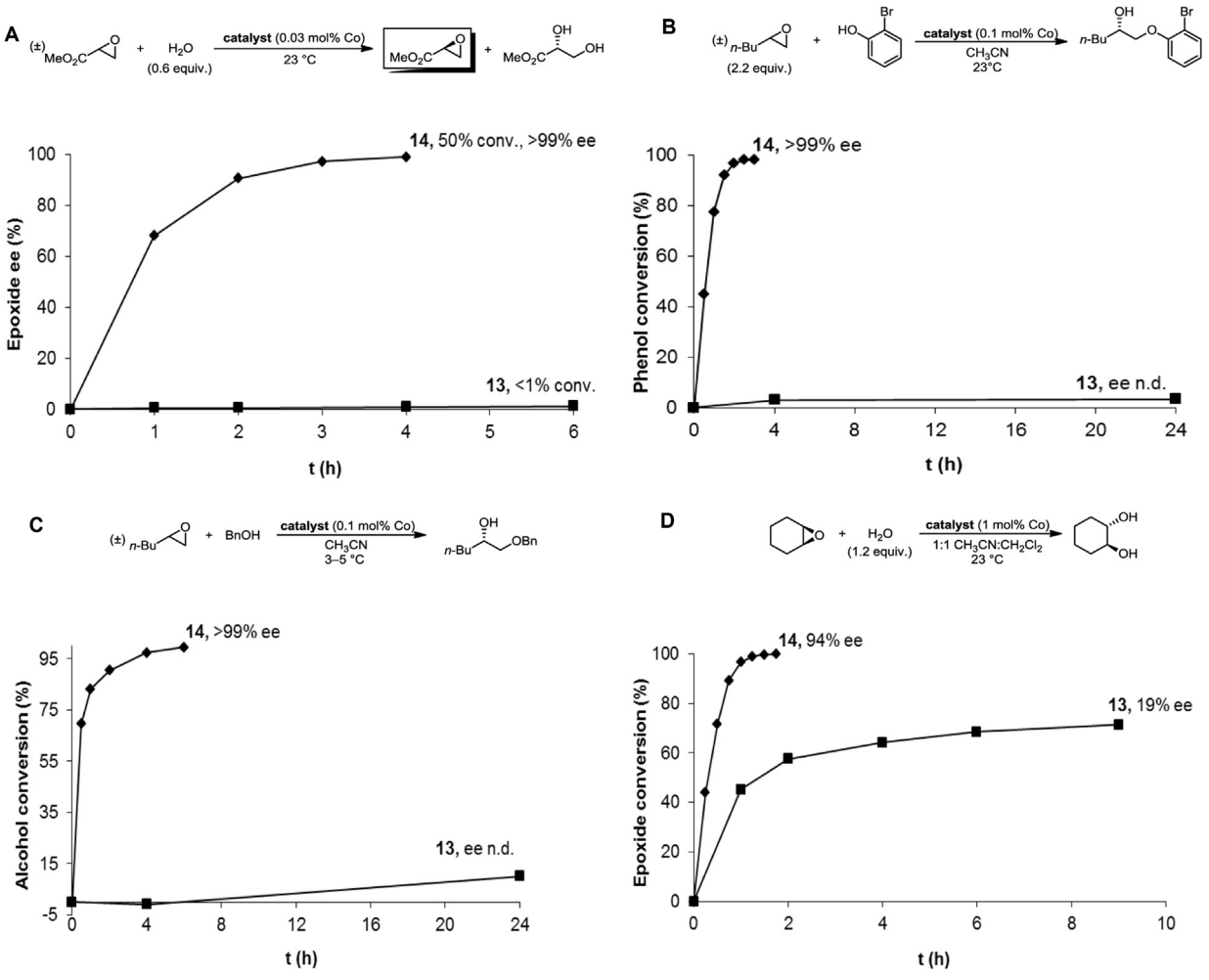


Fig. 10. Comparison of monomer **13** to linear dimer analog **14**. Conversions were determined by GC analysis relative to an internal standard or by ^{1}H NMR analysis. Enantiomeric excesses were determined by chiral GC or HPLC analysis. Numerical conversion and ee values are provided for the last data point of each curve. n.d.=not determined.

acyclic catalysts **14** and **15** possess nearly identical reactivity in HKR and PKR reactions (Fig. 11A and B), and the dimer is only slightly more reactive in the AKR and meso epoxide hydrolysis reactions (Fig. 11C and D). Whereas macrocyclization has a negative impact on the reactivity of the dimeric catalysts (**4a**$_{n=1}$ vs **14**), it results in considerable enhancement in reactivity of the trimeric catalysts (**4a**$_{n=2}$ vs **15**). As a result, the cyclic trimer **4a**$_{n=2}$ displays the highest level of reactivity of any of the catalysts in all four representative epoxide ring-opening reactions, with the greatest advantages seen in the AKR and meso epoxide hydrolysis reactions.

2.4.4. Summary of mechanistic findings. From the data obtained from this and earlier mechanistic studies, a clear picture emerges

