

# Nonlinear Effects in Kinetic Resolutions

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**Abstract:** The impact of nonlinear effects in the asymmetric catalysis of kinetic resolutions is analyzed. It is found with minimal assumptions that the kinetics of homocompetitive reactions should apply generally to kinetic resolutions involving partially resolved catalysts, and this is supported by experimental observations with the Jacobsen hydrolytic kinetic resolution of epoxides. The criterion for a nonlinear effect in asymmetric catalysis, a nonlinear correlation between the enantiomeric excess in a chiral ligand and the product enantiomeric excess obtained from a reaction, is examined. The nonlinear effect idea is found to be generalizable to kinetic resolutions and other reactions by replacing consideration of the product enantiomeric excess with the quantity  $(k_R/k_S - 1)/(k_R/k_S + 1)$ , a differential kinetic enantiomeric enhancement (DKEE). A nonlinear effect may then be defined by a nonlinear correlation between the DKEE and the chiral ligand enantiomeric excess. The application of these ideas to previously reported kinetic resolutions of sulfoxides and to nonlinear effects in the Jacobsen hydrolytic kinetic resolution is described. Relatively small nonlinear effects in kinetic resolutions are sufficient to obtain large asymmetric amplifications.

## Introduction

The emerging field of asymmetric amplification involves the development of reactions for which the optical yield exceeds the optical purity of an asymmetric catalyst.<sup>1–3</sup> This phenomenon is derived from a nonlinear correlation between the enantiomeric excess in a chiral ligand and the enantiomeric excess obtained from a reaction. Many different asymmetric reactions have been shown to demonstrate asymmetric amplification. These reactions include reduction of ketones,<sup>4</sup> alkylation of aldehydes,<sup>5–7</sup> oxidation of sulfides,<sup>2,8</sup> aldol reactions,<sup>2,3b,9</sup> Diels–Alder reactions,<sup>10</sup> conjugate additions to  $\alpha,\beta$  unsaturated carbonyl compounds,<sup>11</sup> ene reactions,<sup>12</sup> Sharpless epoxidation of allylic alcohols,<sup>2</sup> and allylation reactions.<sup>13</sup> Some spectacular examples include the observation of 95% ee in the product of

addition of a diethylzinc to benzaldehyde using only 15% ee in a catalytic ligand,<sup>6</sup> and 96% ee in a Diels–Alder reaction employing only 20% ee in the catalyst.<sup>10d</sup> However, the asymmetric amplification observed in most cases is more modest.

The difficulty in obtaining high asymmetric amplification arises from a series of hurdles: (1) The reaction must involve asymmetric catalysis and be highly enantioselective when enantiopure catalyst is used. This in itself has been a major challenge for organic chemists in recent years. (2) A nonlinear correlation of enantioselectivity with catalyst enantiomeric excess requires interaction between two molecules of a chiral catalyst or chiral catalyst ligand. Most asymmetric catalysis involves independently reactive catalyst systems.<sup>5b</sup> (3) The interaction between chiral catalyst or ligand molecules may take several forms but must be strong. The interaction must also lead to greater reactivity as opposed to lesser reactivity of the catalyst enantiomer in excess (a “positive” nonlinear effect).

The generation of optically active material in reactions may occur in two distinct ways: asymmetric synthesis, in which achiral materials are converted into optically active chiral materials, and kinetic resolution, in which one enantiomer of a racemate is selectively “destroyed”.<sup>14</sup> It has long been recognized that the two are subject to very different considerations and that each has advantages and disadvantages. In asymmetric

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synthesis the enantiomeric excess is limited by the relative rates of formation of the two enantiomeric products. In contrast, any kinetic resolution can in principle result in an arbitrarily high enantiomeric excess in unreacted starting material.

In this paper we analyze the impact of nonlinear effects on asymmetric amplification in kinetic resolutions, and explore this idea in the simple example of the Jacobsen hydrolytic kinetic resolution of epoxides.<sup>15</sup> Our results establish a basis for the description of nonlinear effects in kinetic resolutions and show how modest nonlinear effects can result in high asymmetric amplification.

