

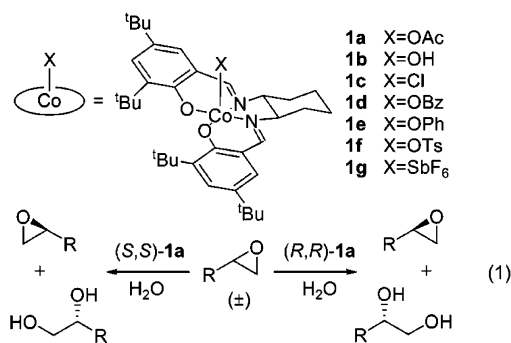
Mechanistic Investigation Leads to a Synthetic Improvement in the Hydrolytic Kinetic Resolution of Terminal Epoxides

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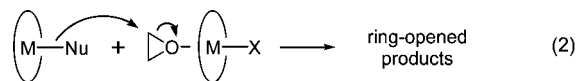
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The hydrolytic kinetic resolution (HKR) catalyzed by (salen)-Co(III) complex **1a** (eq 1) has emerged as a general and effective method for the preparation of highly enantioenriched terminal epoxides, having found widespread use in both academic and industrial contexts.¹ Exceptionally high selectivities for a wide range of structurally and electronically varied terminal epoxides ($k_{\text{rel}} > 500$ for some substrates, > 100 for almost all examined) constitute the most striking feature of this reaction and suggest an interesting mechanism of catalysis. Preliminary kinetic studies on the HKR indicated a second-order dependence on Co catalyst,^{1a} consistent with observations made in other (salen)metal-catalyzed epoxide ring-opening reactions.^{2,3} The acetate complex **1a**, prepared by aerobic oxidation of (salen)Co(II) in the presence of acetic acid, has been the most widely used catalyst to date; however, beneficial effects of other counterions on catalyst reactivity have been noted.⁴ We describe here our efforts to develop a complete kinetic profile of the HKR and to elucidate the mechanistic basis for the counterion effect. These studies have revealed a fascinating mechanism of catalysis and have led to development of improved monomeric catalysts for the HKR.

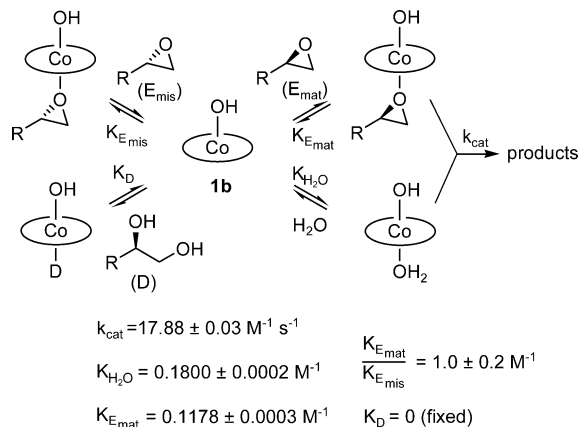


Given the second-order dependence on Co catalyst, we considered a cooperative bimetallic mechanism for the HKR analogous to other asymmetric ring-opening (ARO) reactions with (salen)-metal complexes (eq 2). Within the context of this general

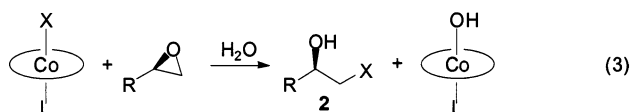


mechanism, the simplest system involves the (salen)Co-OH complex **1b** serving as both nucleophilic and Lewis acidic components (Nu = X = OH). Unfortunately, it has not been possible to characterize **1b** directly, in contrast to the (salen)Cr-catalyzed ARO of epoxides with azide² and the (salen)Co-catalyzed phenolic kinetic resolution,⁵ where the corresponding (salen)metal-