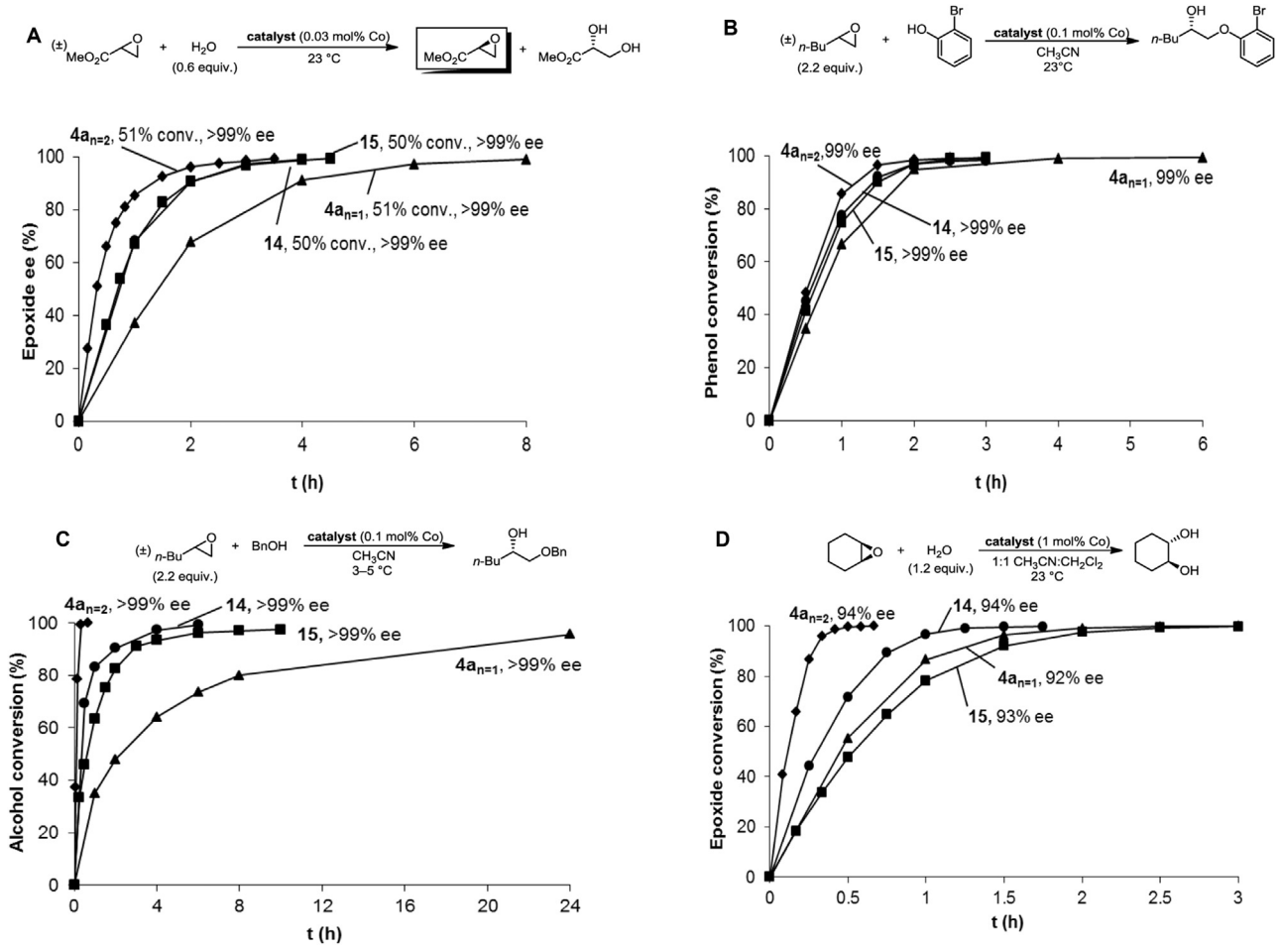


Fig. 11. Comparison of the cyclic dimer **4a**$_{n=1}$ and the cyclic trimer **4a**$_{n=2}$ with the linear dimer **14** and the linear trimer **15**. Conversions were determined by GC analysis relative to an internal standard or by ^{1}H NMR analysis. Enantiomeric excesses were determined by chiral GC analysis or HPLC analysis. Numerical conversion and ee values are provided for the last data point of each curve.

regarding the structural features responsible for the enhanced catalytic properties of tethered (salen)Co complexes:

2.4.4.1. The tether is crucial. Tethering the (salen)Co units through the etherdiester linker as in **4** is the predominant feature that leads to significant improvement in reactivity in all reactions examined (Figs. 6 and 10). As established in earlier studies,[19,20,22] the tether must be located appropriately and flexible enough to allow optimal relative positioning of the reacting (salen)Co units, balance opposing electronic requirements for nucleophile and electrophile activation, and provide adequate solubility of the catalyst for the reproducible and practical application of the catalyst.

*2.4.4.2. The cyclic trimer (**4a**$_{n=2}$) is the most reactive catalyst component.* Catalyst **4a** is composed of a mixture of dimeric and trimeric cyclic complexes, with the former being the dominant species present but the latter displaying generally higher reactivity. The macrocyclic nature of **4a** has an unexpected effect on catalytic activity: the cyclic dimer **4a**$_{n=1}$ is less reactive than its acyclic analog (**14**), whereas the cyclic trimer **4a**$_{n=2}$ displays enhanced reactivity relative to its acyclic analog (**15**). However, the effects are quite complex and reaction-dependent, with small rate differences between the cyclic and acyclic catalysts in reactions such as the phenolic ring-opening of epoxides (the PKR), but quite significant in reactions of primary alcohols with epoxides (the AKR).

2.4.4.3. Stereoselectivity is insensitive to oligomer size or cyclization. Perhaps the most unexpected finding is that very similar stereoselectivities are observed across a variety of epoxide ring-opening reactions for either cyclic or acyclic dimeric and trimeric catalysts. This indicates that the stereoselectivity-inducing transition structure geometries in these reactions are largely insensitive to whether two or three catalyst units are present or to macrocyclization. This has the practical benefit that the mixture of oligomers in **4a** affords consistently high stereoselectivity and is not sensitive to the precise ratio of its components.

Extensive studies on the mechanism of the HKR catalyzed by monomer catalyst **1** have led to a coherent stereochemical model wherein the two reacting (salen)Co complexes are canted relative to one another in the stereoselectivity-determining transition structure (Fig. 12A).[15] Given the high stereoselectivities observed with the cyclic, dimeric catalyst, the flexible tether linking the (salen)Co units in **4a**$_{n=1}$ appears to allow access to a similar relative geometry (Fig. 12C). The same canted geometry is not only accessible in the trimer (**4a**$_{n=2}$), but in fact may be preferred (Fig. 12D). We propose that the trimer possesses not only a larger, more accessible active site, but also a higher proportion of low energy conformers with the appropriate geometric alignment of the two

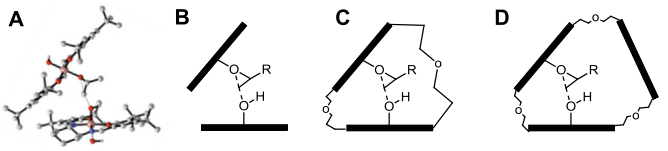


Fig. 12. (A) Calculated, lowest energy transition structure for the HKR with monomeric catalyst, optimized at the B3LYP/6-31G(d) level of theory. The canted relationship of the (salen)Co units is clearly displayed (adapted from Ref. 15). (B) Schematic representation of the calculated structure in panel A, with the thick lines symbolizing the salen frameworks. (C) Schematic representation of the HKR transition structure with cyclic dimeric catalyst $\mathbf{4a}_{n=1}$. (D) Schematic representation of the HKR transition structure with cyclic trimeric catalyst $\mathbf{4a}_{n=2}$.

salen units, and these factors account for the higher reactivity of this complex.

2.5. Catalyst selection guide

Even though the oligomeric catalyst **4a** is readily prepared on any scale (Scheme 2) and is available commercially, the monomeric complex **1** is of course considerably simpler and more accessible. As such, the obvious practical question facing a chemist interested in performing a stereoselective epoxide ring-opening reaction is which catalyst to use to achieve the desired results. Since the relative advantages of the oligomeric catalyst **4a** are reaction-dependent, we offer a comparative guide to aid in selecting the most appropriate catalyst for a given transformation (Table 7). The nucleophilic ring-opening reactions catalyzed by (salen)Co complexes can be divided into three categories.

*2.5.1. Class I: monomer **1** is viable but less efficient.* The HKR of terminal epoxides[2a,c,13a] and the intramolecular alcoholytic and phenolytic desymmetrization of oxetanes[25,51] are catalyzed effectively by monomer complex **1**. However, substantial reductions in catalyst loading are realized consistently with complex **4a**, and improved stereoselectivity is observed in certain cases. Only a few examples of (salen)Co-catalyzed carbamate additions to terminal epoxides (CKR reactions) have been reported,[7a] but available data indicate that similarly high stereoselectivities can be obtained with monomeric or oligomeric catalysts. In the one case where a direct comparison was made, much higher catalytic efficiencies were achieved with oligomer **4a**. For each of these Class I reactions, the ease of access to complex **1** must be weighed against the improved rates and turnover numbers achieved with complex **4a**.

2.5.2. Class II: reaction is substrate-dependent. The addition of phenols to terminal epoxides (PKR) is catalyzed with high stereoselectivity by monomer **1** as long as the phenol is relatively unhindered.[6] Reactions of more hindered phenols, particularly those bearing ortho substituents, require the use of oligomer **4a**. Even in cases where complex **1** is viable, complex **4a** offers substantial improvements in reaction rate.

*2.5.3. Class III: oligomer **4** is uniquely effective.* The addition of primary alcohols to terminal epoxides (AKR reactions) and the enantioselective opening of meso epoxides with either water[11] or carbamates[25b] require the use of oligomer **4a**, as monomer **1** is either unreactive or very poorly stereoselective in these reactions.

Table 7
Catalyst selection guide for epoxide ring-opening reactions mediated by monomeric (salen)Co complex **1** and/or oligomeric (salen)Co complex **4a**

Reaction class	Electrophile	Nucleophile	Monomer **1** viable?	Co loading reduction with oligomer **4a**[a]	Enhanced stereoselectivity or substrate scope with oligomer **4a**?[a]
I	Terminal epoxides	Water	Yes	22–667-fold[b]	Yes
		Carbamates	Yes	22-fold[c]	n.d.[d]
	Oxetanes	Intramolecular primary alcohols	Yes	100-fold[e]	Yes
		Intramolecular phenols	Yes	10–500-fold[e]	No
II	Terminal epoxides	Phenols	Substrate-dependent	59–587-fold[f]	Yes
III	Terminal epoxides	Primary alcohols	No	—	—
	meso Epoxides	Water	No	—	—
		Carbamates	No	—	—

[a] Based on reported values for reactions employing identical substrates under optimized conditions for each catalyst.
[b] Based on Refs. 2a,2c, and 13a. Comparison for styrene oxide based on oligomer **4b.**
[c] Based on a single example from Ref. 7a.
[d] n.d.=not determined.
[e] Based on Ref. 25a.
[f] Based on Ref. 6.