Kinetic resolutions are intrinsically inefficient, it is traditionally argued, because most of the starting material is wasted. To be fair, however, it must be recognized that efficiency is not a central goal in the study of asymmetric amplification, as it will almost always be more practical to use approximately enantiopure catalysts in asymmetric synthesis.<sup>16</sup> For other potential goals in this area, such as the detection of small enantiomeric excesses or the mechanistic information provided by nonlinear effects, kinetic resolutions are as serviceable as asymmetric synthesis, and the results here highlight some special advantages of kinetic resolutions.

## Theory

**Kinetic Resolutions Involving Complex Rate Laws.** Kinetic resolutions have often been analyzed in a simplified fashion by assuming overall unimolecular kinetics in the reaction of the two enantiomers.<sup>17</sup> However, the kinetics of reactions involving nonlinear effects can be complex, involving multiple terms in the rate law.<sup>18</sup> Nonetheless, kinetic resolutions may be readily analyzed with the minimal assumptions that (1) each term in the rate law for each enantiomer is unimolecular in the enantiomer itself and (2) each term is the same order in reagents whose concentration varies as the reaction proceeds. These assumptions will not apply to reactions involving asymmetric autocatalysis<sup>7</sup> or stoichiometric chiral reagents but should apply to most reactions involving chiral catalysts. Under these assumptions, the variable concentrations of enantiomers R and S and other reagents A, B, C, etc. can be factored out as in eqs 1 and 2. Time is readily eliminated from these differential equations to give eq 3. Assuming that the concentrations of enantiomeric catalysts Cat<sub>R</sub> and Cat<sub>S</sub> are constant, the terms in parentheses may be replaced by the overall rate constants  $k_R$  and  $k_S$ . Equation 3 is readily integrated to give the classical formula for homocompetitive reactions in eq 4.<sup>19</sup>

$$-\frac{d[R]}{dt} = (k_1[\text{Cat}_R]^2 + k_2[\text{Cat}_R] + k_3[\text{Cat}_R][\text{Cat}_S] + \dots) \frac{[R][A][B]\dots}{[C]\dots} \quad (1)$$

$$-\frac{d[S]}{dt} = (k_1[\text{Cat}_S]^2 + k_2[\text{Cat}_S] + k_3[\text{Cat}_S][\text{Cat}_R] + \dots) \frac{[S][A][B]\dots}{[C]\dots} \quad (2)$$

$$\frac{d[R]}{d[S]} = \frac{(k_1[\text{Cat}_R]^2 + k_2[\text{Cat}_R] + k_3[\text{Cat}_R][\text{Cat}_S] + \dots) [R]}{(k_1[\text{Cat}_S]^2 + k_2[\text{Cat}_S] + k_3[\text{Cat}_S][\text{Cat}_R] + \dots) [S]} = \frac{k_R [R]}{k_S [S]} \quad (3)$$

$$\frac{[R]}{[R_0]} = \left( \frac{[S]}{[S_0]} \right)^{k_R/k_S} \quad (4)$$

Equations related to eq 4 have been found to apply to diverse situations ranging from kinetic resolutions to separations to kinetic isotope effects.<sup>20–22</sup> The analysis here suggests that the same relationship should usually apply to the complex situation of kinetic resolution using reactions involving partially resolved catalysts. Experimental verification of this relation will be presented below. In analyzing kinetic resolutions eq 4 has been reformulated in terms of enantiomeric excess (vide infra), but the problem arises that it becomes impossible to express enantiomeric excess analytically in terms of  $k_R/k_S$  and the total conversion of  $R_0$  and  $S_0$ . If instead we define  $F$  as the fractional conversion of just enantiomer S, then  $S/S_0 = 1 - F$ . Dividing this equation into eq 4 and allowing that  $R_0 = S_0$  for a racemic mixture results in eq 5.

$$\frac{[R]}{[S]} = (1 - F)^{(k_R/k_S - 1)} \quad (5)$$

Equation 5 is useful for understanding the basic properties of kinetic resolutions without the necessity of previous graphical analyses.<sup>17,23</sup> As the reaction approaches completion ( $F \rightarrow 1$ ), if  $k_R/k_S > 1$  then  $[R]/[S]$  approaches 0. If  $k_R/k_S < 1$ , then  $[R]/[S]$  grows without bound. The alternative formulation of eq 4 in terms of fractional enantiomeric excess of S ( $ee_S$ ) and fractional conversion of the total racemate  $R_0 + S_0$  ( $C$ ) in the manner of previous workers<sup>21,14</sup> gives eq 6. This equation is useful for determining  $k_R/k_S$  and can be used graphically to predict the enantiomeric excess expected from a reaction at a given total conversion.<sup>23</sup>