Scheme 1. Kinetic Parameters for the HKR of 1-Hexene Oxide Catalyzed by **1b**



Nu species were isolated and characterized fully. However, the intermediacy of **1b** could be inferred from several pieces of evidence. Treatment of 1-hexene oxide with **1a** or **1c** followed by addition of water led to formation of counterion addition products **2a** or **2c** (eq 3)^{6,7} and initiation of the epoxide hydrolysis pathway, which was monitored kinetically using reaction calorimetry. Given



a sufficient delay before addition of water, the same rate profiles were accessed with precatalysts **1a** and **1c**, consistent with the exclusive participation of the catalytically active, common intermediate **1b** once counterion addition was complete. Kinetic analysis of epoxide hydrolysis using solutions of **1b** generated in situ from **1c** revealed excellent agreement with the rate law in eq 4, consistent with the mechanism in Scheme 1.⁸

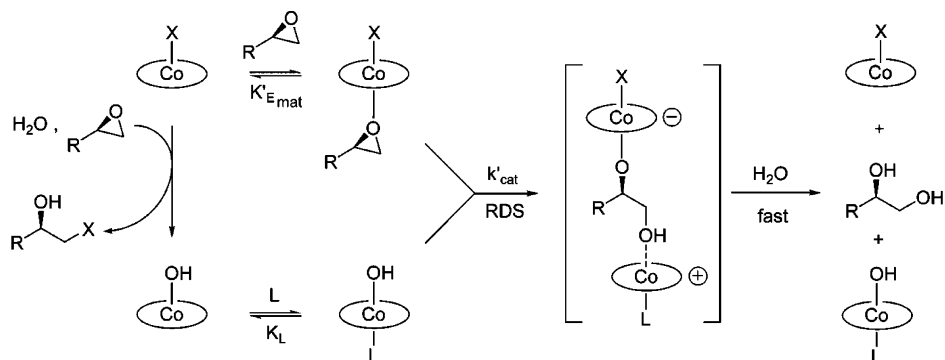
rate =

$$\frac{k_{\text{cat}} K_{\text{H}_2\text{O}} K_{\text{E}_{\text{mat}}} [\text{H}_2\text{O}] [\text{E}_{\text{mat}}] [\text{Co-OH}]_{\text{tot}}^2}{(1 + K_{\text{H}_2\text{O}} [\text{H}_2\text{O}] + K_{\text{E}_{\text{mat}}} [\text{E}_{\text{mat}}] + K_{\text{E}_{\text{mis}}} [\text{E}_{\text{mis}}] + K_{\text{D}} [\text{D}])^2} \quad (4)$$

Analysis of this double Michaelis-Menten system reveals several interesting and unexpected aspects of the HKR. Both epoxide enantiomers bind to Co-OH complex **1b** with similar affinity ($K_{\text{E}_{\text{mat}}} \approx K_{\text{E}_{\text{mis}}}$); thus, the high selectivity in the HKR results not from selective binding to the chiral catalyst, but instead from selective reaction of one of the epoxide complexes. Despite the presence of several potential Lewis bases in the reaction medium (epoxide, water, diol), kinetic data are consistent with the aquo complex **1b**·H₂O as the dominant nucleophilic component in the rate-

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Scheme 2. Dominant Catalytic Cycle in HKR Reactions Catalyzed by Co–X (X ≠ OH) Where Addition of X to Epoxide Is Incomplete

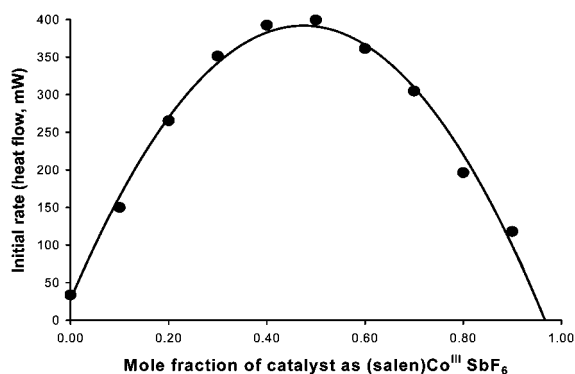
determining bimetallic step. Water and epoxide bind with similar affinity, an unexpected but crucial factor for efficient reactivity over a range of conditions.

