Asymmetric Catalysis of Epoxide Ring-Opening Reactions

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ABSTRACT

The discovery of the metal salen-catalyzed asymmetric ring-opening (ARO) of epoxides is chronicled. A screening approach was adopted for the identification of catalysts for the addition of $TMSN_3$ to *meso*-epoxides, and the chiral (salen)CrN_3 complex was identified as optimal. Kinetic and structural studies served to elucidate the mechanism of catalysis, which involves cooperative activation of both epoxide and azide by two different metal centers. Covalently linked bimetallic complexes were constructed on the basis of this insight, and shown to catalyze the ARO with identical enantioselectivity but 1−2 orders of magnitude greater reactivity than the monomeric analogues. Extraordinarily high selectivity is observed in the kinetic resolution of terminal epoxides using the (salen)-CrN_3/$TMSN_3$ system. A search for a practical method for the kinetic resolution reaction led to the discovery of highly enantiomer-selective hydrolytic ring-opening using the corresponding (salen)-Co^{III} catalyst. This system displays extraordinary substrate generality, and allows practical access to enantiopure terminal epoxides on both laboratory and industrial scales.

Introduction

Most reactions that have been subjected successfully to asymmetric catalysis involve the generation of new sp^3 stereocenters from prochiral sp^2-hybridized precursors. These include a wide range of alkene oxidation and reduction reactions, carbonyl and imine additions, and carbon−carbon-bond-forming reactions involving alkene or π-allyl precursors.[1] Stereospecific substitution reactions of sp^3-hybridized substrates certainly represent a less straightforward target for asymmetric catalysis, and understandably, this approach is far less well-developed. Nonetheless, this type of transformation can be applied in two important contexts, the desymmetrization of meso substrates, and the kinetic resolution of racemic compounds (Figure 1). In fact, nucleophilic substitution reactions can provide a surprisingly powerful approach to the preparation of enantioenriched compounds.

My group's interest in this area grew out of our studies in the more traditional realm of olefin oxidation catalysis. Our work on asymmetric epoxidation with manganese salen complexes led us to a simplified stereochemical

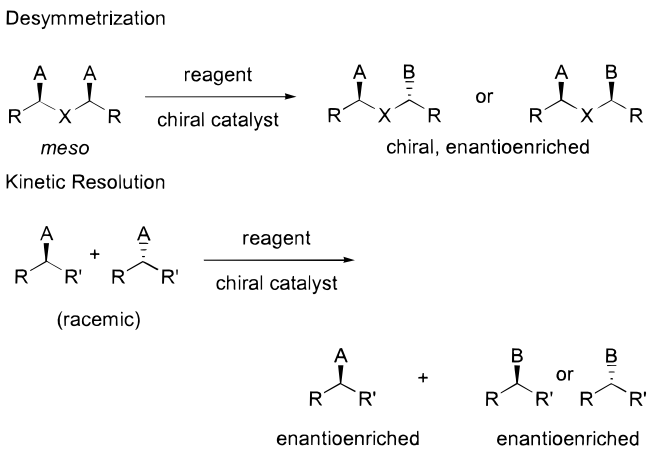

FIGURE 1. Strategies for enantioselective synthesis by means of stereospecific nucleophilic substitution reactions of sp^3-hybridized substrates.

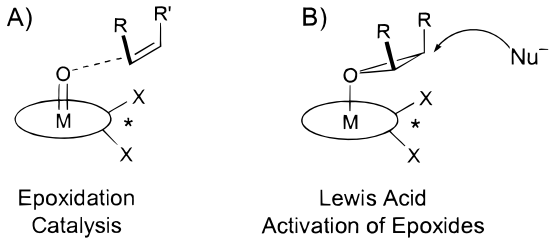

FIGURE 2. (A) Schematic representation of the side-on approach model for olefin epoxidation by chiral metal salen complexes. (B) Possible mode of epoxide activation to asymmetric ring-opening by similar catalysts.

model for oxygen atom transfer wherein the alkene is proposed to attack the oxygen atom of a metal oxo intermediate in a side-on approach (Figure 2A).[2] This model was first proposed by Groves in 1985 in the context of asymmetric epoxidations with metal porphyrin complexes,[3] and is consistent with a wide range of reactivity and enantioselectivity data. While considerable debate persists regarding the precise sequence of bond-forming events in these oxidation reactions,[4] the side-on approach model for olefin epoxidation by metals coordinated to tetradentate ligands has proceeded to gain wide acceptance.

Groves was also the first to note the relationship between the transition state of oxo transfer from metal porphyrin and related complexes and the ground-state structures of epoxide complexes of metals bearing the same ligands.[5] The apparent relationship between the transition state for epoxidation and the ground-state structure of epoxides coordinated to metal complexes led us to ask the following question: can the same chiral salen ligands that discriminate effectively between the enantiotopic faces of an approaching olefin also create an effective dissymmetric environment for nucleophilic attack at a bound epoxide? This would presuppose a mechanism of ring-opening involving activation of epoxide by a chiral, Lewis acidic metal salen complex (Figure 2B). As described in this Account, the answer to the question turned out to

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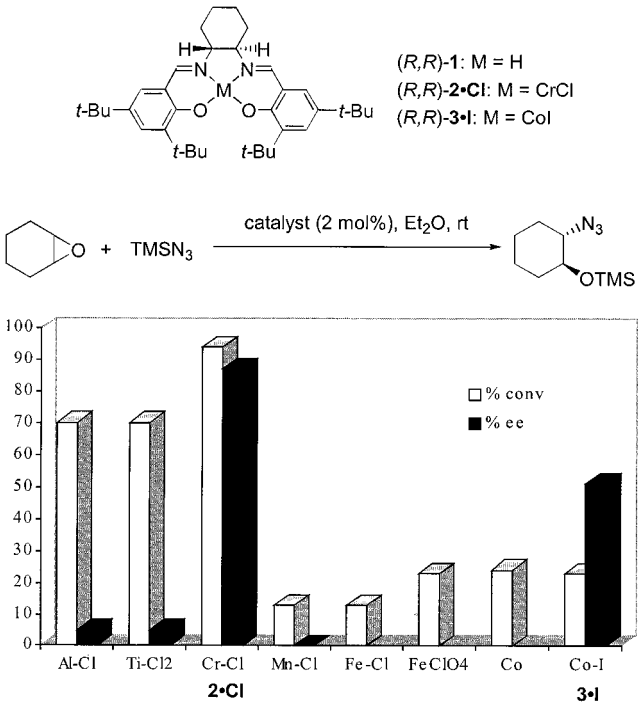


FIGURE 3. Preliminary screen of metal salen complexes for catalysis of the ARO of cyclohexene oxide with $TMSN_3$.

