^{1}H NMR (400 MHz, trace TFA/$CDCl_3$, monocation): $\delta = -3.68$ (1H, br s), -2.37 (1H, br s), -1.16 (2H, br s), 1.65 (6H, t, $J = 7$ Hz), 3.14 (6H, s), 3.72 (4H, br q), 7.51 – 7.55 (2H, br m), 8.25 (5H, br m), 8.87 (2H, s), 9.44 (2H, s), 9.75 (2H, br d, $J = 7.5$ Hz); ^{1}H NMR (400 MHz, TFA/$CDCl_3$, dication): $\delta = -0.90$ (2H, br s), 1.49 (1H, s), 1.58 (6H, t, $J = 7.4$ Hz), 3.04 (6H, s), 3.59 (4H, br q), 4.33 (2H, br s), 8.40 (2H, m), 8.51 (3H, m), 9.26 (2H, m), 9.42 (2H, s), 9.73 (2H, m), 9.79 (2H, s); ^{13}C NMR (100 MHz, TFA/$CDCl_3$): $\delta =$ 10.60, 16.10, 19.69, 35.82 (internal CH_2), 106.84, 118.18, 124.40, 127.49, 131.56, 134.01, 134.49, 139.48, 140.27, 140.67, 144.46, 146.71, 151.92, 152.02, 152.04, 154.99; HRMS (FAB): calculated for $C_{37}H_{32}N_2 + H$: m/z 505.2642; found: 505.2644; elemental analysis (%) calcd for $C_{37}H_{32}N_2 \cdot \frac{1}{2}H_2O$: C 86.51, H 6.47, N 5.45; found: C 86.26, H 6.24, N 5.66.

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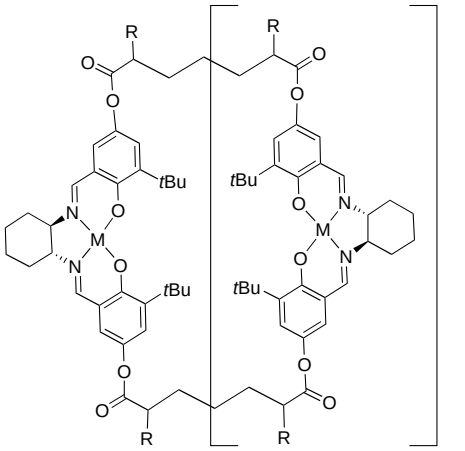
A Practical Oligomeric [(salen)Co] Catalyst for Asymmetric Epoxide Ring-Opening Reactions**

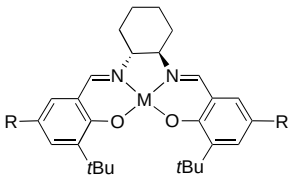
Joseph M. Ready and Eric N. Jacobsen*

The development of catalysts that are not only enantioselective and high yielding but also useful from a practical standpoint persists as a challenging goal in asymmetric synthesis. In the ideal case, a catalyst should be readily available or easily synthesized on any scale and should display both high reactivity (turnover frequency) and durability (turnover number). In this context, substantial progress has been made over the past several years in the discovery of chiral salen-metal-based catalysts (H_2salen = bis(salicylidene)ethylenediamine) for the asymmetric ring-opening of epoxides, and attention has focused recently on the development of these catalysts from a practical perspective.[1] We describe herein a significant advance in this regard, with the development of easily synthesized and highly active oligomeric [(salen)Co] catalysts for the asymmetric hydrolysis of *meso*-epoxides and kinetic resolution of terminal epoxides.