3. Conclusions and outlook

The discovery that (salen)Co-catalyzed epoxide ring-opening reactions proceed by cooperative, bimetallic mechanisms laid the foundation for the development of simple, oligomeric catalysts possessing substantially improved reactivity, stereoselectivity, and substrate scope relative to the original monomeric catalysts. Oligomeric (salen)Co catalyst **4** is readily prepared in multigram quantities from inexpensive, commercially available materials and can be used under practical conditions at any scale. Analysis of the structural changes relative to monomeric complex **1** has revealed the key elements responsible for the enhanced catalytic properties of the oligomer and has provided new design principles for future generations of catalysts. In particular, the cyclic, trimeric component of catalyst **4a** displays particularly high reactivity in certain reactions. Application of this insight to new catalyst designs and in other classes of bimetallic (salen)metal-catalyzed reactions appears highly worthwhile.

4. Experimental section

4.1. General

Equipment: All reactions were performed open to the air unless otherwise noted. All reactions performed under N_2 were conducted

in round-bottomed flasks fitted with rubber septa. Air- and moisture-sensitive chemicals were transferred via syringe or stainless steel cannula. Flash chromatography was performed using silica gel 60 (230–400 mesh) purchased from EM Science. Preparatory TLC was performed on 20×20 cm silica gel 60 F_{254} plates (0.25 mm thickness) precoated with a fluorescent indicator purchased from EM Science.

Materials: Unless otherwise stated, all reagents were purchased from Acrōs, Sigma-Aldrich, Alfa Aesar, Lancaster, Pfaltz & Bauer, Strem, EM Science, or EMD Chemicals Inc. and used as received. Racemic methyl glycidate was received as a generous gift from Rhodia ChiRex. Solvent was distilled over CaH_2 (CH_2Cl_2, CH_3CN), Na (benzene, toluene), or Na/benzophenone ketone (THF) where indicated; otherwise, solvent was used directly from the bottle. Anhydrous DMF, MeOH, and EtOH were obtained from Sigma-Aldrich and packaged in a Sure/Seal™ bottle. Unless otherwise stated, catalyst loadings were not corrected for the presence of residual solvent. Measured values are rounded for convenience; calculations were performed prior to rounding.

Instrumentation: All solution state ^{1}H NMR, ^{13}C NMR, and ^{19}F NMR spectra were recorded using an Inova-600 (600 MHz), an Inova-500 (500 MHz), or a Varian Mercury-400 (400 MHz) spectrometer. Chemical shifts for hydrogen are reported in parts per million (ppm) downfield from tetramethylsilane and are referenced to the resonances of residual protium in the NMR solvent: pyridine-d_5 (δ 8.71, 7.55, 7.19); $CDCl_3$ (δ 7.26); D_2O (δ 4.79); CD_3OD (δ 4.78, 3.30); DMSO-d_6 (δ 2.49); acetone-d_6 (δ 2.04). H_2O appears as a broad singlet between δ 4.5 and δ 5.5 in pyridine-d_5. Chemical shifts for carbon are reported in parts per million (ppm) downfield from tetramethylsilane and are referenced to the resonances of the NMR solvent, except D_2O: pyridine-d_5 (δ 149.9, 135.5, 123.5); $CDCl_3$ (δ 77.0); CD_3OD (δ 49.0); DMSO-d_6 (δ 39.5); acetone-d_6 (δ 206.0, 29.8). Chemical shifts for carbon in D_2O are reported in parts per million (ppm) downfield from the hydrogen resonances of the trimethylsilyl group of added of 3-(trimethylsilyl)-1-propanesulfonic acid, sodium salt (δ 0). IR spectra were recorded as KBr discs or as thin films on either NaCl or KBr plates on a Perkin–Elmer FTIR 1600 or a Galaxy Series FTIR 3000 spectrophotometer. Optical rotations were measured using a 2 mL cell with a 1 dm path length on a Jasco DIP 370 digital polarimeter. Mass spectrometric data was obtained at the Harvard University mass spectrometry facility or on a Waters Micromass® ZQ™ mass spectrometer. Preparative HPLC purification was performed on an Agilent 1100 Series instrument. Chiral GC analyses were performed on a Hewlett Packard 5890 Series II gas chromatograph. Chiral HPLC analyses were performed on a Hewlett-Packard 1050 or a Shimadzu VP-series instrument. Chiral SFC analysis was performed on a Berger instrument.

4.2. Representative procedure for the HKR of terminal epoxides with catalyst (*R*,*R*)-4a: (*R*)-butadiene monoxide

A 50-mL round-bottomed flask equipped with a stir bar was charged with oligomeric cyclic (*R*,*R*)-(salen)Co(III) triflate **4a** (26.0 mg, 0.033 mmol) and placed in a room temperature water bath. (±)-Butadiene monoxide (10.5 mL, 130 mmol) immediately followed by H_2O (1.64 mL, 91 mmol) in one portion were added. The reaction flask was sealed with a septum secured by copper wire to prevent substrate evaporation (CAUTION! An initial pressure buildup is observed due to the volatility of the epoxide under the exothermic reaction conditions. Care should be taken to use equipment adequate for elevated pressures.). After stirring 24 h at room temperature, resolved epoxide and excess H_2O were vacuum transferred (0.45 mm Hg, reaction pot: room temperature) to a −78 °C receiving flask. The epoxide was dried over $MgSO_4$ and filtered through a sand plug to give 3.28 g of a clear liquid containing 1% by mass 3-butene-1,2-diol. The corrected yield was 35%. Observed >99% ee as determined by chiral HPLC analysis of the 2-naphthylsulfide derivative [obtained by ring opening with 0.8 equiv 2-naphthalenethiol and 0.8 equiv Et_3N in MeOH (0.75 M) at 4 °C and subsequent purification of the terminal addition product by preparatory TLC (40% EtOAc/hexanes); Chiracel® OD, 5% *i*-PrOH/hexanes, 1 mL/min, 254 nm, t_R (minor)=18.4 min; t_R (major)=22.3 min]. $[\alpha]_D^{31}$ +6.19° (neat); lit.[52] $[\alpha]_D^{22}$ +14.8° (*c* 1.18, Et_2O).