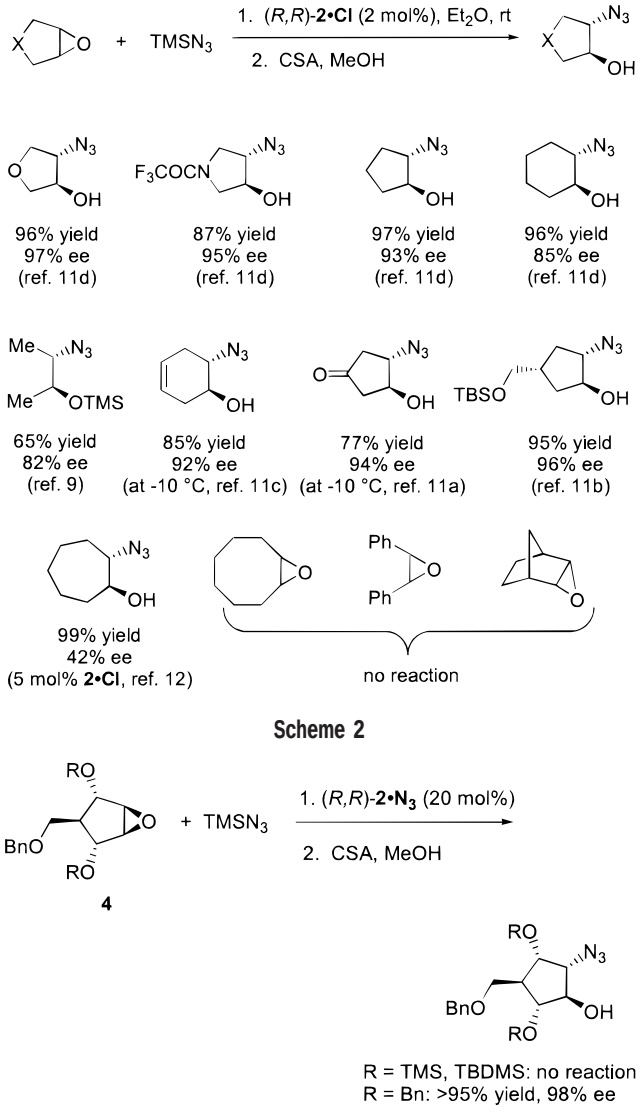
be decidedly in the affirmative, but it also turned out that the mechanism of epoxide ring-opening with metal salen complexes would be much more complicated—and interesting—than we anticipated.

Discovery of the (salen)Cr-Catalyzed Asymmetric Ring-Opening of Meso Epoxides

To test the hypothesis outlined in Figure 2, we evaluated a series of metal complexes of ligand **1** for the opening of cyclohexene oxide by $TMSN_3$. We chose this particular reaction as a model because of the seminal studies by Sinou[6] and the significant successes achieved by Nugent[7] in the asymmetric catalysis of the same transformation.[8]

Our only anticipation in these early screening experiments was that it would be unlikely that the Mn(salen) complex would emerge as an effective catalyst. We knew from our studies of epoxidation catalysis that this complex did not coordinate to epoxides to any measurable extent and was therefore unlikely to serve as a Lewis acid catalyst for epoxide ring-opening. While the Mn(salen) complex indeed displayed very poor reactivity and negligible enantioselectivity, the screen did reveal the rather surprising result that the Cr(III) complex **2·Cl** was a most effective catalyst with regard to both reactivity and enantioselectivity (Figure 3).[9] It was interesting to observe that the titanium and aluminum analogues catalyzed the ring-opening with similarly good reactivity, but <5% enantioselectivity. Given that the dissymmetric ligand environments in the Cr, Ti, and Al complexes of **1** are presumably fairly similar,[10] the observation of such different levels of enantioselection suggested a unique mechanism of catalysis for chromium, and provided our first clue that the asymmetric ring-opening (ARO) with complex **2** might not

Scheme 1

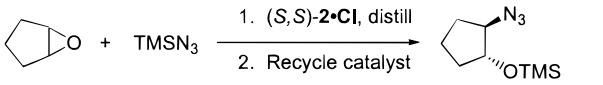


Scheme 2

proceed by a simple Lewis acid mechanism (vide infra). The cobalt complex **3·I** proved to be the only other catalyst that diplayed promising enantioselectivity, but it was substantially less reactive than chromium complex **2** in the ARO with $TMSN_3$.

The (salen)$Cr^{III}Cl$ complex **2·Cl** serves as an effective catalyst for the enantioselective ring-opening of a variety of *meso*-epoxides (Scheme 1).[9,11] In general, five-membered-ring-fused epoxides afford higher enantioselectivities than six-membered-ring analogues, and this stands in sharp contrast to Nugent's zirconium alkoxide catalyst which shows a reversed trend.[7] Catalyst **2** is quite sensitive to the steric environment surrounding the epoxide. Thus, cycloheptene oxide underwent ARO with much lower enantioselectivity than the smaller ring analogues, and cyclooctene oxide was effectively unreactive.[12] In an especially nice illustration of this effect, Ganem and coworkers found a sharp dependence on protective groups in the ARO of the highly substituted epoxide **4** (Scheme 2). The ring-opening product derived was further elaborated to the natural product (−)-allosamidin.[13]

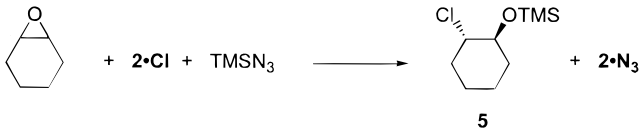
Table 1. Recycling of Cr(salen) Complex 2 in the Solvent-Free ARO of Cyclopentene Oxide with $TMSN_3$



cycle	yield (%)	ee (%)	cycle	yield (%)	ee (%)
1	84	93	7	95	94
2[a]	92	94	8	94	94
3	93	94	9	95	94
4	95	94	10	95	95
5	91	94	11	92	95
6	95	94			

[a] Catalyst recovered after the first cycle was determined to be **2·N₃** (see Scheme 3 and accompanying discussion).