We reported recently the preparation of mixtures of cyclic oligomeric [(salen)Co] complexes (**1**), which were designed to enforce the cooperative bimetallic mechanism common to many epoxide ring-opening reactions.[2] Catalyst system **1** displayed substantial improvements in reactivity and enantioselectivity relative to monomeric analogues, with kinetic behavior consistent with cooperative reactivity within the



1: M = Co(OTs), R = Cl, n =1 - 5
2: M = Co, R = H, n = 1 - 3
3: M = Co(csa), R = H, n = 1 - 3
4: M = Co(nbs), R = H, n = 1 - 3



5: R = *t*Bu
6: R = OC(O) *t*Bu
7: R = OC(O)CH(Cl)CH_3
8: R = OC(O)$C(Cl)_2CH_3$

a: M = Co(OTs)
b: M = Co(csa)

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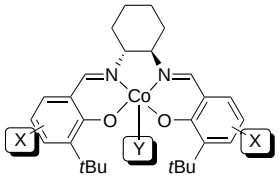
cyclic framework. In addition, the local C_2 symmetry in the individual salen units allowed oligomerization to be effected simply by condensation of dialdehyde and 1,2-diamine in a 1:1 molar ratio. However, problems tied to the structure and synthesis of **1** detract from the utility of this catalyst system. Specifically, installation of the chlorine substituents in the α and α' positions of the linker units requires harsh conditions and proceeds in only moderate yield, with the requisite purification limiting mass throughput. Once installed, the chlorine substituents activate the adjacent carbonyl groups and render the oligomer sensitive to decomposition under the conditions of epoxide ring-opening. Finally, a statistical mixture of diastereomeric linker units was generated and introduced into the oligomer; the synthesis of **1** could thereby produce in excess of 1000 discrete compounds considering all possible diastereomers of the observed ring sizes.[3] This presents an obvious barrier to understanding how the cyclic oligomeric salen framework imparts both high reactivity and enantioselectivity in epoxide ring-opening reactions.

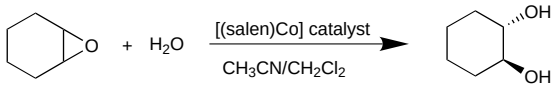
The issues outlined above are all tied to the presence of the chlorine substituents in the linker unit of **1** and would be circumvented if a simpler pimelate-linked system derived from **2** were employed instead.[4] The impetus for introducing the chlorine substituents in the first place arose from an empirical screen of monomeric model systems. This study revealed that electronic tuning of carboxylate-substituted ligands as in **6**–**8** was important to achieve reactivity comparable to that observed with **5**, the benchmark salen catalyst for asymmetric ring-opening reactions. However, there is an alternative site for electronic tuning on the [(salen)Co] catalysts: the ancillary ligand(s) that do not participate directly in catalysis (Scheme 1). Only recently has it become apparent that this might be a viable option for optimization of salen-based catalysts for epoxide ring-opening.[5] Clearly, it suggests a more straightforward strategy for tuning the electronic environment of the metal center in the oligomeric complexes.



Scheme 1. Sites for electronic tuning of the [(salen)Co] catalysts. X: ligand tuning; Y: counterion tuning.

Pimelate-linked oligomeric [(salen)Co^{II}] complex (**2**) was prepared and oxidized with air in the presence of a variety of Brønsted acids (HX) to provide the corresponding [(salen)-Co^{III}(X)] oligomers. These complexes were evaluated for their ability to catalyze the asymmetric hydrolysis of cyclohexene oxide. Whereas oxidation with air/*p*-toluenesulfonic acid led to a catalyst that was less effective than **1**, catalysts generated by oxidation with camphorsulfonic acid (**3**, CSA = 10-camphorsulfonate) and 3-nitrobenzenesulfonic acid (**4**, NBS = 3-nitrobenzenesulfonate) displayed comparable reactivity and slightly improved selectivity relative to **1** (Table 1, entries 1 versus 3 and 5).[6, 7] Longer reaction times and decreased reaction temperature were required to obtain highly enantioenriched diol product using catalyst **1** (Table 1, entry 2).

Table 1. Asymmetric hydrolysis of cyclohexene oxide catalyzed by [(salen)-Co] complexes.[a]



Entry	Catalyst[b] [mol %]	t [h]	Yield[c] [%]	*ee* [d] [%]
1	**1** (1.5)	3	95	86
2[e]	**1** (1.5)	11	98	94
3	**3** (1.5)	4	97	93
4	**3** (0.5)	12	90	93
5	**4** (1.5)	4	91	93
6	**4** (0.5)	12	92	93
7	**6b** (1.5)	36	72	71
8	**6b** (0.5)	96	16	51

[a] Reactions carried out with [epoxide]$_0$ = 2.5 M in 1:1 CH_3CN/CH_2Cl_2 at room temperature unless indicated otherwise. See Supporting Information for details. [b] mol % Co relative to epoxide. [c] Yield of isolated product. [d] Determined by chiral GC analysis. [e] Reaction carried out at 4 °C.