$$k_R/k_S = \frac{\ln[(1 - C)(1 - ee_S)]}{\ln[(1 - C)(1 + ee_S)]} \quad (6)$$

**Nonlinear Effects in Asymmetric Catalysis.** To understand “nonlinear effects” in kinetic resolutions it is necessary to first analyze the expectation of linearity in normal asymmetric catalysis on a deeper level than previous analysis. For the conversion of an achiral substrate into alternative enantiomers R and S, the enantiomeric catalysts Cat<sub>R</sub> and Cat<sub>S</sub> are most commonly monomeric and independently reactive.<sup>5b</sup> The rate laws for formation of R and S would then be of the form shown in eqs 7 and 8.

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$$\frac{d[R]}{dt} = (k_1[\text{Cat}_R] + k_2[\text{Cat}_S]) \frac{[\text{substrate}][A][B] \dots}{[C] \dots} \quad (7)$$

$$\frac{d[S]}{dt} = (k_1[\text{Cat}_S] + k_2[\text{Cat}_R]) \frac{[\text{substrate}][A][B] \dots}{[C] \dots} \quad (8)$$

$$\frac{d[R]}{d[S]} = \frac{k_1[\text{Cat}_R] + k_2[\text{Cat}_S]}{k_1[\text{Cat}_S] + k_2[\text{Cat}_R]} = \frac{k_R}{k_S} \quad (9)$$

The formation of R and S would be related by eq 9. If the concentrations of  $\text{Cat}_R$  and  $\text{Cat}_S$  are constant then the terms in parentheses in eqs 7 and 8 can as above be described by the overall rate constants  $k_R$  and  $k_S$ , and the ratio of products  $[R]/[S]$  will equal  $d[R]/d[S]$  and  $k_R/k_S$ . There will not generally be a linear relationship between  $[\text{Cat}_R]/[\text{Cat}_S]$  and  $d[R]/d[S]$ ,  $[R]/[S]$ , or  $k_R/k_S$ . However, the enantiomeric excess in the product and the equivalent  $(k_R/k_S - 1)/(k_R/k_S + 1)$  will be linearly related to the enantiomeric excess in the catalyst as shown in eq 10, which is readily obtained from manipulation of eq 9.

$$\underbrace{\frac{[R]}{[S]} - 1}_{\text{ee in product}} = \frac{\frac{k_R}{k_S} - 1}{\frac{k_R}{k_S} + 1} = \frac{(k_1 - k_2)}{(k_1 + k_2)} \underbrace{\frac{[\text{Cat}_R] - [\text{Cat}_S]}{[\text{Cat}_R] + [\text{Cat}_S]}}_{\text{ee in catalyst}} \quad (10)$$

Unfortunately, the linearity versus nonlinearity of the relationship between the enantiomeric excess in the catalyst and the enantiomeric excess in the product becomes meaningless in many situations. This includes reactions in which the products are subject to racemization, reactions for which  $k_R/k_S$  is not constant, reactions which start with some excess of an enantiomeric product present, and kinetic resolutions. However, the relationship of  $(k_R/k_S - 1)/(k_R/k_S + 1)$  to the enantiomeric excess in the catalyst is not subject to these limitations. The quantity  $(k_R/k_S - 1)/(k_R/k_S + 1)$  represents a *differential* kinetic enantiomeric enhancement which we will designate as "DKEE". We would like to suggest that the term "nonlinear effect" be defined as applying to reactions for which the DKEE does not vary linearly with the ee of the catalyst. This allows generalization of the idea of nonlinearity, most particularly to include kinetic resolutions. The value of the DKEE will also be useful in quantifying nonlinear effects (vide infra).

**Nonlinear Effects in Kinetic Resolutions.** As illustrated by eq 5 any kinetic resolution has the potential to provide an unlimited "asymmetric amplification", at least from the standpoint that the optical yield in unreacted starting material can exceed the ee of the catalyst to any arbitrary extent as the reaction approaches completion. However, this amplification is limited practically in the absence of a nonlinear effect. If a kinetic resolution involves simple monomeric, independently reactive catalysts, so that  $k_R = k_1[\text{Cat}_R] + k_2[\text{Cat}_S]$  and  $k_S = k_1[\text{Cat}_S] + k_2[\text{Cat}_R]$ , then the DKEE is again linearly related to the ee of the catalyst exactly as in eq 10. In such a reaction the DKEE cannot exceed the ee of the catalyst. If the ee of the catalyst is 20% then  $k_R/k_S$  is at most 1.5, which from eq 6 corresponds to a 45% ee in the starting material at 90% conversion.