As compared to the pure Co–OH system, HKR reactions carried out under conditions in which both Co–OH and Co–X are present display dramatic increases in activity (up to 30-fold with X = OTs). The elementary rate law for the HKR in the mixed counterion case is given in eq 5. The two terms reflect the fact that both complexes can play the role of Lewis acid to activate the epoxide. However, more electronegative counterions are expected to result in both stronger epoxide binding ($K_{E'}^{\prime}$) and more rapid addition of the Co–OH complex **1b** to the bound epoxide (k_{cat}'). With the most Lewis acidic Co–X complexes, the first term in eq 5 may be neglected and the mixed counterion catalytic cycle in Scheme 2 (X ≠ OH) dominates over the cycle shown in Scheme 1. In that case, the expanded rate law is approximated by eq 6, where f is a function that accounts for the rate dependence on water, matched epoxide, and mismatched epoxide concentrations. According to this rate expression, a first-order rate dependence on each catalyst component is expected. In addition, a parabolic relationship between rate and partitioning of the Co–OH and Co–X complexes should be seen,⁹ with the maximum rate arising when $[Co–OH]_{tot} = [Co–X]_{tot}$. The general form of eq 6 was confirmed experimentally using mixtures of **1c** (aged to allow complete chloride addition) and **1g** (a complex bearing a nonnucleophilic counterion) (Figure 1).

$$\text{rate} = k_{cat}[\mathbf{1b} \cdot \text{H}_2\text{O}][\mathbf{1b} \cdot \text{E}] + k_{cat}'[\mathbf{1b} \cdot \text{L}][(\text{Co}–\text{X}) \cdot \text{E}] \quad (5)$$

$$\text{rate} = k_{cat}'f[\text{Co}–\text{OH}]_{tot}[\text{Co}–\text{X}]_{tot} \quad (6)$$

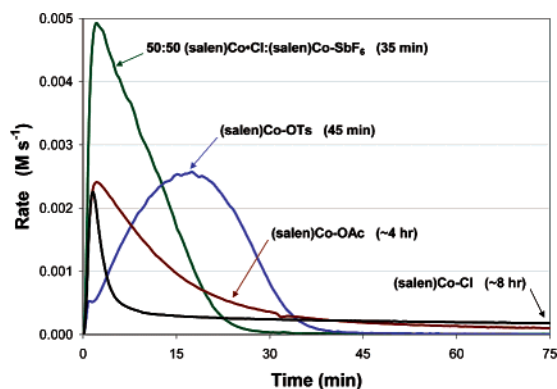
The counterion effect in the HKR thus lies at the heart of a complex mechanism involving catalyst partitioning between two species that react together in the rate-determining step. The degree of partitioning changes during the course of the HKR as a function

**Figure 1.** Parabolic dependence of rate on partitioning between Co–OH (**1b**) and Co–SbF₆ (**1g**).

of irreversible X-group addition to epoxide (Scheme 2).⁷ As emphasized graphically in Figure 1, low rates result when addition of X to epoxide has occurred to very small or very great extents, and fastest rates are obtained during intermediate stages.

Rate versus time profiles shown in Figure 2 illustrate the practical differences in behavior and reactivity among the different catalysts. The chloride catalyst **1c** undergoes such rapid counterion addition to epoxide that the majority of the HKR occurs in the slow Co–OH regime. The acetate catalyst **1a** is more efficient, but still stalls in the final stages of the HKR. The tosylate catalyst **1f** effects complete substrate conversion much more rapidly in part because counterion addition is slower; catalyst partitioning is closer to 50:50 Co–OH/Co–X near the end of the reaction.¹⁰ By comparison, fixing catalyst partitioning using a 50:50 mix of **1c** and **1g** leads to a faster reaction, albeit only slightly relative to catalyst **1f** alone.