4.3. Representative procedure for the PKR of terminal epoxides with catalyst (*R*,*R*)-4a: (2*S*)-1-phenoxyhexan-2-ol

A 5-mL round-bottomed flask equipped with a stir bar was charged with phenol (235 mg, 2.5 mmol), (±)-1,2- epoxyhexane (0.67 mL, 5.6 mmol), and distilled CH_3CN (0.27 mL). A stock solution of oligomeric cyclic (*R*,*R*)-(salen)Co(III) triflate **4a** in distilled CH_3CN (0.0125 M, 15 μL, 0.00019 mmol) was added, and the flask was sealed with a plastic cap. The reaction mixture was then stirred for 16 h at room temperature, at which time pyridinium *p*-toluenesulfonate (1 mg, 0.004 mmol) was added to quench the catalyst and ensure complete oxidation to Co(III). The reaction was diluted with Et_2O (3 mL) and applied to a pad of silica gel. The pad was eluted with Et_2O (200 mL), and the filtrate washed with 1 N NaOH (3×25 mL) and brine, respectively. After drying over $MgSO_4$, solvent was removed from the filtrate by rotary evaporation. The bulk of remaining epoxide was removed from the crude product under high vacuum. The product was purified by flash chromatography on silica gel (15% EtOAc/hexanes) to give 445 mg (92%) of a clear oil in 99% ee as determined by chiral HPLC analysis [Chiracel® OD, 5% EtOH/hexanes, 1 mL/min, 220 nm, t_R (minor)=6.9 min; t_R (major)=10.1 min]. ^{1}H NMR (CD_3OD) δ 7.22–7.27 (m, 2H), 6.88–6.94 (m, 3H), 3.82–3.92 (m, 3H), 1.58–1.67 (m, 1H), 1.45–1.58 (m, 2H), 1.31–1.45 (m, 3H), 0.94 (dd, *J*=7.2, 7.2 Hz, 3H). ^{13}C NMR (CD_3OD) δ 160.5, 130.4, 121.7, 115.6, 73.2, 71.0, 34.3, 28.9, 23.8, 14.4. IR (thin film) ν 3407, 3063, 3042, 2957, 2932, 2872, 1599, 1497, 1458, 1379, 1335, 1300, 1244, 1173, 1136, 1078, 1040, 922, 883, 814, 754, 691, 613, 509 cm^{-1}. $[\alpha]_D^{30}$ +19.4° (*c* 2.03, CH_2Cl_2); lit.[6] $[\alpha]_D^{25}$ +18.7° (*c* 1.25, CH_2Cl_2). MS (ApCI) *m/z* calcd for $C_{12}H_{17}O$ 177.1, found 177.1 (100%) $[M-OH]^+$; calcd for $C_{12}H_{19}O_2$ 195.1, found 195.1 (26%) $[M+H]^+$; calcd for $C_{12}H_{22}NO_2$ 212.2, found 212.1 (9%) $[M+NH_4]^+$.

4.4. Representative procedure for the AKR of terminal epoxides with catalyst (*R*,*R*)-4a: (2*S*)-1-benzyloxy-2-hexanol

A 5-mL round-bottomed flask equipped with a stir bar was charged with benzyl alcohol (0.26 mL, 2.5 mmol), (±)-1,2-epoxyhexane (0.67 mL, 5.6 mmol), and distilled CH_3CN (0.066 mL). The flask was sealed with a plastic cap, and cooled to 4 °C. A room temperature stock solution of oligomeric cyclic (*R*,*R*)-(salen)Co(III) triflate **4a** in distilled CH_3CN (0.0126 M, 200 μL, 0.0025 mmol) was added, and the flask was resealed with the plastic cap. The reaction mixture was then stirred for 24 h at 4 °C, at which time pyridinium *p*-toluenesulfonate (2 mg, 0.008 mmol) was added to quench the catalyst and ensure complete oxidation to Co(III). The reaction mixture was diluted with Et_2O (3 mL) and applied to a pad of silica gel after warming to room temperature. The pad was eluted with Et_2O (200 mL), and solvent was removed from the filtrate by rotary evaporation. The bulk of remaining epoxide was removed from the crude product under high vacuum. Purified by flash chromatography on silica gel (20% EtOAc/hexanes) to give 480 mg (92%) of a clear liquid in >99% ee as determined by chiral HPLC analysis [(*R*,*R*)-Whelk-01 (Pirkle), 2% *i*-PrOH/hexanes, 1 mL/min, 215 nm, t_R (minor)=10.6 min; t_R (major)=11.5 min]. ^{1}H NMR (CD_3OD) δ 7.29–7.37 (m, 4H), 7.26 (tt, *J*=2.1, 6.8 Hz, 1H), 4.54 (d, *J*=12.4 Hz, 1H), 4.52 (d, *J*=12.5 Hz, 1H), 3.71 (dddd, *J*=4.4, 6.5, 6.5, 7.4 Hz, 1H), 3.42 (dd, *J*=4.2, 9.8 Hz, 1H), 3.37, (dd, *J*=6.4, 9.8 Hz, 1H), 1.46–1.55 (m, 1H), 1.26–1.46 (m, 5H), 0.91 (dd, *J*=7.1, 3H). ^{13}C NMR

δ 139.8, 129.3, 128.9, 128.6, 75.7, 74.3, 71.4, 34.5, 28.8, 23.8, 14.4. IR (thin film) ν 3442, 3088, 3064, 3030, 2955, 2931, 2860, 1496, 1466, 1454, 1378, 1364, 1331, 1311, 1270, 1204, 1101, 1028, 736, 698 cm^{-1}. $[\alpha]_D^{26}$ +6.22° (*c* 2.04, CH_2Cl_2); lit.[19] $[\alpha]_D^{23}$ +5.1° (*c* 2.01, CH_2Cl_2). MS (ApCI) *m/z* calcd for $C_6H_{13}O_2$ 117.1, found 117.0 (100%) $[M-PhCH_2]^+$; calcd for $C_{13}H_{21}O_2$ 209.2, found 209.1 (24%) $[M+H]^+$.

4.5. Representative procedure for the hydrolytic desymmetrization of endocyclic meso epoxides with catalyst (*R,R*)-4a: (1*S*)-*trans*-cyclopentane-1,2-diol

A 100-mL round-bottomed flask equipped with a stir bar was charged with oligomeric cyclic (*R,R*)-(salen)Co(III) triflate **4a** (805 mg, 1.01 mmol) and CH_3CN (32 mL), respectively. To this solution was added H_2O (2.18 mL, 121 mmol). Cyclopentene oxide (8.8 mL, 101 mmol) was then added over 1 h via syringe pump, and the reaction mixture was stirred an additional 23 h at room temperature. At 24 h total time, pyridinium *p*-toluenesulfonate (760 mg, 3.02 mmol) was added to quench the catalyst and ensure complete oxidation to Co(III). The reaction mixture was diluted with EtOAc (400 mL) to precipitate out the bulk of the catalyst and then applied to a pad of silica gel. The pad was eluted with EtOAc (1 L), and solvent was removed from the filtrate by rotary evaporation. Residual solvent was then distilled away at 45 mm Hg over 15 min with a bath temperature of 50–55 °C. Short path distillation at 4 mm Hg into a 0 °C receiving flask then afforded 8.77 g (85%) of the product diol as a colorless low-melting solid in approximately 98% purity by ^1H NMR analysis. The yield was uncorrected. Observed 96% ee as determined by chiral GC analysis of the bis(trifluoroacetate) derivative [obtained by treating product with neat TFAA, followed by evaporation of excess TFAA under a stream of N_2; Chiraldex™ γ-TA, 65 °C, isothermal, t_R (minor)=4.4 min; t_R (major)=6.9 min]. ^1H NMR (CD_3OD) δ 3.89–3.93 (m, 2H), 1.90–1.99 (dtd, *J*=5.5, 7.8, 13.0 Hz, 2H), 1.71 (td, *J*=7.5, 15.2 Hz, 2H), 1.47–1.55 (m, 2H). ^{13}C NMR (CD_3OD) δ 79.7, 32.5, 21.4. IR (thin film) ν 3331, 2965, 1437, 1344, 1296, 1086, 1038, 974, 876 cm^{-1}. $[\alpha]_D^{29}$ +24.7° (*c* 1.17, EtOH); lit.[53] $[\alpha]_D^{20}$ +24.54° (*c* 5.4, EtOH). MS (CI) *m/z* calcd for $C_5H_{14}NO_2$ 120, found 120 (100%) $[M+NH_4]^+$; calcd for $C_5H_{17}N_2O_2$ 137, found 137 (9%) $[M+NH_4+NH_3]^+$.