Catalysts **3** and **4** were prepared on large scale under chromatography-free conditions from inexpensive components (Scheme 2).[8] Coupling of phenol **9**[2] with pimelic acid in the presence of 1,3-diisopropylcarbodiimide (DIC) and a catalytic amount of dimethylaminopyridine (DMAP) provided **10** in 99 % purity following extraction and filtration. The free base of (*R*,*R*)-1,2-diaminocyclohexane was generated in situ from the commercially available tartrate salt and condensed with dialdehyde **10** in quantitative yield. Metal insertion followed by air oxidation in the presence of one equivalent of a sulfonic acid derivative provided the oligomeric catalysts **3** and **4**.[9] Mass spectral and NMR data indicated the exclusive formation of cyclic oligomers containing 2–4 metal–salen units.

Complexes **3** and **4** were found to display remarkable activity in the hydrolytic kinetic resolution (HKR) of terminal epoxides. Styrene oxide and styrenediol were obtained in high yield and enantiomeric excess after 2.5 h using 0.08 mol % Co [Eq. (1)]. In contrast, under otherwise identical conditions, 24 h were required to obtain epoxide in 99 % *ee* using **1**. The results with propylene oxide highlight the practical aspects of reactions using **4**: 1.5 mol epoxide were resolved in 24 h at 23 °C using only 5 mg catalyst to provide 39 g recovered epoxide in > 99 % *ee* and 59 g diol in 97 % *ee* [Eq. (2)].

While complexes **3** and **4** displayed similar activity in the HKR, complex **4** proved superior for the kinetic resolution of terminal epoxides with alcohols and phenols. As demonstrated by the data in Equations (3)–(5), monoprotected 1,2-diols and 1-aryloxy alcohols were synthesized regioselectively in high yield and optical purity. It is noteworthy that the results in Equation (3) were obtained with an eightfold decrease in catalyst loading and a fourfold decrease in reaction time relative to the results obtained previously with **1**.[2]

Catalyst **1** exists as a complicated mixture of diastereoisomers and ring sizes,[2] whereas **3** and **4** were synthesized as mixtures of only three compounds (dimer, trimer, and tetramer). It was anticipated that this simplification would aid our efforts to understand the differences in enantioselectivity between oligomeric and monomeric [(salen)Co] com-