Scheme 3



One of the most impressive features of the (salen)Cr catalyst system is its effectively indefinite stability under ARO conditions. The ring-opened products of typical substrates are liquids, and it is generally possible to carry the ARO reaction under solvent-free conditions and to isolate the azido silyl ether products in nearly quantitative yield by vacuum transfer distillation. The residual catalyst retains full activity, and can be recycled repeatedly (Table 1). As such, this process generates no waste whatsoever and can be considered to be an extreme example of "atom economy".[14]

Mechanism of the ARO

Soon after the discovery of the (salen)Cr-catalyzed ARO, it became apparent that the active catalyst was not the chloride complex **2·Cl**, but rather the corresponding azide complex **2·N₃**.[10b] Thus, reaction of cyclohexene oxide with $TMSN_3$ in the presence of **2·Cl** led to initial formation of the chlorohydrin product **5** in a yield commensurate with the amount of **2·Cl** employed (Scheme 3).[15] The metal-containing complex generated after the first cycle was isolated and characterized as the (salen)CrN_3 complex **2·N₃** on the basis of elemental analysis and a characteristic strong and broad IR stretch centered at ca. 2060 cm^{-1} (Figure 4A). Complex **2·N₃** is insoluble in all common noncoordinating solvents, but it dissolves rapidly in donor solvents such as THF. Crystals of **2·N₃** grown from THF were characterized by X-ray diffraction, and the structure was elucidated to be that of a six-coordinate chromium(III) azide complex bearing an axial THF ligand (Figure 5). The IR spectrum of THF solutions of **2·N₃** displays a sharp azide stretch at 2053 cm^{-1} (Figure 4B), and this presumably corresponds to the THF adduct as well. In contrast, the broadening of the azide stretch in the solvent-free complex can be ascribed to a polymeric structure with bridging azide units. When TBME suspensions of **2·N₃** are treated with ARO substrates such as cyclopentene oxide, the complex dissolves and a transient species is generated with a metal−azide IR stretching frequency identical to that of the THF adduct (Figure 4C).

The observed axial coordination of THF to **2·N₃** and the IR spectroscopic evidence that epoxides bind in a similar manner allow formulation of the resting state of the active catalyst as (salen)Cr(N_3)(epoxide). The fact that the catalyst is capable of activating both the nucleophilic and the electrophilic reacting partners of the ARO begs the question of how this catalyst system actually operates. Evidence that epoxide complexation is critical to catalysis was gleaned from the observation that donor ligands such as THF severely inhibit the ARO. On the other hand, evidence that the azido ligand in **2·N₃** serves as the nucleophile in the ARO was provided by observation of stoichiometric azide transfer from **2·N₃** to cyclopentene oxide in the absence of $TMSN_3$. This led to formation of an azido alkoxide intermediate, **6**, which could be isolated and characterized crystallographically as its THF adduct (Figure 6). Treatment of **6** with a protic acid source released azido alcohol product in ee's similar to those obtained in the catalytic reaction (Scheme 4).

It was ascertained that catalytic amounts of water were essential for the ARO with $TMSN_3$, as the active reagent in the ring-opening is in fact HN_3.[10b] Thus, careful exclusion of water led to inactive systems, while addition of trace amounts of water or use of HN_3 in place of $TMSN_3$ led to restoration of full reactivity. A catalytic cycle consistent with the identification of **2·N₃** and **6** as intermediates and the observed effect of water is presented in Scheme 5.

While the general features of the catalytic reaction were thus elucidated, the question of whether **2·N₃** functions as a Lewis acid catalyst for epoxide activation or as an azide-delivery agent remained unanswered until a detailed kinetic study revealed that the catalyst in fact plays both roles.[10b] The reaction of HN_3 with cyclopentene oxide in the presence of catalytic levels of **2·N₃** obeys the following rate law:

$$\text{rate} = k[\mathbf{2{\cdot}N_3}]^2[\text{epoxide}]^{-1}[HN_3]^0$$

Thus, the reaction between epoxide and azide is independent of one and inhibited by the other! To our knowledge, this is the only example of such a rate expression, in what is effectively a simple addition of two reacting partners. While the dependence on nucleophile and electrophile was baffling at first, the observation of a second-order dependence on **2·N₃** provided the key clue to the mechanism of catalysis. This phenomenon requires that two molecules of the catalyst are involved in the rate-determining step, and the simplest mechanism consistent with this is one where azide is delivered from one metal to the bound epoxide of another to generate azido alkoxide complex **6**. The zero-order dependence on HN_3 is then ascribable to kinetically rapid protonolysis of **6** to generate azido alcohol and **2·N₃** (Scheme 6).

Interpretation of the rate inhibition by epoxide is less straightforward, but it clearly suggests that epoxide must dissociate from the catalyst for reaction to occur. Given

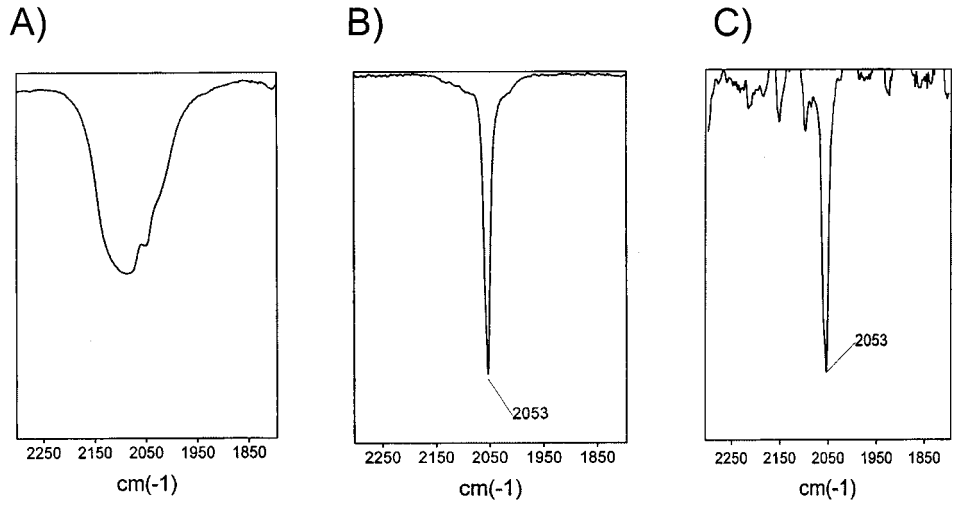


FIGURE 4. IR spectra of **2·N$_3$**: (A) Nujol mull of the solvent free complex; (B) in THF solution; (C) in TBME solution in the presence of cyclopentene oxide. The latter was acquired within 60 s of addition of epoxide. Upon standing, this species undergoes further reaction to the ring-opened product (see Scheme 4).