4.6. Representative procedure for the CKR of terminal epoxides with catalyst (*S,S*)-4a: ((*R*)-2-hydroxy-hexyl)-carbamic acid, *tert*-butyl ester

A 5-mL round-bottomed flask equipped with a stir bar was charged with oligomeric cyclic (*S,S*)-(salen)Co(III) triflate *ent*-**4a** (4.4 mg, contained 8% by mass toluene, 0.0051 mmol), *tert*-butyl carbamate (293 mg, 2.5 mmol, recrystallized from TBME/hexanes), distilled CH_3CN (0.22 mL), and (±)-1,2-epoxyhexane (0.67 mL, 5.6 mmol, distilled from CaH_2), respectively, and sealed with a plastic cap. The reaction mixture was then stirred for 24 h at room temperature, at which time it was diluted with EtOAc (3 mL) and applied to a pad of silica gel. The pad was eluted with EtOAc (200 mL), and solvent was removed from the filtrate by rotary evaporation. The bulk of the remaining epoxide and residual carbamate were removed from the crude product under high vacuum. Purified by flash chromatography on silica gel (30% EtOAc/hexanes) to give 514 mg of a faintly yellow oil containing <1% by mass residual solvent by ^1H NMR analysis. The corrected yield was 94%. Observe 98% ee as determined by chiral HPLC analysis of the *O*-benzyl derivative [obtained by etherification with 2.1 equiv NaH, 1.2 equiv benzyl bromide and 0.2 equiv tetrabutylammonium iodide in THF (0.18 M, distilled from Na/benzophenone ketone) at 0 °C to room temperature under an N_2 atmosphere and subsequent purification by flash chromatography on silica gel (10% EtOAc/hexanes); Chiracel® AS, 2% *i*-PrOH/hexanes, 1 mL/min, 220 nm, t_R (minor)=4.9 min; t_R (major)=5.6 min]. ^1H NMR (CD_3OD) δ 3.52–3.60 (m, 1H), 3.11 (dd, *J*=4.4, 13.7 Hz), 2.95 (dd, *J*=6.8, 13.7 Hz, 1H), 1.40–1.50 (m, 2H), 1.43 (s, 9H), 1.27–1.40 (m, 4H), 0.92 (dd, *J*=7.1 Hz, 3H). ^{13}C NMR (CD_3OD) δ 158.6, 80.1, 71.7, 47.5, 35.3, 28.8, 28.7, 23.8, 14.4. IR (thin film) ν 3367, 2960, 2933, 2873, 2863, 1692, 1520, 1457, 1392, 1367, 1275, 1252, 1173, 1090, 1042, 1017, 972, 893, 880, 781 cm^{-1}. $[\alpha]_D^{26}$ −11.7° (*c* 1.24, $CHCl_3$); lit.[7a] $[\alpha]_D^{rt}$ +14.2° (*c* 0.9, $CHCl_3$), *S* enantiomer. MS (ApCI) *m/z* calcd for $C_7H_{16}NO_3$ 162.1, found 162.1 (100%) $[M-t\text{-}Bu+2H]^+$; calcd for $C_{11}H_{24}NO_3$ 218.2, found 218.1 (17%) $[M+H]^+$.

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Supplementary data

Experimental procedures and characterization data for the preparation of (salen)Co complexes **1a** (X=OTf), **1c** (X=(1*S*)-(+)-10-camphorsulfonate), **4a**, $\mathbf{4a}_{n=1}$, $\mathbf{4a}_{n=2}$, **4b**, and **13**–**15** as well as for previously unreported epoxide ring-opening reactions (PDF). Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2014.03.043.

References and notes

1. Larrow, J. F.; Jacobsen, E. N. *Top. Organomet. Chem.* **2004**, *6*, 123–152.
2. (a) Tokunaga, M.; Larrow, J. F.; Kakiuchi, F.; Jacobsen, E. N. *Science* **1997**, *277*, 936–938; (b) Jacobsen, E. N. *Acc. Chem. Res.* **2000**, *33*, 421–431; (c) Schaus, S. E.; Brandes, B. D.; Larrow, J. F.; Tokunaga, M.; Hansen, K. B.; Gould, A. E.; Furrow, M. E.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 1307–1315.
3. For reviews of applications of the HKR reaction in industrial and natural products synthesis, see: (a) Larrow, J. F.; Hemberger, K. E.; Jasmin, S.; Kabir, H.; Morel, P. *Tetrahedron: Asymmetry* **2003**, *14*, 3589–3592; (b) Schneider, C. *Synthesis* **2006**, 3919–3944; (c) Kumar, P.; Naidu, V.; Gupta, P. *Tetrahedron* **2007**, *63*, 2745–2785; (d) Furukawa, Y.; Suzuki, T.; Mikami, M.; Kitaori, K.; Yoshimoto, H. *J. Synth. Org. Chem. Jpn.* **2007**, *65*, 308–319; (e) Kumar, P.; Gupta, P. *Synlett* **2009**, 1367–1382; (f) Pellissier, H. *Adv. Synth. Catal.* **2011**, *353*, 1613–1666.
4. For other examples of hydrolytic kinetic resolutions of terminal epoxides, see: (a) Chengjun, J. *Kinet. Catal.* **2011**, *52*, 691–696; (b) Park, J.; Lang, K.; Abboud, K. A.; Hong, S. *Chem.—Eur. J.* **2011**, *17*, 2236–2245; (c) Jiang, C. J.; Chen, Z. R. *Kinet. Catal.* **2008**, *49*, 474–478; (d) Kawthekar, R. B.; Kim, G.-J. *Synth. Commun.* **2008**, *38*, 1236–1248; (e) Thakur, S. S.; Chen, S.-W.; Li, W.; Shin, C.-K.; Koo, Y.-M.; Kim, G.-J. *Synth. Commun.* **2006**, *36*, 2371–2383; (f) Thakur, S. S.; Li, W.; Shin, C.-K.; Kim, G.-J. *Catal. Lett.* **2005**, *104*, 151–156; (g) Thakur, S. S.; Li, W.; Kim, S.-J.; Kim, G.-J. *Tetrahedron Lett.* **2005**, *46*, 2263–2266; (h) Shin, C.-K.; Kim, S.-J.; Kim, G.-J. *Tetrahedron Lett.* **2004**, *45*, 7429–7433; (i) Cavazzini, M.; Quici, S.; Pozzi, G. *Tetrahedron* **2002**, *58*, 3943–3949; (j) Thakur, S. S.; Li, W.; Kim, S.-J.; Kim, G.-J. *Stud. Surf. Sci. Catal.* **2006**, *159*, 205–208; (k) Thakur, S. S.; Li, W.-J.; Shin, C.-K.; Kim, G.-J. *Chirality* **2006**, *18*, 37–43; (l) Thakur, S. S.; Chen, S.-W.; Li, W.; Shin, C.-K.; Kin, S.-J.; Koo, Y.-M.; Kim, G.-J. *J. Organomet. Chem.* **2006**, *691*, 1862–1872; (m) Jain, S.; Venkatasubbaiah, K.; Jones, C. W.; Davis, R. J. *J. Mol. Catal. A.: Chem.* **2010**, *316*, 8–15; (n) Berkessel, A.; Ertürk, E. *Adv. Synth. Catal.* **2006**, *348*, 2619–2625; (o) Dijk, E. W.; Feringa, B. L.; Roelfes, G. *Tetrahedron: Asymmetry* **2008**, *19*, 2374–2377.
5. For reviews on the enzymatic hydrolysis of epoxides, see: (a) Schober, M.; Faber, K. *Trends Biotechnol.* **2013**, *31*, 468–478; (b) Lin, H.; Liu, J.-Y.; Wang, H.-B.; Ahmed, A. A. Q.; Wu, Z.-L. *J. Mol. Catal. B: Enzym.* **2011**, *72*, 77–89; (c) Bala, N.; Chimni, S. S. *Tetrahedron: Asymmetry* **2010**, *21*, 2879–2898; (d) Choi, W. J. *Appl. Microbiol. Biotechnol.* **2009**, *84*, 239–247; (e) Smit, M. S.; Labuschagne, M. *Curr. Org. Chem.* **2006**, *10*, 1145–1161; (f) Choi, W. J.; Choi, C. Y. *Biotechnol. Bioprocess Eng.* **2005**, *10*, 167–179; (g) Smit, M. S. *Trends Biotechnol.* **2004**, *22*, 123–129; (h) de Vries, E. J.; Janssen, D. B. *Curr. Opin. Biotechnol.* **2003**, *14*, 414–420; (i) Steinreiber, A.; Faber, K. *Curr. Opin. Biotechnol.* **2001**, *12*, 552–558; (j) Archelas, A.; Furstoss, R. *Curr. Opin. Chem. Biol.* **2001**, *5*, 112–119; (k) Sinha, S. C.; Keinan, E.; Reymond, J.-L. *J. Am. Chem. Soc.* **1993**, *115*, 4893–4894.
6. Ready, J. M.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1999**, *121*, 6086–6087.
7. (a) Bartoli, G.; Bosco, M.; Carlone, A.; Locatelli, M.; Melchiorre, P.; Sambri, L. *Org. Lett.* **2004**, *6*, 3973–3975; (b) Bartoli, G.; Bosco, M.; Carlone, A.; Locatelli, M.; Melchiorre, P.; Sambri, L. *Org. Lett.* **2005**, *7*, 1983–1985.
8. For other approaches to the phenolytic kinetic resolution of terminal epoxides, see: (a) Aral, T.; Karakaplan, M.; Hosgören, H. *Catal. Lett.* **2012**, *142*, 794–802; (b) Kawthekar, R. B.; Lee, Y.-H.; Kim, G.-J. *J. Porous Mater.* **2009**, *16*, 367–378; (c)