A useful way of representing the HKR involves a three-dimensional graphical depiction of the rate of the reaction (z -axis) as a function of the partitioning between Co–X and Co–OH (x -axis) and a function of conversion (y -axis) (Figure 3). Each Co–X catalyst has a different intrinsic Lewis acidity (reflected in k_{cat}' and $K_{E_{mat}}^{\prime}$) and is therefore described by a unique kinetic surface. The relative rate of counterion addition to epoxide (X vs OH) determines the path over which a particular reaction traverses that surface. Reactions with three different catalysts are represented. The acetate catalyst **1a** undergoes acetate addition at a moderate rate; however, counterion addition is complete by the late stages of the HKR. At that point, only the pure Co–OH pathway contributes to rate and the resolution requires long reaction times to reach completion (>99% ee). The tosylate catalyst **1f** is more efficient because counterion addition is slow and has not passed beyond the optimal 50:50 partitioning by the end of the HKR.¹¹

**Figure 2.** Hydrolysis of 1-hexene oxide catalyzed by different Co–X complexes as monitored by reaction calorimetry (completion times in parentheses). All runs were carried out at the same total catalyst concentration.

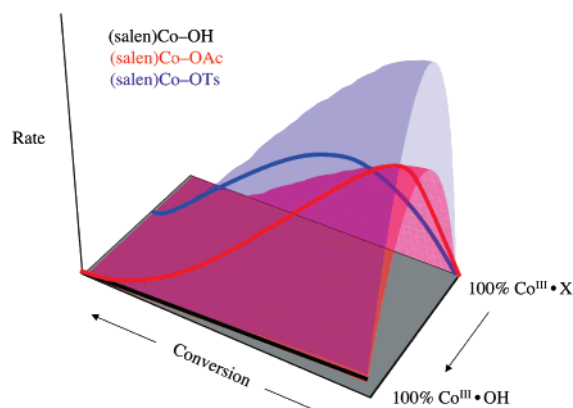


Figure 3. Representation of the HKR using three-dimensional kinetic surfaces. The lines track the progress of the reactions with different catalysts as a function of rate and catalyst partitioning.

Table 1. HKR of Representative Epoxides

substrate	method ^a	catalyst (mol %) ^b	time (h)	yield (%) ^c
	A	0.5	16	43
	B	0.15	3	44
	A ^d	0.5	16	43
	B ^d	0.2	16	42
	A	2.0	24	43
	B	0.5	16	42
	A	0.5	16	47
	B	0.06	16	45
	A	2.0	48	40
	B	1.2	48	39

^a Method A: As in ref 1b using catalyst **1a**. Method B: Catalyst **1f** added to epoxide (0.1–0.4 mol) and water (0.7 equiv) under solvent-free conditions at room temperature. ^b Catalyst loading based on racemic epoxide. ^c Isolated yield of >99% ee epoxide based on racemate (theoretical maximum = 50%). ^d Reaction at 0–4 °C.

For reasons that are now well understood mechanistically, there is a significant counterion dependence on the rate of the HKR. Remarkably, perhaps, there is relatively little effect on enantioselectivity, as k_{rel} values remain very high for all counterions examined.¹² This can be ascribed to the fact that the counterion occupies the site trans to the bound epoxide. The ligand conformation and steric environment in the selectivity-determining ring-opening events are most likely quite similar. It is interesting to note that high ee's were observed in the X-addition products,⁶ suggesting that all counterion addition processes (both X = OH and X ≠ OH) may occur by analogous cooperative bimetallic mechanisms.

It is now clear that the acetate complex **1a** represents a reasonable catalyst choice for the HKR because acetate addition to epoxide is facile but not much faster than the HKR process. However, this study has revealed the interesting fact that catalysts such as Co-OTs complex **1f** with more weakly nucleophilic counterions can represent much better alternatives. The generality of this phenomenon is illustrated with a series of representative epoxides (Table 1).¹³ Terminal epoxides containing halide, ester, ether, and both hindered and unhindered aliphatic substituents underwent resolution to >99% ee with yields similar to those obtained with acetate complex **1a**, but with lower catalyst loadings and/or less time.