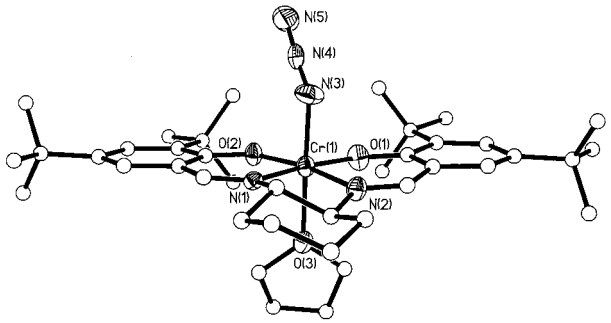


FIGURE 5. Structure of **2·N$_3$·THF**. Thermal ellipsoids represent 50% electron probability, and hydrogen atoms are omitted for clarity.

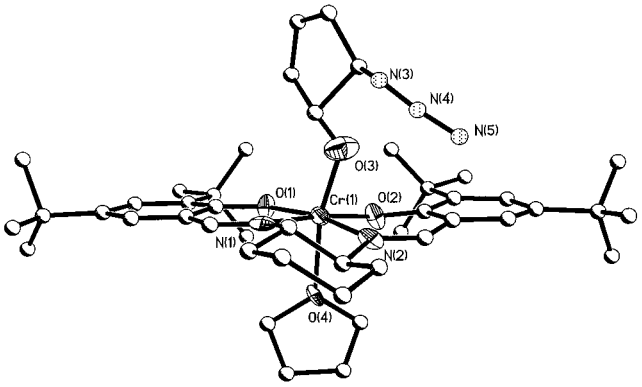
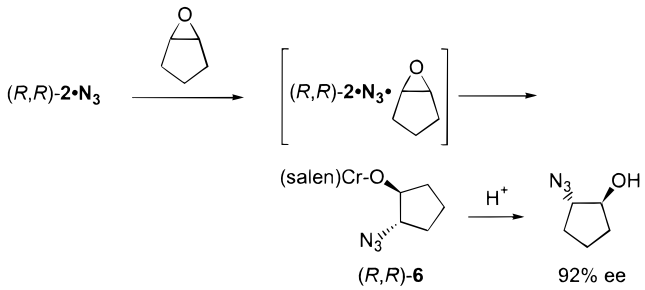
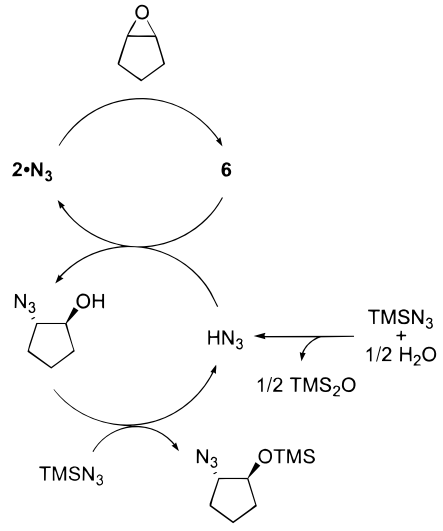


FIGURE 6. Structure of **6·THF**. The metal and local coordination sphere are displayed as 40% electron probability ellipsoids, and hydrogen atoms are omitted for clarity.

Scheme 4



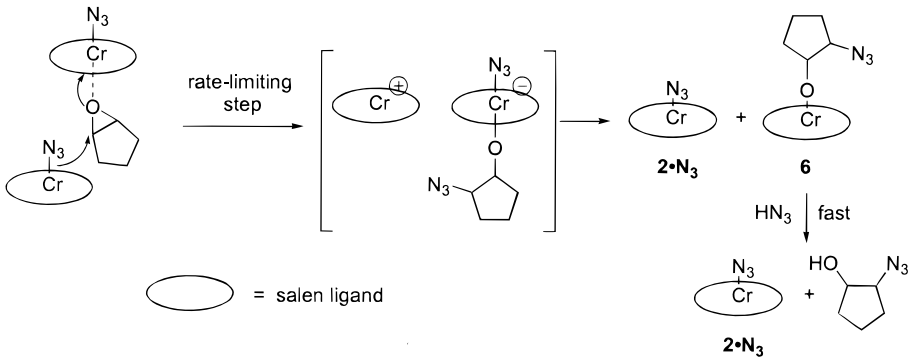
Scheme 5



that the resting state of the catalyst is (salen)Cr(N_3)-(epoxide) (vide supra), reversible dissociation of epoxide would lead to transient, five-coordinate **2·N$_3$**. It is in fact reasonable to expect the azide ligand in the five-coordinate complex to be more labile (i.e., nucleophilic) than in the six-coordinate species, as six-coordinate Cr(III) complexes are notoriously inert.[16]

While the unusual kinetic dependence on epoxide concentration in the ARO is certainly intriguing, it is likely that the second-order dependence on the catalyst has greater implications for catalyst design. In particular, it suggests the possibility of linking two catalyst units together in a bimetallic complex to enforce cooperative catalysis. We undertook the construction of dimeric chiral (salen)Cr complexes, using flexible tethers to link the salen units.[17] Two limiting geometries were envisioned for the selectivity-determining step wherein the epoxide and azide are effectively "sandwiched" between two catalyst units. One is a head-to-head alignment of the salen ligands

Scheme 6



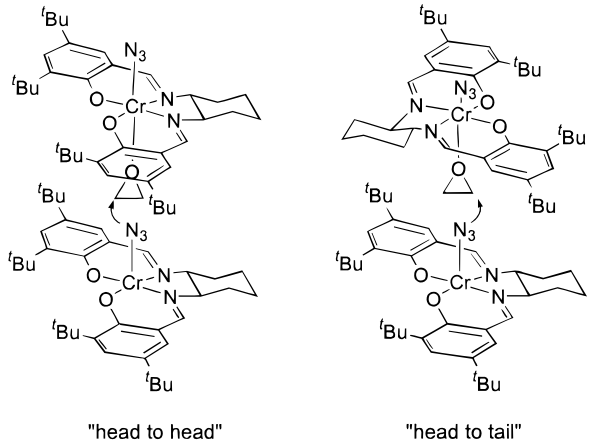


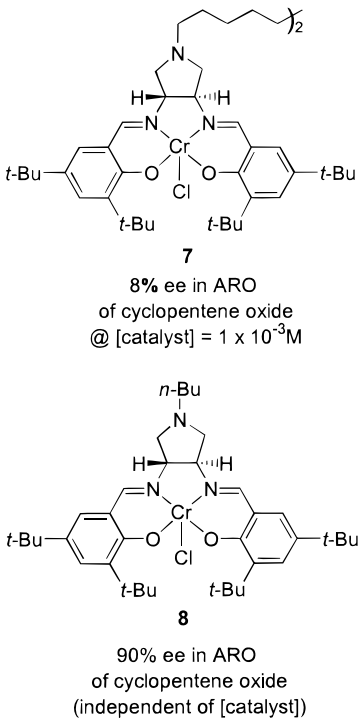
FIGURE 7. Two limiting geometries for the enantioselectivity-determining transition state of the ARO catalyzed by **2·N$_3$**.

wherein the diimine backbones are overlaid in an eclipsed orientation, and another is a head-to-tail arrangement corresponding to rotation of one of the salen units by 180° (Figure 7).