Kim, Y.-S.; Guo, X.-F.; Kim, G.-J. *Top. Catal.* **2009**, *52*, 197–204; (d) Lee, K.-Y.; Lee, Y.-H.; Shin, C.-K.; Kim, G.-J. *Stud. Surf. Sci. Catal.* **2007**, *165*, 467–470; (e) Lee, K.-Y.; Lee, C.-Y.; Kim, G.-J. *React. Kinet. Catal. Lett.* **2008**, *93*, 75–83; (f) Kawthekar, R. B.; Ahn, C.-H.; Kim, G.-J. *Catal. Lett.* **2007**, *115*, 62–69; (g) Solodenko, W.; Jas, G.; Kunz, U.; Kirschning, A. *Synthesis* **2007**, 583–589; (h) Karadeniz, L.; Koz, G.; Aydin, K.; Astley, S. T. *Turk. J. Chem.* **2010**, *34*, 711–718.

9. For additional examples of the aminolytic kinetic resolution of terminal and internal epoxides, see: (a) Bao, H.; Wang, Z.; You, T.; Ding, K. *Chin. J. Chem.* **2013**, *31*, 67–71; (b) Plancq, B.; Ollevier, T. *Chem. Commun.* **2012**, 3806–3808; (c) Hu, X.; Gao, B.; Chu, Y.; Li, W.; Liu, X.; Lin, L.; Feng, X. *Chem.—Eur. J.* **2012**, *18*, 3473–3477; (d) Arai, K.; Lucarini, S.; Salter, M. M.; Ohta, K.; Yamashita, Y.; Kobayashi, S. *J. Am. Chem. Soc.* **2007**, *129*, 8103–8111; (e) Arai, K.; Salter, M. M.; Yamashita, Y.; Kobayashi, S. *Angew. Chem., Int. Ed.* **2007**, *46*, 955–957; (f) Kureshy, R. I.; Kumar, M.; Agrawal, S.; Khan, N. H.; Abdi, S. H. R.; Bajaj, H. C. *Tetrahedron: Asymmetry* **2010**, *21*, 451–456; (g) Bartoli, G.; Bosco, M.; Carlone, A.; Locatelli, M.; Massaccesi, M.; Melchiorre, P.; Sambri, L. *Org. Lett.* **2004**, *6*, 2173–2176.
10. Intramolecular additions of alcohols to terminal and meso epoxides could be effected with good enantioselectivity using monomer **1**: Wu, M. H.; Hansen, K. B.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **1999**, *38*, 2012–2014.
11. The desymmetrization of meso epoxides with benzoic acid as nucleophile is catalyzed with moderate-to-high enantioselectivity using monomer **1**: Jacobsen, E. N.; Kakiuchi, F.; Konsler, R. G.; Larrow, J. F.; Tokunaga, M. *Tetrahedron Lett.* **1997**, *38*, 773–776.
12. For a discussion of practical considerations in the HKR and other kinetic resolution processes, see: Keith, J. M.; Larrow, J. F.; Jacobsen, E. N. *Adv. Synth. Catal.* **2001**, *343*, 5–26.
13. (a) Nielsen, L. P. C.; Stevenson, C. P.; Blackmond, D. G.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 1360–1362; (b) Nielsen, L. P. C.; Zuend, S. J.; Ford, D. D.; Jacobsen, E. N. *J. Org. Chem.* **2012**, *77*, 2486–2495.
14. The cooperative, bimetallic mechanism for epoxide ring-opening was first established in the (salen)Cr(III)-catalyzed asymmetric opening of meso epoxides with $TMSN_3$: Hansen, K. B.; Leighton, J. L.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1996**, *118*, 10924–10925 Also see Ref. 2b.
15. The transition structure representation in Fig. 1 is based on detailed experimental and computational analyses reported in: Ford, D. D.; Nielsen, L. P. C.; Zuend, S. J.; Musgrave, C. B.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2013**, *135*, 15595–15608.
16. For reviews, see Ref. 1 and: (a) Madhavan, N.; Jones, C. W.; Weck, M. *Acc. Chem. Res.* **2008**, *41*, 1153–1165; (b) Haak, R. M.; Wezenberg, S. J.; Kleij, A. W. *Chem. Commun.* **2010**, 2713–2723; (c) Matsunaga, S.; Shibasaki, M. *Synthesis* **2013**, 421–437.
17. (a) Konsler, R. G.; Karl, J.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1998**, *120*, 10780–10781; (b) Peukert, S.; Jacobsen, E. N. *Org. Lett.* **1999**, *1*, 1245–1248; (c) Annis, D. A.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1999**, *121*, 4147–4154; (d) Breinbauer, R.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2000**, *39*, 3604–3607; (e) Belser, T.; Jacobsen, E. N. *Adv. Synth. Catal.* **2008**, *350*, 967–971.
18. For examples of tethered (salen)Co catalyst systems possessing C_1 symmetric salen units, see Ref. 17 and (a) Kleij, A. W. *Eur. J. Inorg. Chem.* **2009**, 193–205; (b) Kureshy, R. I.; Khan, N. H.; Abdi, S. H. R.; Patel, S. T.; Jasra, R. V. *J. Mol. Catal. A: Chem.* **2002**, *179*, 73–77; (c) Song, Y.; Chen, H.; Hu, X.; Bai, C.; Zheng, Z. *Tetrahedron Lett.* **2003**, *44*, 7081–7085; (d) Kureshy, R. I.; Singh, S.; Khan, N. H.; Abdi, S. H. R.; Ahmad, I.; Bhatt, A.; Jasra, R. V. *Chirality* **2005**, *17*, 590–594; (e) Holbach, M.; Weck, M. *J. Org. Chem.* **2006**, *71*, 1825–1836; (f) Zheng, X.; Jones, C. W.; Weck, M. *Chem.—Eur. J.* **2006**, *12*, 576–583; (g) Rossbach, B. M.; Leopold, K.; Weberskirch, R. *Angew. Chem., Int. Ed.* **2006**, *45*, 1309–1312; (h) Solodenko, W.; Jas, G.; Kunz, U.; Kirschning, A. *Synthesis* **2007**, 583–589; (i) Zheng, X.; Jones, C. W.; Weck, M. *J. Am. Chem. Soc.* **2007**, *129*, 1105–1112; (j) Kureshy, R. I.; Prathap, K. J.; Singh, S.; Agrawal, S.; Khan, N. H.; Abdi, S. H. R.; Jasra, R. V. *Chirality* **2007**, *19*, 809–815; (k) Gill, C. S.; Venkatasubbaiah, K.; Phan, N. T. S.; Weck, M.; Jones, C. W. *Chem.—Eur. J.* **2008**, *14*, 7306–7313; (l) Goyal, P.; Zheng, X.; Weck, M. *Adv. Synth. Catal.* **2008**, *350*, 1816–1822; (m) Beigi, M.; Roller, S.; Haag, R.; Liese, A. *Eur. J. Org. Chem.* **2008**, 2135–2141; (n) Gill, C. S.; Long, W.; Jones, C. W. *Catal. Lett.* **2009**, *131*, 425–431; (o) Zhu, X.; Venkatasubbaiah, K.; Weck, M.; Jones, C. W. *J. Mol. Catal. A: Chem.* **2010**, *329*, 1–6; (p) Thomas, R. M.; Widger, P. C. B.; Ahmed, S. M.; Jeske, R. C.; Hirahata, W.; Lobkovsky, E. B.; Coates, G. W. *J. Am. Chem. Soc.* **2010**, *132*, 16520–16525; (q) Wezenberg, S. J.; Kleij, A. W. *Adv. Synth. Catal.* **2010**, *352*, 85–91; (r) Liu, Y.; Rawlston, J.; Swann, A. T.; Takatani, T.; Sherrill, C. D.; Ludovice, P. J.; Weck, M. *Chem. Sci.* **2011**, *2*, 429–438; (s) Kahn, M. G. C.; Weck, M. *Catal. Sci. Technol.* **2012**, *2*, 386–389; (t) Kahn, M. G. C.; Stenlid, J. H.; Weck, M. *Adv. Synth. Catal.* **2012**, *354*, 3016–3024; (u) Zhu, C.; Yuan, G.; Chen, X.; Yang, Z.; Cui, Y. *J. Am. Chem. Soc.* **2012**, *134*, 8058–8061; (v) Ma, D.-Y.; Xiao, Z.-Y.; Etxabe, J.; Warnmark, K. *ChemCatChem* **2012**, *4*, 1321–1329; (w) Matkiewicz, K.; Bukowska, A.; Bukowski, W. *J. Mol. Catal. A: Chem.* **2013**, *368–369*, 43–52; (x) Venkatasubbaiah, K.; Feng, Y.; Arrowood, T.; Nickias, P.; Jones, C. W. *ChemCatChem* **2013**, *5*, 201–209; (y) Ahmed, S. M.; Poater, A.; Childers, M. I.; Widger, P. C. B.; LaPointe, A. M.; Lobkovsky, E. B.; Coates, G. W.; Cavallo, L. *J. Am. Chem. Soc.* **2013**, *135*, 18901–18911.
19. Ready, J. M.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2001**, *123*, 2687–2688.
20. Ready, J. M.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2002**, *41*, 1374–1377.