The impact of nonlinear effects on kinetic resolutions is most easily discussed within the context of a model kinetic system

and we will apply here Kagan's  $\text{ML}_2$  model.<sup>2,24</sup> In this model the rate laws of eqs 1 and 2 would include only terms for the dimeric catalysts  $\text{Cat}_{RR}$ ,  $\text{Cat}_{SS}$ , and  $\text{Cat}_{RS}$  formed from combinations of two monomeric enantiomeric ligands.  $\text{Cat}_{RS}$  is a meso complex that would react equally well with enantiomers R and S in the starting racemic mixture. Equation 3 would then become eq 11. If we define the term  $\text{DKEE}_0$  as  $(k_1 - k_2)/(k_1 + k_2)$ , which is the DKEE when using enantiomerically pure catalyst, then eq 12 will relate the DKEE to the enantiomeric excess  $ee_{\text{aux}}$  in a ligand for the chiral catalyst. Equation 12 is equivalent to the equation of Kagan and co-workers relating product enantiomeric excess to  $ee_{\text{aux}}$ ,<sup>2,24</sup> and may be derived in an identical fashion. However, the framing of the  $\text{ML}_2$  model in terms of the DKEE makes eq 12 applicable to kinetic resolutions and other complex situations (vide supra). Equation 12 becomes equivalent to the linear relationship in eq 10 when  $\beta = 0$  or  $g = 1$ . Positive nonlinear effects would be observed when the formation of the meso catalyst  $\text{Cat}_{RS}$  is favored at equilibrium and  $\text{Cat}_{RS}$  is less reactive than the chiral catalysts ( $g < 1$ ).

$$\frac{d[R]}{d[S]} = \frac{(k_1[\text{Cat}_{RR}] + k_2[\text{Cat}_{SS}] + k_3[\text{Cat}_{RS}]) [R]}{(k_1[\text{Cat}_{SS}] + k_2[\text{Cat}_{RR}] + k_3[\text{Cat}_{RS}]) [S]} = \frac{k_R}{k_S} \frac{[R]}{[S]} \quad (11)$$

$$\text{DKEE} = \text{DKEE}_0 \times ee_{\text{aux}} \times \frac{1 + \beta}{1 + g\beta} \quad (12)$$

$$\beta = \frac{[\text{Cat}_{RS}]}{[\text{Cat}_{RR}] + [\text{Cat}_{SS}]} \quad g = \frac{2k_3}{k_1 + k_2}$$

The difficulty of obtaining high asymmetric amplification in regular asymmetric catalysis can be seen from a hypothetical example in which several factors have been engineered favorably: (1) The chiral catalysts are perfectly selective, i.e.,  $\text{DKEE}_0 = 1.0$ . (2) The equilibrium constant ( $K = [\text{Cat}_{RS}]^2/[\text{Cat}_{RR}][\text{Cat}_{SS}]$ ) favors  $\text{Cat}_{RS}$  by a factor of 10. (3) The meso catalyst is less reactive than the chiral catalysts by a factor of 10 ( $g = 0.1$ ). Under these circumstances an  $ee_{\text{aux}}$  of 50% results in a product enantiomeric excess of only 82%.<sup>25</sup> In contrast, under identical circumstances a kinetic resolution amplifies a 50%  $ee_{\text{aux}}$  at 72% conversion into a 99% enantiomeric excess in unreacted starting material!