The notion of a complex serving as both precatalyst and cocatalyst is new in asymmetric catalysis. Indeed, irreversible change to a catalyst during the course of a reaction, as is the case

in the HKR, is generally seen as detrimental to highly enantioselective processes. Nonetheless, we anticipate that this mechanistic framework is relevant to a range of Lewis acid-promoted asymmetric reactions. We are currently exploring new methodologies involving cooperative bimetallic catalysis that may build on the principles set forth in this paper.

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Supporting Information Available: Details of several of the kinetic experiments and characterization of catalysts **1a**, **1c**, **1f**, and **1g** (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>. An animation expanding upon Figure 3 may be found at <http://www.chem.harvard.edu/groups/Jacobsen/publications.htm>.

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- The acetate addition products **2b** are isolated in high (>90%) ee and are stable to the conditions of the HKR. (Salen)Co complexes catalyze addition of carboxylic acids to epoxides: Jacobsen, E. N.; Kakiuchi, F.; Kinsler, R. G.; Larrow, J. F.; Tokunaga, M. *Tetrahedron Lett.* **1997**, *38*, 773–776. Catalysts bearing other nucleophilic counterions also afforded addition products in high ee (R = ⁿBu): **2c** (94% ee), **2d** (83% ee), **2e** (99% ee). The maximum amount of counterion addition product (X ≠ OH) is equal to the catalyst loading and therefore contributes minimally to epoxide conversion.
- The rate of counterion addition depends on both the nucleophilicity of the bound counterion and the Lewis acidity of the corresponding Co complex. The chloride complex **1c** effected counterion addition most rapidly among the catalysts examined. In contrast to results reported in ref 4b with catalyst **1g**, complexes bearing very nonnucleophilic counterions (e.g., SbF₆⁻, complex **1g**) were unreactive when purified carefully. We found that the hydrolytic reactivity of the purified SbF₆⁻ complex could be initiated by addition of a noncoordinating Brønsted base such as 2,6-lutidine, presumably by deprotonation of coordinated water to generate **1b**.
- Independent experiments established that diol does not bind appreciably to catalyst, so K_D was fixed at 0 for the purposes of kinetic modeling. See the Supporting Information for a detailed description of these experiments.
- Because the total catalyst loading is assumed to be constant in these experiments, the rate equation as a function of $x = [\text{Co-X}]_{\text{tot}}$ at any fixed set of concentrations ([E], [H₂O], [D]) takes the general form of a concave-down parabola shifted to the right: $[\text{Co-OH}]_{\text{tot}} + [\text{Co-X}]_{\text{tot}} = [\text{cat}]_{\text{tot}}$. Substituting into eq 6: $\text{rate} = k_{\text{cat}}f([\text{cat}]_{\text{tot}} - [\text{Co-X}]_{\text{tot}})[\text{Co-X}]_{\text{tot}} = k_{\text{cat}}f[\text{cat}]_{\text{tot}}[\text{Co-X}]_{\text{tot}} - k_{\text{cat}}f[\text{Co-X}]_{\text{tot}}^2 = ax - bx^2$.
- In addition to irreversible counterion addition, catalyst partitioning can also be controlled by converting Co-OH into Co-X by addition of HX. See the Supporting Information.
- Because both the rate of counterion addition and the rate of the HKR depend on the concentration of Co-X, the catalyst partitioning near the end of the reaction is expected to vary at different catalyst loadings.
- With all catalysts, 1-hexene oxide can be recovered in >99% ee and >40% yield based on racemic epoxide.
- An important exception: catalyst **1f** is less effective than **1a** with aryl-, vinyl-, and alkynyl-substituted epoxides, presumably as a result of participation of less selective S_N1 pathways. For such substrates, less Lewis acidic catalysts such as **1a** remain the most effective in the HKR. Schiffler, M. A., work in progress.

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