Complex **7** was designed with the notion that the head-to-head transition-state geometry would be reinforced within this catalyst. At low concentrations (1×10^{-3} M) designed to favor intramolecular pathways relative to interdimer pathways, **7** catalyzed the ARO of cyclopentene oxide with $TMSN_3$ in only 8% ee. In contrast, the monomeric analogue **8** catalyzed the same reaction with enantioselectivity comparable to that of the standard catalyst **2** (Scheme 7). This clearly suggested that, first, cooperative reactivity was in fact occurring within the dimeric complex, second, the placement of the tether—and thus the relative orientations of the salen units—was criticial to enantioselectivity, and, third, that the head-to-head arrangement was not the optimal geometry.

In light of the results obtained with **7**, the dimeric catalyst was redesigned to allow head-to-tail reactive geometries in an intramolecular reaction. Complexes **9a**−**g** (Chart 1) were prepared, wherein a diester linkage of variable length was introduced to connect the salen units via one of the salicylidene groups. The monomeric analogue **10** (Chart 1) was prepared for the purposes of comparison. In sharp contrast to dimer **8**, catalysts **9a**−**g** catalyzed the ARO with ee's comparable to those obtained with the monomeric catalysts (Table 2). A slight improvement in enantioselectivity was observed with increasing tether length, with optimal values achieved with catalysts linked through five or more methylene units.

Scheme 7



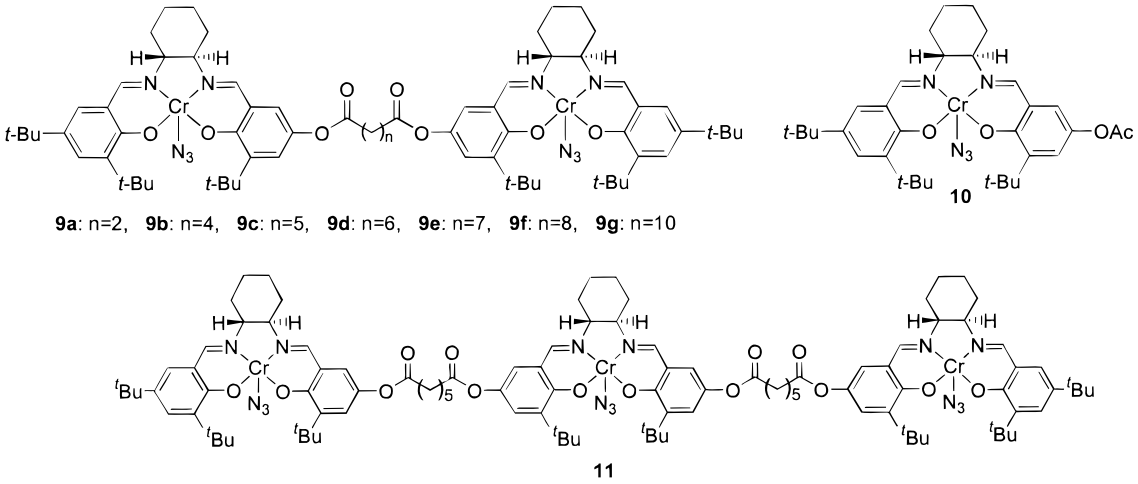
Kinetic studies were carried out to ascertain whether catalysis with **9** was indeed occurring through an intramolecular, cooperative reaction. While reactions with the monomeric complexes **2** and **10** displayed clean second-order dependence on the catalyst, reactions with catalysts **9a**−**g** followed a more complex, two-term rate expression:

$$\text{rate} = k_{\text{intra}}[\text{catalyst}] + k_{\text{inter}}[\text{catalyst}]^2$$

Plots of k_{obs}/[catalyst] vs [catalyst] for each catalyst afforded straight lines with nonzero intercepts and slopes, consistent with the operation of both the desired intramolecular pathways (k_{intra}) and interdimer second-order pathways (k_{inter}). The results of these kinetic experiments are summarized in Table 2.

The dimeric catalysts display reactivity 1−2 orders of magnitude greater than that of the monomeric catalyst **2**

Chart 1



9a: n=2, **9b**: n=4, **9c**: n=5, **9d**: n=6, **9e**: n=7, **9f**: n=8, **9g**: n=10

Table 2. Rate Constants and Enantioselectivity Data for the Ring-Opening of Cyclopentene Oxide Catalyzed by (salen)Cr−N_3 Complexes

catalyst	*n*	% ee of product[a]	k_{intra} (min^{-1} × 10^{-2})[b]	k_{inter} (M^{-1} min^{-1})[b]	M_{eff} (M × 10^{-3})[b]
2		93		0.6	
10		94		1.2	
9a	2	90	4.4	15.7	2.8
9b	4	90	5.4	15.1	3.6
9c	5	93	42.9	27.4	15.7
9d	6	93	31.7	15.8	20.1
9e	7	93	20.9	7.9	26.3
9f	8	94	14.7	10.5	14.0
9g	10	92	3.8	4.4	8.6

[a] From the reaction of cyclopentene oxide with $TMSN_3$. [b] Kinetic studies were carried out using HN_3 as the azide source.

or **10**. This is ascribable both to the existence of an intramolecular pathway which is obviously not available to the monomeric catalysts and to an enhancement of the intermolecular pathway as well. As might be expected, the intramolecular pathway displays a strong dependence on the length of the tether linking the two catalyst units. The observation that the k_{inter} term is larger for the dimeric catalysts than with the monomeric catalysts was more surprising, as it indicates that dimer reacts more rapidly with dimer, than does monomer with monomer.[17] This most unexpected result points to the participation of highly reactive multimetallic assemblies in the ARO, and suggests that the design of covalently linked systems bearing three or more metal salen units may be worthwhile. In that context, preliminary experiments with trimeric complex **11** (Chart 1) reveal that it is indeed 2−3 times more reactive than dimeric catalyst **9c**, while still maintaining the same levels of enantioselectivity in the ARO.[18]

Practical Application of the ARO: Discovery of the Hydrolytic Kinetic Resolution (HKR) Reaction

The ARO of *meso*-epoxides provides an elegant route to synthetically useful compounds in optically active form,[19] and the ring-opening of *meso*-epoxides catalyzed by **2** has found application in the synthesis of a variety of biologically interesting molecules.[11a−c,13,20] However, it is clearly the case that *meso*-epoxides constitute a relatively narrow subset of cis-disubstituted and tetrasubstituted epoxides (Figure 8), and the vast majority of epoxides are in fact chiral. Unfortunately, despite significant advances in the development of asymmetric catalysts for epoxide synthesis,[4,21] access to chiral epoxides in highly enantioenriched form remains limited to certain types of trisubstituted, cis-disubstituted, and trans-disubstituted systems. Perhaps most significant, no useful methods exist for the direct, enantioselective synthesis of terminal epoxides, arguably the most useful subset of these compounds from a synthetic standpoint.