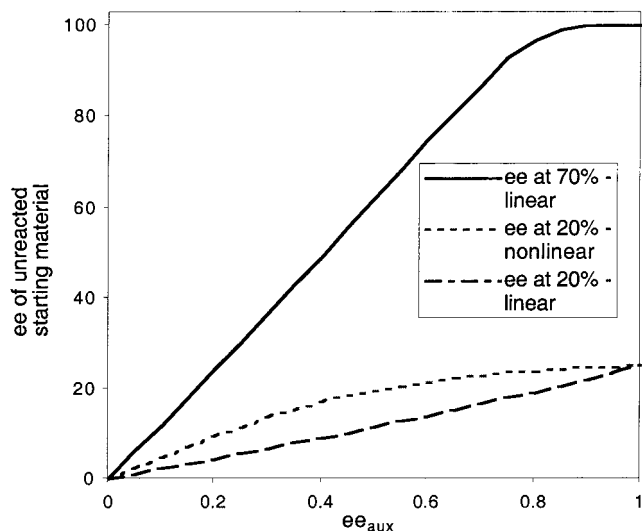
The advantage of kinetic resolutions in this regard is the result of two factors. The first is the unlimited growth in the ee with higher conversion as already discussed, though this factor has the offsetting disadvantage of decreased chiral-material recovery with higher conversion. A second advantage of kinetic resolutions, however, is that small amounts of reaction of the less-reactive enantiomer do not impact substantially on the ee of the starting material. In contrast, small amounts of the minor product enantiomer formed in normal asymmetric catalysis substantially decrease the possible ee in the product, and this is exceedingly difficult to avoid when the catalyst is not enantioselective.

## Applications

**Kinetic Resolution of Sulfoxides.** The only previous report of a "nonlinear" effect in a kinetic resolution is due to Uemura and co-workers and involves the kinetic resolution of racemic

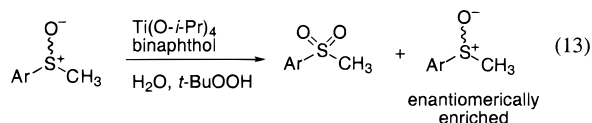
(24) Guillaneux, D.; Zhao, S.-H.; Samuel, O.; Rainford, D.; Kagan, H. B. *J. Am. Chem. Soc.* **1994**, *116*, 9430.

(25) This is calculated from eq 12, obtaining  $\beta$  from  $K$  by the equation of Kagan (see ref 24). The calculation of  $\beta$  is equally valid for asymmetric catalysis and kinetic resolutions.



**Figure 1.** Plot of the enantiomeric excess in unreacted starting material versus the enantiomeric excess in a ligand for a chiral catalyst ( $ee_{\text{aux}}$ ), assuming either a linear effect of  $ee_{\text{aux}}$  ( $\text{DKEE} = \text{DKEE}_0 \times ee_{\text{aux}}$ ) or a nonlinear  $\text{ML}_2$  model (see text).

sulfoxides catalyzed by a titanium–binaphthol complex (eq 13).<sup>26</sup> The evidence cited for a positive nonlinear effect was



2-fold: curvature in a plot of the ee of recovered sulfoxide at 70% conversion versus ee of the catalyst ligand binaphthol, and curvature in a plot of initial rate ratios  $k_S/k_R$  versus ee of the binaphthol.

These criteria are incorrect. Figure 1 shows the ee in recovered starting material at 70% conversion found by numerically solving eq 6 versus  $ee_{\text{aux}}$ , assuming no nonlinear effect ( $\text{DKEE} = \text{DKEE}_0 \times ee_{\text{aux}}$ ) and that  $\text{DKEE}_0 = 1$ . Such a plot is necessarily curved at high  $ee_{\text{aux}}$  and 70% conversion because the ee of recovered starting material approaches a maximum of 100%. At 20% conversion with no nonlinear effect the plot is nearly linear, which is interestingly the experimental observation in the sulfoxide resolutions. However, a sufficiently large nonlinear effect would lead to a visibly curved plot at 20% conversion (Figure 1 shows the expected plot based on an  $\text{ML}_2$  model with the equilibrium constant favoring  $\text{Cat}_{R5}$  by a factor of 10 and with  $g = 0.1$  as in the example above). Such curvature was not observed with the sulfoxide resolutions, though a smaller nonlinear effect would be difficult to discern.