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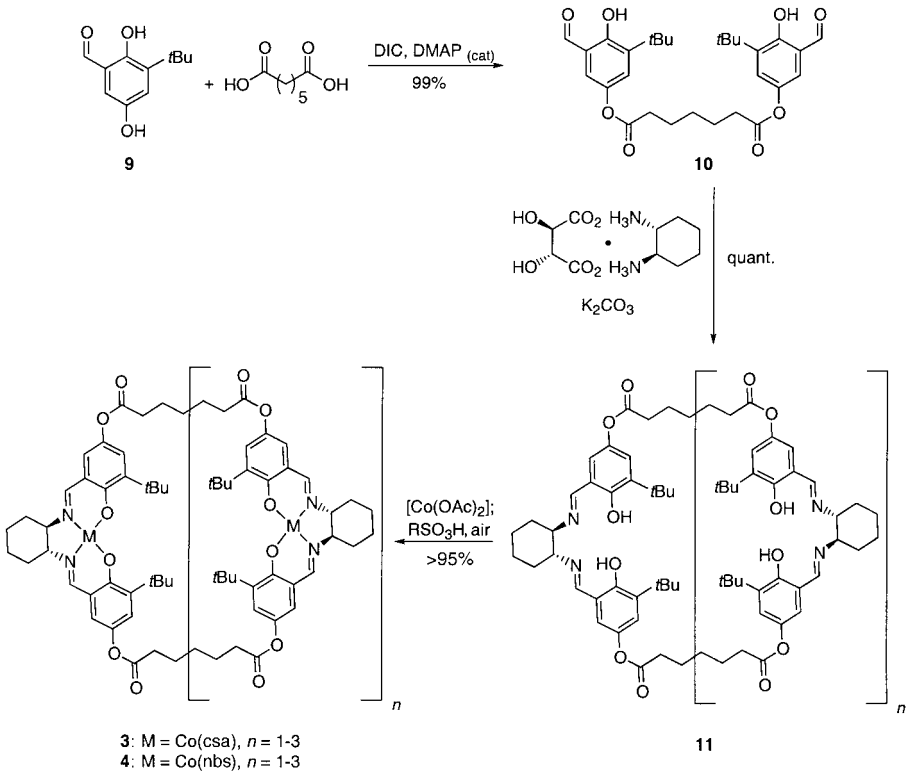
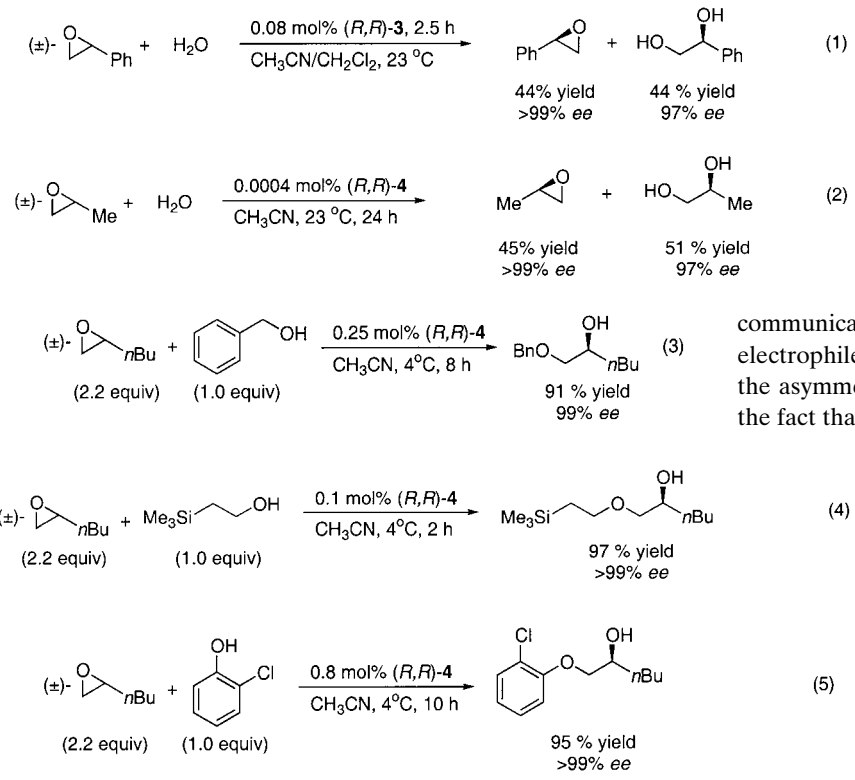


Scheme 2. Chromatography-free synthesis of **3** and **4**.



plexes. The discrete components of the catalyst mixture were prepared independently following the strategy shown in Scheme 3.[9, 10] Catalysts **3a–c** were evaluated in the asymmetric hydrolysis of cyclohexene oxide to determine the effect of ring size on reactivity and selectivity. As revealed by the data in Figure 1, the trimer **3b** is more enantioselective and reactive than either **3a** or **3c**. As expected, the activity and selectivity of the mixture reflects an average of the mixture's components. Whereas **3b** is clearly the superior catalyst, it is nonetheless remarkable that all three components of **3** provide substantially higher enantiomeric excesses than the monomeric analogue **6b** (Table 1, entries 7 and 8).

In reactions catalyzed by monomeric metal–salen complexes, decreases in product *ee* were observed when catalyst loading was decreased (Table 1, entries 7 and 8). These observations are consistent with a competition between a second-order, bimetallic pathway and a less selective monometallic pathway.[11] In contrast, the enantioselectivity displayed by **3** and **4** was independent of catalyst loading (Table 1, entries 3 and 4, entries 5 and 6) indicating that a highly selective intramolecular, cooperative process dominates over a range of oligomer concentrations.[12] Even under optimal conditions, however, monomeric catalysts display lower enantioselectivity than **3** or **4**. The intervention of a monometallic pathway therefore does not account solely for the observed enhancement in selectivity.