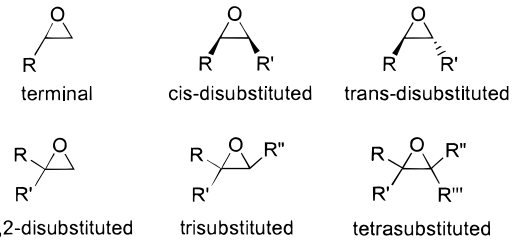
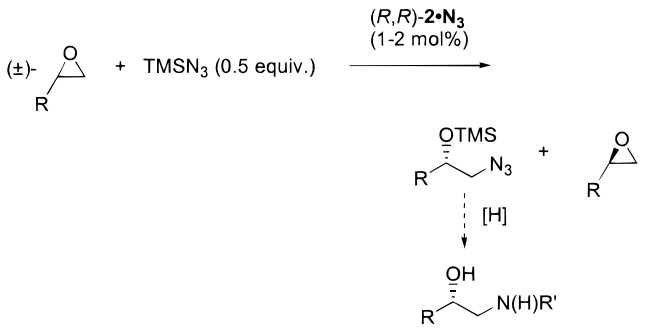


FIGURE 8. Classes of substituted epoxides.

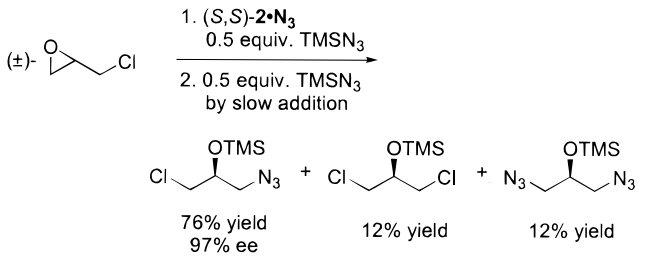
We considered the possibility of applying the ARO reaction to the kinetic resolution of terminal epoxides.[22] Given the fact that most terminal epoxides are readily available and inexpensive as racemates, the application of a kinetic resolution approach could, in principle, even hold practical potential. Initially, we were interested in applying such a strategy to the synthesis of optically active 1,2-amino alcohols, and we envisaged that a highly regioselective ring-opening of racemic terminal epoxides with $TMSN_3$ could provide a most attractive route (Scheme 8). Our preliminary investigations, however, proved somewhat discouraging. We selected two epoxides, epichlorohydrin and styrene oxide, as model substates.[9] While both did undergo resolution, high substrate conversion was necessary to obtain recovered epoxide in >96% ee. As a result, only mediocre yields of epoxide (ca. 20%) were obtainable by this method.

As luck would have it, we had selected the two most difficult substrates possible for the kinetic resolution.

Scheme 8



Scheme 9



Styrene oxide displays poor (<3:1) regioselectivity in the ring-opening with azide due to conflicting steric and electronic biases to nucleophilic attack. In fact, a complex mixture of ring-opening and other byproducts was obtained, and it is actually surprising that any kinetic resolution was achieved in such a messy reaction. Epichlorohydrin is susceptible to chloride-catalyzed racemization, and this pathway proved impossible to suppress completely under the conditions of catalytic ARO with **2·N_3**. While this made it impractical to use the ARO with $TMSN_3$ for accessing resolved epichlorohydrin, it presented an interesting possibility for preparing the ring-opened product in enantioenriched form via a *dynamic* kinetic resolution pathway.[23] Indeed, controlled addition of a full equivalent of $TMSN_3$ to a solution of racemic epichlorohydrin and catalytic **2·N_3** led to formation of the desired azide product in 76% yield and 97% ee (Scheme 9).[24]

The kinetic resolution with **2·N_3** and $TMSN_3$ proved to be a remarkably general and effective method for accessing 1-azido 2-alcohol derivatives from the corresponding terminal epoxides (Figure 9).[25,26] In these examples, the epoxides are not susceptible to racemization, so a maximum yield of 50% based on racemate is achievable. Within that constraint, however, highly enantioenriched products were obtainable in nearly quantitative yields. As in the case of the ARO of *meso*-epoxides, the kinetic resolutions could be carried out under solvent-free conditions, and the unreacted epoxide and ring-opened product could be separated conveniently by simple vacuum distillation of the reaction mixture.

While these results were most gratifying, we recognized that the ARO with $TMSN_3$ was unlikely to serve as an attractive method for accessing terminal epoxides in enantioenriched form. The nucleophile in this reaction, $TMSN_3$, is too valuable to be discarded in a byproduct of the resolution reaction. In addition, the heat sensitivity of azides renders their use somewhat unattractive absent appropriate precautions, especially on a large scale.[27] It was largely for these reasons that we undertook a systematic investigation of other nucleophiles, with an eye toward reagents that might be inexpensive and easily handled.

Our first significant advance in this area came with the discovery that carboxylic acids are competent nucleophiles for the ARO of *meso*-epoxides using the Co(salen) complex **3** as catalyst (Scheme 10).[28] In our efforts to extend this to the kinetic resolution of terminal epoxides using benzoic acid as the nucleophile, we made the serendipitous discovery that 1,2-diol was being generated as a byproduct in high ee (Scheme 11). While this was clearly due to the presence of adventitious water in the reaction mixture, it was less obvious whether diol was being generated by enantioselective epoxide hydrolysis or by simple hydrolysis of the benzoate ester ring-opened product.

Naturally, we hoped that that the former, epoxide hydrolysis pathway was operating, since it would be difficult to imagine a more perfect nucleophile than water for the kinetic resolution of epoxides. However, our preliminary investigations of possible hydrolytic kinetic resolution (HKR) yielded confusing results. Whereas 1-hexene oxide, one of our model substrates, underwent hydrolysis cleanly and highly enantioselectively in the presence of catalyst **3**, other epoxides such as propylene oxide or 1-decene oxide were completely unreactive (Scheme 12). Once again, luck was playing a big role, but this time it was on our side. Commercial 1-hexene oxide is contaminated with 1−2% acetic acid, a byproduct of the epoxidation of 1-hexene with peracetic acid. The acetic acid contaminant was actually necessary for the HKR reaction, as it promoted the aerobic oxidation of the Co(II) complex **3** to the catalytically active Co(III) complex **3·OAc** (Scheme 13). Thus, the discovery of the HKR relied on two accidents: the presence of water contamination in the kinetic resolutions with benzoic acid (Scheme 10), and the presence of carboxylic acid contamination in one of the epoxide model substrates.