As for the second criterion of curvature in a plot of  $k_S/k_R$  versus  $ee_{\text{aux}}$ , such curvature is unavoidable. This can be understood simply from consideration of a perfectly enantioselective linear reaction when  $ee_{\text{aux}}$  is changed from 0.99 to 1.0. For this small change in  $ee_{\text{aux}}$ ,  $k_S/k_R$  jumps to infinity!<sup>27</sup>

The appropriate test for a nonlinear effect is a plot of  $ee_{\text{aux}}$  versus DKEE. Toward that end, DKEEs were calculated in two ways from the literature data for the resolution of methyl *p*-tolyl sulfoxide: from the initial rate ratios  $k_S/k_R$  previously reported and using eq 6 with the observed enantiomeric excesses obtained

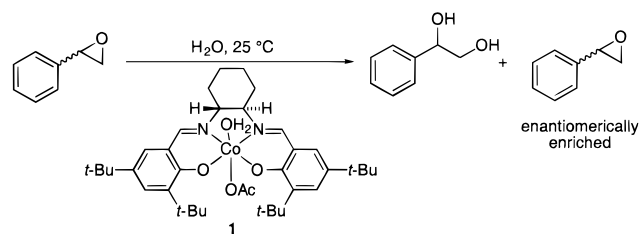
(26) Komatsu, N.; Hashizume, M.; Sugita, T.; Uemura, S. *J. Org. Chem.* **1993**, *58*, 7624.

(27) The detailed curvature of the plot of  $k_S/k_R$  versus ee of the binaphthol in ref 26 cannot be modeled without assuming a nonlinear effect. However, because all such plots are curved, their use to distinguish nonlinear effects is at best complicated.

at 70% conversion. The results are summarized in Figure 2. The curvature of the plots in Figure 2 is an accurate indication of the positive nonlinear effect in this reaction, and demonstrates that Uemura's hypothesis of a nonlinear effect was in fact correct. This nonlinear effect is not surprising based on previous observations of nonlinear effects in titanium-catalyzed enantioselective oxidations of achiral sulfides and allylic alcohols,<sup>2</sup> and is consistent with two (or more) molecules of binaphthol being involved in the active titanium catalyst.

Figure 2 highlights an additional advantage of analyzing kinetic resolutions in terms of DKEE. The difference in the curves for DKEE calculated from initial rates and DKEE calculated from ee values at 70% conversion shows that the catalyst selectivity increases substantially as the reaction proceeds. This was not apparent from the original data. The proportional increase in selectivity is similar at all values of  $ee_{\text{aux}}$ . This has the surprising implication that the basic selectivity of the reaction changes while the nonlinear effect stays approximately constant.

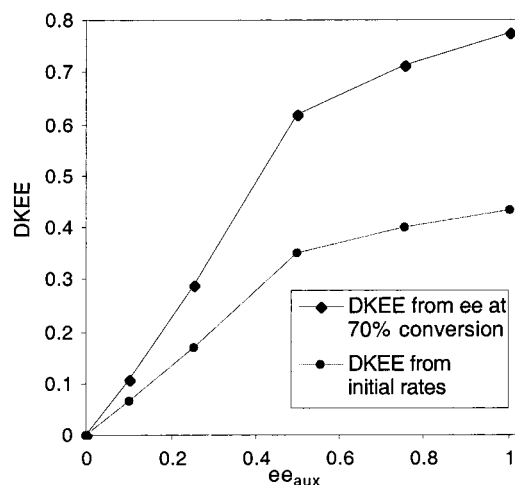
**The Jacobsen Hydrolytic Kinetic Resolution.** In searching for a more substantial nonlinear effect in a kinetic resolution, we were intrigued by the report of Jacobsen and co-workers that the highly selective hydrolytic kinetic resolution of epoxides catalyzed by the cobalt salen complex **1** was second order in catalyst.<sup>15</sup> In addition, a nonlinear effect was observed in the asymmetric azido ring opening of meso epoxides catalyzed by similar chromium salen complexes.<sup>28</sup> These observations suggested that the Jacobsen hydrolytic kinetic resolution (HKR) of epoxides was a good candidate for the study of asymmetric amplification and nonlinear effects in kinetic resolutions.