A second factor that may be responsible for the improved enantioselectivity displayed by **3** and **4** involves the range of reactive conformations available to oligomeric versus monomeric complexes. Incorporation of salen units into a cyclic framework may enforce conformations in which the salen units are in the appropriate relative orientation for optimal stereochemical communication. The chirality of both the nucleophile and electrophile components plays an important role in defining the asymmetric environment in the reaction, as indicated by the fact that nonlinear effects have been observed in both the HKR[13] and the [(salen)Cr]-catalyzed addition of HN_3 to *meso*-epoxides.[14] We propose that the structures of **3** and **4** enforce a selective head-to-tail arrangement of the reacting salen units (Figure 2).[15] The subtle differences in selectivity observed between **3a–3c** likely reflect differences in available reactive conformations. The data suggest that the trimer combines sufficient rigidity to minimize nonselective pathways while maintaining enough flexibility to access the optimal transition state.

Catalysts **3** and **4** appear to hold significant promise from both a fundamental and a practical perspective. The sterically diverse range of reacting partners accommodated by these catalysts within the confines of a rigidified cyclic architecture is, to the best of our knowledge, unprecedented in asymmetric catalysis. As a result of the ease of their synthesis, we hope

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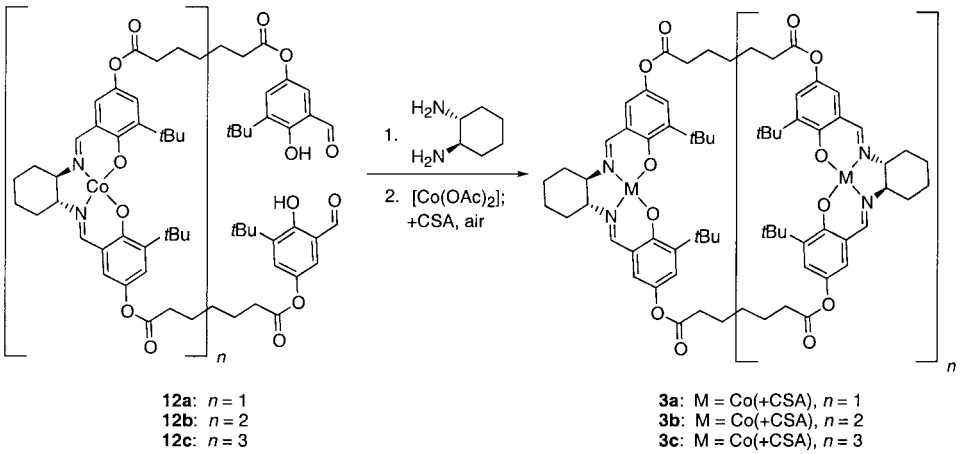

Scheme 3. Synthesis of cyclic oligomeric [(salen)Co] complexes **3a–c**.

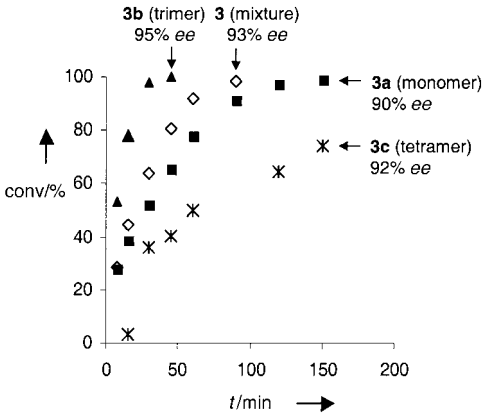

Figure 1. Asymmetric hydrolysis of cyclohexene oxide catalyzed by oligomeric [(salen)Co] complexes. Reactions were carried out with $[\text{epoxide}]_0 = 2.5\,\text{M}$ and 2.5 mol% Co catalyst ($[\text{Co}]_{\text{total}} = 0.0625\,\text{M}$) in 1:1 CH_3CN/CH_2Cl_2 at 23 °C. Conversion determined by GC analysis relative to an internal standard.