21. For other examples of tethered (salen)Co catalyst systems possessing C_2 symmetric salen units, see: (a) Song, Y.; Yao, X.; Chen, H.; Bai, C.; Hu, X.; Zheng, Z. *Tetrahedron Lett.* **2002**, *43*, 6625–6627; (b) Kwon, M.-A.; Kim, G.-J. *Catal. Today* **2003**, *87*, 145–151; (c) Gianneschi, N. C.; Bertin, P. A.; Nguyen, S. T.; Mirkin, C. A.; Zakharov, L. N.; Rheingold, A. L. *J. Am. Chem. Soc.* **2003**, *125*, 10508–10509; (d) Gianneschi, N. C.; Cho, S.-H.; Nguyen, S. T.; Mirkin, C. A. *Angew. Chem., Int. Ed.* **2004**, *43*, 5503–5507; (e) Welbes, L. L.; Scarrow, R. C.; Borovik, A. S. *Chem. Commun.* **2004**, 2544–2545; (f) Kureshy, R. I.; Singh, S.; Khan, N. H.; Abdi, S. H. R.; Agrawal, S.; Jasra, R. V. *Tetrahedron: Asymmetry* **2006**, *17*, 1638–1643; (g) Haak, R. M.; Belmonte, M. M.; Escudero-Adan, E. C.; Benet-Buchholz, J.; Kleij, A. W. *Dalton Trans.* **2010**, *39*, 593–602; (h) Zulauf, A.; Mellah, M.; Schulz, E. *Chem.—Eur. J.* **2010**, *16*, 11108–11114; (i) Kureshy, R. I.; Prathap, K. J.; Kumar, M.; Bera, P. K.; Khan, N. H.; Abdi, S. H. R.; Bajaj, H. C. *Tetrahedron* **2011**, *67*, 8300–8307; (j) Sadhukhan, A.; Khan, N. H.; Roy, T.; Kureshy, R. I.; Abdi, S. H. R.; Bajaj, H. C. *Chem.—Eur. J.* **2012**, *18*, 5256–5260; (k) Hong, X.; Mellah, M.; Bordier, F.; Guillot, R.; Schulz, E. *ChemCatChem* **2012**, *4*, 1115–1121; (l) Kumar, M.; Kureshy, R. I.; Shah, A. K.; Das, A.; Khan, N. H.; Abdi, S. H. R.; Bajaj, H. C. *J. Org. Chem.* **2013**, *78*, 9076–9084; (m) Hong, X.; Billon, L.; Mellah, M.; Schulz, E. *Catal. Sci. Technol.* **2013**, *3*, 723–729.
22. White, D. E.; Jacobsen, E. N. *Tetrahedron: Asymmetry* **2003**, *14*, 3633–3638.
23. The improved performance of catalyst **4b** in the HKR of styrene oxide can be ascribed to its lower Lewis acidity relative to catalyst **4a**. The more Lewis acidic catalyst promotes competitive and less enantiomer-selective opening of the epoxide at the internal position.
24. Selected examples of the application of **4a** in the synthesis of complex targets: (a) Peloruside, A.; McGowan, M. A.; Stevenson, C. P.; Schiffler, M. A.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2010**, *49*, 6147–6150; (b) Sch 642305: Snider, B. B.; Zhou, J. *Org. Lett.* **2006**, *8*, 1283–1286; (c) Moenomycin, A.; Adachi, M.; Zhang, Y.; Leimkuhler, C.; Sun, B.; LaTour, J. V.; Kahne, D. E. *J. Am. Chem. Soc.* **2006**, *128*, 14012–14013; (d) Hexose derivatives: Covell, D. J.; Vermeulen, N. A.; Labenz, N. A.; White, M. C. *Angew. Chem., Int. Ed.* **2006**, *45*, 8217–8220; (e) Indolodioxane U86192A: Chae, J.; Buchwald, S. L. *J. Org. Chem.* **2004**, *69*, 3336–3339; (f) Reserpine: Rajapaksa, N. S.; McGowan, M. A.; Rienzo, M.; Jacobsen, E. N. *Org. Lett.* **2013**, *15*, 706–709.
25. (a) Loy, R. N.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2009**, *131*, 2786–2787; (b) Birrell, J. A.; Jacobsen, E. N. *Org. Lett.* **2013**, *15*, 2895–2897.
26. An unoptimized version of the first two steps of this procedure has been reported: Vachal, P.; Jacobsen, E. N. *Org. Lett.* **2000**, *2*, 867–870.
27. Samat, A.; Bibout, M. E. M.; Elguéro, J. *Heterocycles* **1982**, *19*, 469–472.
28. Details of the synthetic procedures and characterization studies are provided in Supplementary data.
29. In all of the synthetic applications described herein, catalyst loadings are calculated without correcting for residual solvent, and therefore represent upper limits.
30. While it was possible in certain cases to employ solvent-free conditions in the PKR and AKR of terminal epoxides and the hydrolytic desymmetrization of meso epoxides when using **4a**, generally superior results were obtained using CH_3CN as solvent.
31. Measurement of conversions for runs employing complexes **1** and **3b** shows both catalysts to be highly selective under the reaction conditions.
32. The (1*S*)-(+)-10-camphorsulfonate counterion provides superior results relative to tosylate in the PKR catalyzed by monomeric complex **1** (Ref. 6).
33. Substrates in entries 1, 2 and 4–6 were used as received from commercial suppliers. Allyl glycidyl ether (entry 3) was purified by distillation from CaH_2.
34. In order to avoid catalyst deactivation, it is important to not let catalyst and epoxide sit together for extended periods prior to the addition of nucleophile. The mechanistic basis for this deactivation has been elucidated (Ref. 13b) and involves formation of less reactive (but still highly stereoselective) (salen)Co–OH complexes.
35. In the case of methyl glycidate, considerable foaming hampered distillation of the product mixture on the laboratory scale. However, removal of the diol product by aqueous extraction prior to distillation circumvented the foaming problem, and the epoxide was thus isolated in good yield: Stevenson, C. P.; Nielsen, L. P. C.; Jacobsen, E. N. *Org. Synth.* **2006**, *83*, 162–169.
36. Other solvents are also useful in this regard. For example, *tert*-butyl ethylene oxide was resolved to>99% ee at 56% conversion in 24 h employing **4a** with CH_2Cl_2 as solvent.
37. Catalyst loadings were optimized to correspond to the lowest loadings possible to achieve >95% conversion of nucleophile within 24 h.
38. With monomer **1b**·2,6-lutidine, the resolution of styrene oxide with phenol provided a 3:2 ratio of the undesired internal addition product to the desired α-aryloxy alcohol: Ready, J. M. *Ph.D. Thesis*; Harvard University: Cambridge, MA, 2001.
39. The PKR of styrene with *p*-cresol catalyzed by **4b** afforded a 21:1 ratio of terminal to internal opening products.
40. Secondary alcohols were found to be unreactive under these conditions.
41. For example, see: Dishong, D. M.; Diamond, C. J.; Cinoman, M. I.; Gokel, G. W. *J. Am. Chem. Soc.* **1983**, *105*, 586–593.
42. For examples of phenolytic desymmetrization of meso epoxides, see: (a) Iida, T.; Yamamoto, N.; Matsunaga, S.; Woo, H.-G.; Shibasaki, M. *Angew. Chem., Int. Ed.* **1998**, *37*, 2223–2226; (b) Vogl, E. M.; Matsunaga, S.; Kanai, M.; Iida, T.; Shibasaki, M. *Tetrahedron Lett.* **1998**, *39*, 7917–7920; (c) Matsunaga, S.; Das, J.; Roels, J.; Vogl, E. M.; Yamamoto, N.; Iida, T.; Yamaguchi, K.; Shibasaki, M. *J. Am. Chem. Soc.* **2000**, *122*, 2252–2260; (d) Matsunaga, S.; Ohshima, T.; Shibasaki, M. *Adv. Synth. Catal.* **2002**, *344*, 3–15 For examples of the alcoholytic desymmetrization of meso epoxides, see: (e) Schneider, C.; Skreekanth, A. R.; Mai, E. *Angew. Chem., Int. Ed.* **2004**, *43*, 5691–5694; (f) Tschöp, A.; Marx, A.; Sreekanth, A. R.; Schneider, C. *Eur. J. Org. Chem.* **2007**, 2318–2327 For the catalytic asymmetric co-polymerization of carbon dioxide and meso epoxides to form polycarbonates, see: (g) Nozaki, K.; Nakano, K.; Hiyama, T. *J. Am. Chem. Soc.* **1999**, *121*, 11008–11009; (h) Cheng, M.; Darling, N. A.; Lobkovsky, E. B.; Coates, G. W. *Chem. Commun.* **2000**, 2007–2008.