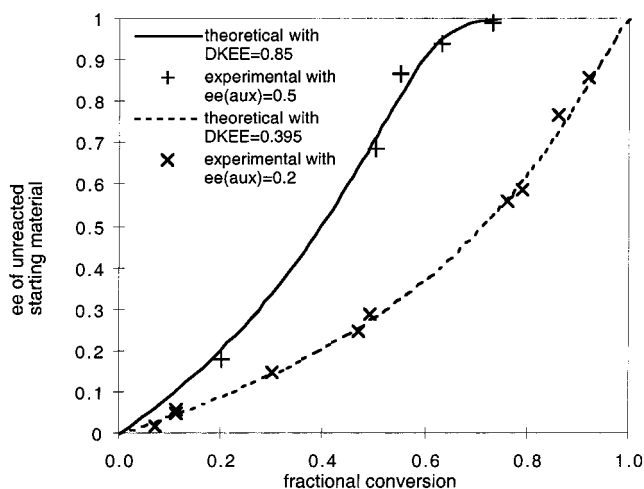
Our initial objective was to check the applicability of homocompetitive reaction kinetics (eq 4 and derived equations) to HKR reactions employing partially resolved **1**. Figure 3 shows the results of HKR of styrene oxide using **1** with either 20% ee or 50% ee of the *R,R* isomer, compared to theoretical values derived from numerical solution of eq 6. The excellent fit of experimental values and the theoretical curve is not surprising, since the equations derived for homocompetitive reactions (eqs 4–6) are essentially algebraic requirements when the selectivity ( $k_R/k_S$  or DKEE) is constant. However, such a fit would not be expected if asymmetric autocatalysis<sup>7</sup> were important in the reaction or if there was a substantial change in the catalyst enantioselectivity as the reaction progresses.

This allows the DKEE to be determined from measurements of enantiomeric excess at measured fractional conversions. The HKR reaction of epoxides catalyzed by **1** is highly selective, and DKEEs in resolutions using enantiomerically pure **1** ( $\text{DKEE}_{0S}$ ) range from 0.9 to >0.995, based on the reported relative rates of reactions of enantiomeric epoxides.<sup>15a</sup> The initial indication of a sizable nonlinear effect in these reactions was that kinetic resolutions of styrene oxide exhibited DKEEs greater than the ee of **1** used in the reactions under a variety of

(28) (a) Konkler, R. G.; Karl, J.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1998**, *120*, 10780. (b) Hansen, K. B.; Leighton, J. L.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1996**, *118*, 10924.



**Figure 2.** Plot of DKEE versus  $ee_{\text{aux}}$  for the kinetic resolution of methyl *p*-tolyl sulfoxide based on data in ref 25. Using the definition of DKEE in eq 10, the lower line was calculated from initial  $k_S/k_R$  data and the upper line was calculated using eq 6 based on observed enantiomeric excesses at 70% conversion.

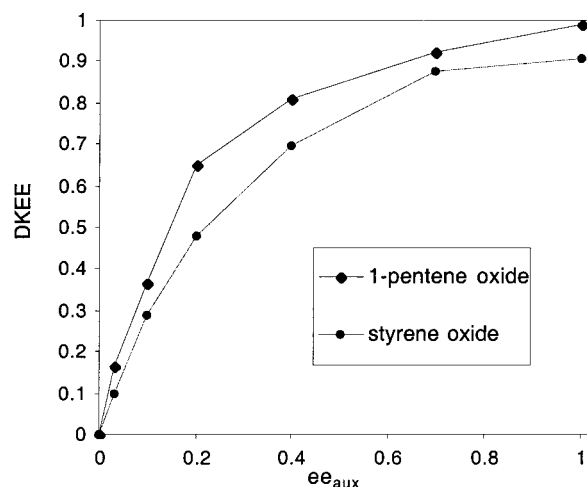


**Figure 3.** Plot of enantiomeric excess in the hydrolytic kinetic resolution of styrene oxide versus fractional conversion for reactions using either 50% ee **1** or 20% ee **1** in acetonitrile solvent. The solid and dashed lines are theoretical for DKEEs of 0.85 and 0.395, respectively.

conditions. For example, the best fit DKEEs in Figure 3 are 0.85 and 0.395 for reactions employing 50% ee **1** and 20% ee **1**, respectively.

The observation of a DKEE greater than the ee in the catalyst by itself establishes a positive nonlinear effect. However, nonlinear effects may be less obvious for reactions in which the DKEE is  $\ll 1$  using enantiopure catalyst or if the nonlinear effect is negative. A plot of the DKEE versus  $ee_{\text{aux}}$  as in Figure 4 gives a more complete view of the positive nonlinear effect in these reactions. For the HKR of 1-pentene oxide in THF the DKEE exceeds  $ee_{\text{aux}}$  by 4–5-fold when the catalyst ee is low. This upward curvature of Figure 4 necessarily decreases as  $ee_{\text{aux}}$  increases, but the positive nonlinear effect allows substantial asymmetric amplification. For example, a 3% ee in the catalyst results in a DKEE of 0.167 and a 35% ee in recovered epoxide at 88% conversion, and 20% ee in the catalyst results in a DKEE of 0.69 and a 94% ee in recovered epoxide at 76% conversion.