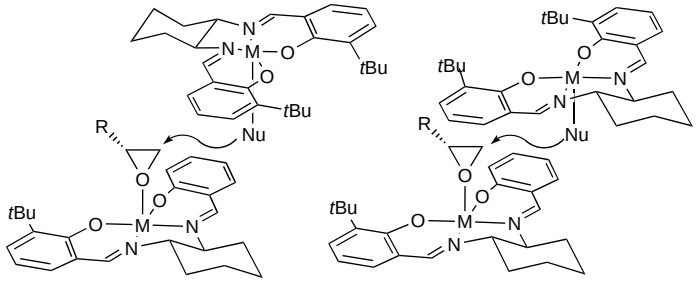

Figure 2. Limiting geometries for the transition state in epoxide ring-opening reaction catalyzed by [(salen)Co] complexes. Some substituents on the aromatic rings are omitted for clarity.

that these oligomeric catalysts will be of immediate utility to the organic chemistry community.

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[1] For reviews, see: E. N. Jacobsen, M. H. Wu in *Comprehensive Asymmetric Catalysis* (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, New York, **1999**, pp. 1309–1326; b) E. N. Jacobsen, *Acc. Chem. Res.* **2000**, *33*, 421–431.
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[3] Calculated by using the formula $\Sigma 3^i$ ($i = 2-6$), where i corresponds to the different oligomers present. There are three stereoisomers of each linker unit (*d*, *l*, and *meso*).
[4] We have also evaluated both shorter (e.g. adipate) and longer (e.g. subarate) linkers. In general, pimelate-based oligosalen systems have proven more reactive and stereoselective.
[5] Recent studies on the hydrolytic kinetic resolution (HKR) of terminal epoxides catalyzed by monomeric [(salen)Co(O_2CR)] complexes have demonstrated a critical role for the carboxylate counterion with respect both to catalyst reactivity and stability (J. Hong, D. G. Blackmond, E. N. Jacobsen, work in progress). These results suggest that the carboxylate is in fact retained within the coordination sphere of at least some portion of the catalytically active complex.
[6] Interestingly, the CSA analogue of **1** displayed similar reactivity but diminished selectivity compared to **3**.
[7] A slight cooperative effect is observed between the stereochemistry of the salen unit and that of the camphorsulfonate derivative, with the 1*S*-10-camphorsulfonate proving slightly more effective than its enantiomer in association with the catalyst derived from (*R*,*R*)-diaminocyclohexane. For example, in the hydrolysis of cyclohexene oxide at room temperature, complex **3** bearing mismatched CSA afforded diol in 92% *ee* (versus 93% *ee* with matched CSA) and 2% lower conversion after 24 h.
[8] Complex **3** has been prepared in our laboratories on a 16 g scale.
[9] See Supporting Information for experimental details and characterization of new compounds.
[10] Attempted synthesis of the macrocycle prior to metal insertion provided a mixture of ring sizes, suggesting that under the conditions of Scheme 2 the formation of **11** is reversible.
[11] The relative rates of a monometallic pathway (v_{mono}) versus a bimetallic pathway (v_{bi}) catalyzed by monomeric complexes are inversely proportional to catalyst concentrations ([cat]) according to $v_{\text{mono}}/v_{\text{bi}} = (k_{\text{mono}}[\text{cat}])/(k_{\text{bi}}[\text{cat}]^2) = (k_{\text{mono}})/(k_{\text{bi}}[\text{cat}])$.
[12] The relative rates of a monometallic pathway (v_{mono}) versus a bimetallic pathway (v_{bi}) catalyzed by **3** and **4** would be independent of catalyst concentration ([cat]) according to $v_{\text{mono}}/v_{\text{bi}} = (k_{\text{mono}}[\text{cat}])/(k_{\text{bi}}[\text{cat}]) = (k_{\text{mono}})/(k_{\text{bi}})$. For preliminary kinetic analysis of reactions of **1**, see ref. [2].
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