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43. For examples of enzymatic hydrolytic desymmetrization of meso epoxides, see: (a) Zhao, L.; Han, B.; Huang, Z.; Miller, M.; Huang, H.; Malashock, D. S.; Zhu, Z.; Milan, A.; Robertson, D. E.; Weiner, D. P.; Burk, M. J. *J. Am. Chem. Soc.* **2004**, *126*, 11156–11157 and references therein; (b) Weijers, C. A. G. M. *Tetrahedron: Asymmetry* **1997**, *8*, 639–647; (c) Hodgson, D. M.; Gibbs, A. R.; Lee, G. P. *Tetrahedron* **1996**, *52*, 14361–14384 and references therein.
44. meso Epoxides derived from acyclic alkenes are relatively poor substrates for hydrolysis catalyzed by **4a**, with lower rates and enantioselectivities obtained in all cases examined. Primary alcohols and phenols were found to be unreactive toward cyclohexene oxide in the presence of **4a**.
45. Servis, K. L.; Noe, E. A. *J. Am. Chem. Soc.* **1973**, *95*, 171–174 and references therein.
46. The commercially available epoxides employed in entries 1, 2 and 4–6 were used as received. For the preparation and purification of the epoxides employed in entries 3 and 7–10, see Supplementary data.
47. For examples of the carbamolytic desymmetrization of meso epoxides, see: (a) Sekine, A.; Ohshima, T.; Shibasaki, M. *Tetrahedron* **2002**, *58*, 75–82; (b) Hou, X.-L.; Wu, J.; Dai, L.-X.; Xia, L.-J.; Tang, M.-H. *Tetrahedron: Asymmetry* **1998**, *9*, 1747–1752; (c) Fu, X.-L.; Wu, S.-H. *Synth. Commun.* **1997**, *27*, 1677–1683; (d) Regati, S.; He, Y.; Thimmaiah, M.; Li, P.; Xiang, S.; Chen, B.; Zhao, J. C.-G. *Chem. Commun.* **2013**, 9836–9838; (e) Azoulay, S.; Manabe, K.; Kobayashi, S. *Org. Lett.* **2005**, *7*, 4593–4595; (f) Mai, E.; Schneider, C. *Synlett* **2007**, 2136–2138; (g) Carrée, F.; Gil, R.; Collin, J. *Org. Lett.* **2005**, *7*, 1023–1026.
48. (a) Chang, S.; McNally, D.; Shary-Tehrany, S.; Hickey, M. J.; Boyd, R. H. *J. Am. Chem. Soc.* **1970**, *92*, 3109–3118; (b) Allinger, N. L.; Tribble, M. T.; Miller, M. A.; Wertz, D. H. *J. Am. Chem. Soc.* **1971**, *93*, 1637–1648.
49. For examples of the desymmetrization of oxetanes with other nucleophiles, see: (a) Wang, Z.; Chen, Z.; Sun, J. *Angew. Chem., Int. Ed.* **2013**, *52*, 6685–6688; (b) Chen, Z.; Wang, Z.; Sun, J. *Chem. Eur. J.* **2013**, *19*, 8426–8430; (c) Mizuno, M.; Kanai, M.; Iida, A.; Tomioka, K. *Tetrahedron: Asymmetry* **1996**, *7*, 2483–2484; (d) Mizuono, M.; Kanai, M.; Iida, A.; Tomioka, K. *Tetrahedron* **1997**, *53*, 10699–10708.
50. For entry 10, (salen)Co monomer **1a** (10 mol %) afforded product in 7% ee at 38% conversion after 96 h. In tetrahydrofuran- and dihydrobenzofuran-forming reactions (entries 1–9), comparable ees ±5% were obtained using monomeric or oligomeric catalyst.
51. The sole exception to this statement observed thus far is in the formation of tetrahydropyrans as described in Section 2.3.6 and Ref. 25a.
52. Chenault, K. M.; Kim, M.-J.; Akiyama, A.; Miyazawa, T.; Simon, E. S.; Whitesides, G. W. *J. Org. Chem.* **1987**, *52*, 2608–2611.
53. Cunningham, A. F., Jr.; Kündig, E. P. *J. Org. Chem.* **1988**, *53*, 1823–1825.

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