Once the identity of an active catalyst for the HKR was established,[29] the development of a practical method for the preparation of highly enantioenriched terminal epoxides proved remarkably straightforward.[30] As illustrated in Scheme 14, the HKR of propylene oxide proceeds with extremely high selectivity using low loadings of catalyst, affording both resolved epoxide and 1,2-diol in extremely high ee. This reaction has been carried out on a multihundred kilogram scale at ChiRex with similar results.[31]

The HKR has proven to be extraordinarily general, with virtually every terminal epoxide examined to date undergoing clean and highly selective resolution. As illustrated in Table 3, use of a slight excess of water (0.55 equiv) allows isolation of epoxide in >99% ee and good yield for a wide range of substrates.[32] Notable substrates include epoxides with aliphatic substituents of varying steric demand (Me to *t*-Bu), electron-deficient epoxides such as

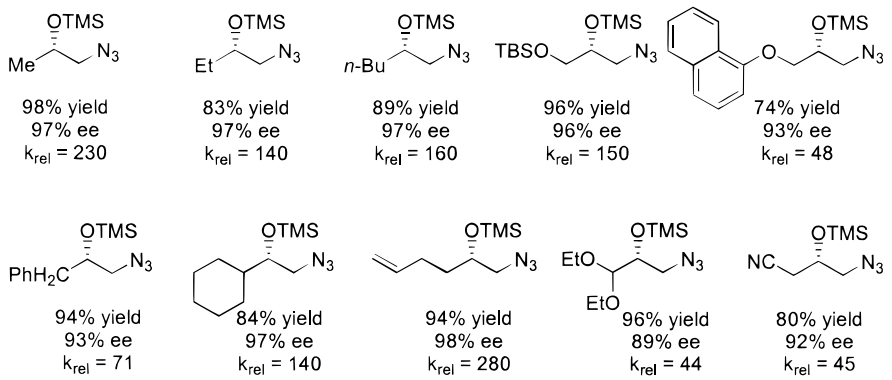
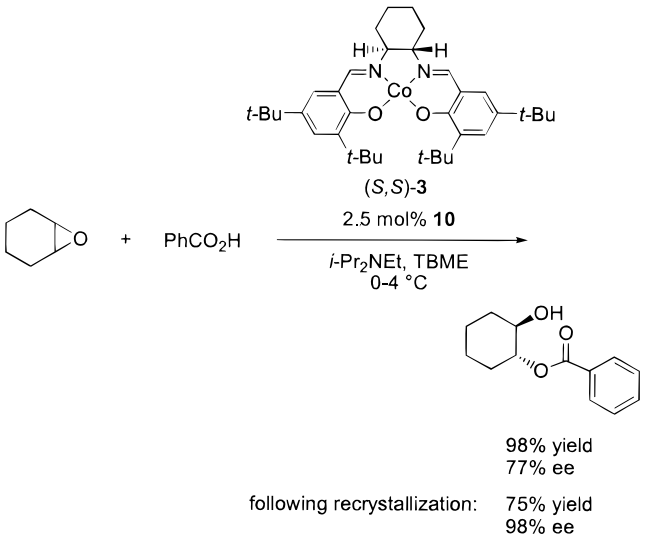
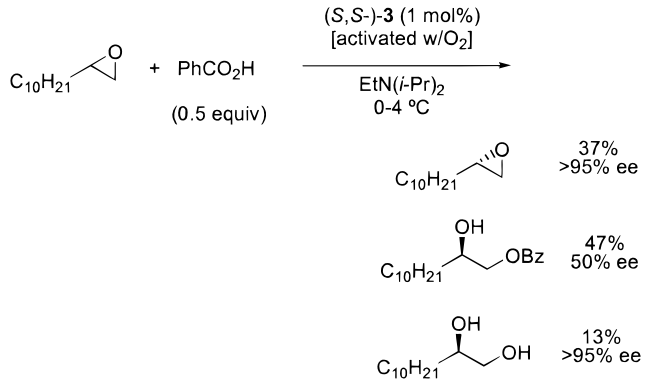


FIGURE 9. Kinetic resolution products obtained using $TMSN_3$ and catalyst **2·N₃**. Conditions are as shown in Scheme 7. Yields correspond to the isolated product based on $TMSN_3$. Values for k_{rel} were calculated using the equation $k_{rel} = \ln[1 - c(1 + ee)]/\ln[1 - c(1 - ee)]$, where the conversion c was set to equal the isolated yield of the ring-opened products. See ref 22b.

Scheme 10



Scheme 11



glycidic esters and epoxy ketones, and styrene oxide derivatives. The HKR of epichlorohydrin can be carried out with effective suppression of chloride-catalyzed racemization, and this has also been carried out on the multihundred kilogram scale.[31,33] In contrast, racemization of epibromohydrin cannot be prevented, and in this case dynamic kinetic resolution to enantioenriched bromopropanediol was possible. While the HKR can be carried out under solvent-free conditions in most cases, the low solubility of water in very hydrophobic epoxides makes the use of small amounts of polar cosolvents beneficial for those substrates.

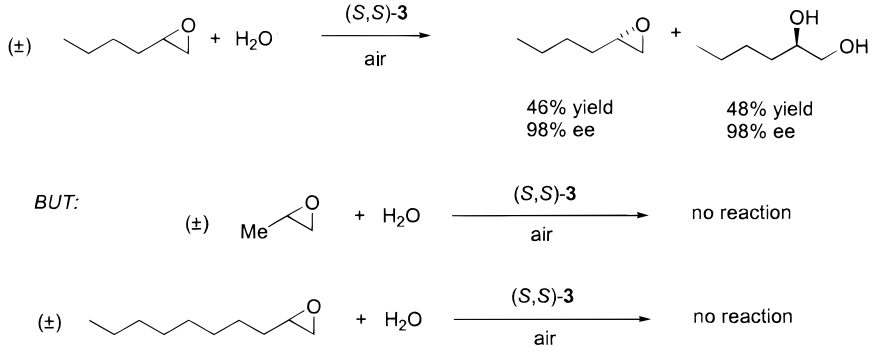
Conclusions and Outlook

Some projects explode onto the scene of a research group, immediately capturing the attention and imagination of research advisor and students alike, while other projects start off slowly but gradually gain momentum. The project outlined in this Account certainly falls into the latter category. It began as an investigation of the addition of $TMSN_3$ to *meso*-epoxides catalyzed by a previously discovered chiral ligand system, by any analysis a relatively narrow reaction and a rather conservative approach. The discovery of high enantioselectivity with Cr(salen) catalyst **2** was encouraging, but it was really a progression of subsequent findings that rendered it significant: (1) the discovery that reactions can be carried out with perfect "atom economy", under solvent-free conditions and indefinite recycling of catalyst; (2) the elucidation of a bimetallic mechanism of catalysis involving dual activation of nucleophile and electrophile by two different metal centers, and the successful design of dimeric catalysts that reinforce this effect; (3) the observation of extraordinarily efficient kinetic resolution of terminal epoxides; (4) the discovery of water—perhaps the ideal reagent from a practical standpoint—as an effective nucleophile for the kinetic resolution reaction; (5) the establishment of complete generality in the hydrolytic kinetic resolution reaction of terminal epoxides with a single catalyst system.

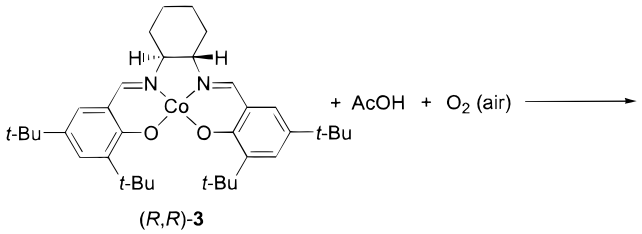
As a result of the last two of these observations, the ARO chemistry has taken on a significant practical dimension wherein a wide variety of terminal epoxides are now readily available for the first time in highly enantioenriched form, and many of these are becoming commercially available at relatively low cost. The ready accessibility of this new "chiral pool" will hopefully have a beneficial impact both on natural product synthesis[34] and on the commercial synthesis of chiral compounds.

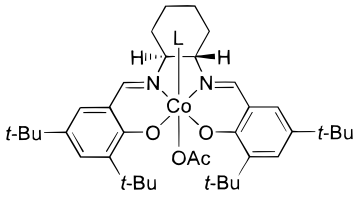
The generality of the HKR appears to extend to other classes of nucleophiles as well. Recently, we have identified that phenols are outstanding nucleophiles for epoxide

Scheme 12

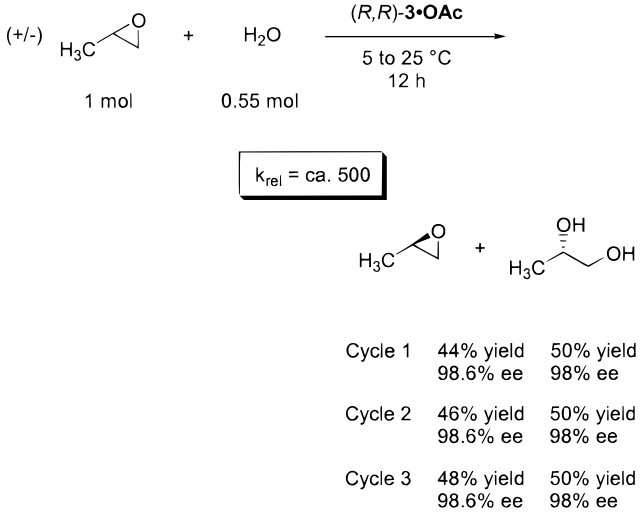


Scheme 13





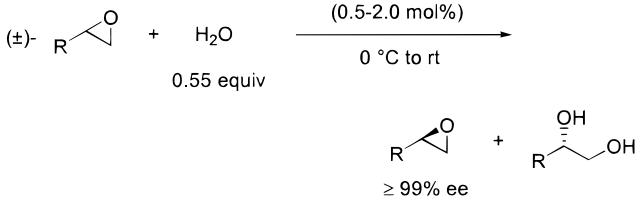
Scheme 14



Cycle 1	44% yield 98.6% ee	50% yield 98% ee
Cycle 2	46% yield 98.6% ee	50% yield 98% ee
Cycle 3	48% yield 98.6% ee	50% yield 98% ee

resolution with **3·OAr**,[35] and this reaction has been applied to the parallel enantioselective synthesis of libraries of α-aryloxy alcohol derivatives using a resin-bound version of catalyst **3**.[36] To our knowledge, this is the first example of the application of asymmetric catalysis in the diversity-generating step of a combinatorial synthesis, and it is likely that other classes of nucleophiles will emerge for epoxide ring-opening and related nucleophile−electrophile reactions.

Table 3. Hydrolytic Kinetic Resolution of Terminal Epoxides Catalyzed by 3·OAc



R	catalyst mol %	solvent	time (h)	yield (%)[a]
CH_3	0.2	none	18	92
$(CH_2)_3CH_3$	0.5	none	18	86
CH_2Ph	0.5	THF	18	92
c-C_6H_{11}	0.5	THF	18	87
t-Bu	2.0	1,2-hexanediol	48	82
CH_2Cl	0.5	THF	18	83
CF_3	0.5	none	18	75
CH_2CO_2Et	0.5	THF	18	92
CH_2NHBoc	2.0	THF	38	72
CO_2Me	2.0	THF	24	86
COMe	2.0	THF	24	80
CH_2OBn	0.5	THF	18	96
m-Cl−C_6H_4	0.8	THF	48	80

[a] Based on a maximum theoretical yield of 50%.

The observation of exacting cooperative effects between chiral catalyst units in the ARO is perhaps most significant. Mechanistic studies on the HKR,[30,36b] and independent studies by other groups,[37] confirm that the cooperative effect is general in asymmetric epoxide ring-opening and probably other reactions as well. Bimetallic activation offers an appealing explanation for the mechanism of stereoinduction in ARO reactions, as the two reactants are sandwiched between two chiral catalyst units. Given the extraordinary levels of enantioselection that have been achieved (e.g., k_{rel} = ca. 500 in the HKR of propylene oxide), it is clear that stereochemical communication is very effective indeed with the metal salen catalyst systems. It is hoped that the rational design and analysis of linked metal systems—of which **9** is simply a starting point—will shed light on the basis of these phenomena and allow their extension into general principles for catalyst design.

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ticipated in it. In particular, I am grateful to Jim Leighton, Karl Hansen, Luis Martinez, Jay Larrow, Scott Schaus, Makoto Tokunaga, Fumitoshi Kakiuchi, Mike Furrow, Mike Wu, Reed Konsler, Allen Annis, Joe Ready, and Jason Hong for their fundamental contributions, both technical and intellectual, that made this Account possible.

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