A number of results show interestingly how the nonlinear effect changes with varying reactions conditions. At high  $ee_{\text{aux}}$  the lower DKEE for styrene oxide compared to 1-pentene oxide



**Figure 4.** Plot of DKEE versus  $ee_{\text{aux}}$  for the kinetic resolution of 1-pentene oxide or styrene oxide in THF.

might be attributed to an intrinsically less selective reaction (as evident from DKEEs with enantiopure catalyst of 0.99 with 1-pentene oxide versus 0.91 for styrene oxide). However, at low  $ee_{\text{aux}}$  the intrinsic selectivity should make little direct difference in the DKEE. This can be seen for the  $ML_2$  model from eq 12: a change in  $DKEE_0$  from 0.99 to 0.91 would have only a proportional effect on the DKEE at low  $ee_{\text{aux}}$ . The larger differences seen in the results with styrene oxide versus 1-pentene oxide suggest that the nonlinear effect itself is substrate dependent. It also appears to be solvent dependent. Using 20% ee **1** with styrene oxide, the greatest nonlinear effects were seen in THF ( $DKEE = 0.47-0.55^{29}$ ). The DKEE decreased to 0.395 in acetonitrile and surprisingly was only 0.29 in 2-methyltetrahydrofuran. These changes are not due to changes in the intrinsic selectivity: using enantiopure catalysts the DKEEs observed were 0.91 for THF, 0.95 in acetonitrile, and 0.96 in 2-methyltetrahydrofuran. Although the difference in these  $DKEE_0$  values is small, the greatest nonlinear effect is seen with the lowest intrinsic selectivity. Such results show that the nonlinear effect must be treated as a separate variable, apart from the reaction's asymmetric selectivity, for optimizations in asymmetric amplifications.

## Conclusions

From one perspective, asymmetric amplification is an intrinsic property of all kinetic resolutions. Any enantiomeric excess in an asymmetric catalyst makes possible, *in principle*, the recovery in high enantiomeric excess of unreacted starting material from a racemic mixture. For this reason, we would suggest that the idea of asymmetric amplification be distinguished from the phenomenon of nonlinear effects in asymmetric reactions. The analysis here has several implications toward nonlinear effects in both kinetic resolutions and other asymmetric reactions. First, it should generally be possible to analyze kinetic resolutions with the mathematics of homocompetitive reactions,<sup>19</sup> even in complex reactions involving incompletely resolved catalysts. Nonlinear effects in kinetic resolutions cannot be analyzed in the simplistic fashion sufficient for normal asymmetric catalysis, but they are readily understood by introducing the idea of a differential kinetic enantiomeric enhancement (DKEE). A

(29) Unlike Figure 3, HKR reactions in THF appear to increase somewhat in selectivity as the reaction proceeds, with upward deviation of a graph of the enantiomeric excess obtained versus fractional conversion, compared to the theoretical curve. The DKEE thus changes somewhat as the reaction proceeds.

nonlinear effect would then be present in reactions for which the DKEE does not vary linearly with the ee of the catalyst. This allows the useful generalization of the idea of nonlinear effects not only to kinetic resolutions but also to other reactions that do not fit the mould of normal asymmetric catalysis.

Kinetic resolution involving nonlinear effects should have some advantage over normal asymmetric catalysis in its ability to afford high enantiomeric excesses, particularly because a kinetic resolution does not depend on a complete obstruction of the minor enantiomeric pathway. Nonlinear effects in kinetic resolutions should be as common as in asymmetric synthesis. The analysis here shows that a nonlinear effect is operative in Uemura and co-workers' kinetic resolution of sulfoxides, and that a substantial nonlinear effect is present in the Jacobsen hydrolytic kinetic resolution of epoxides. In both reactions the nonlinear effect does not appear to be directly related to the intrinsic enantioselectivity of the reaction. Because kinetic resolutions do not require absolute selectivity, it may be useful to optimize nonlinear effects in reactions which are only moderately enantioselective. Overall, the study of asymmetric amplification and nonlinear effects in kinetic resolutions should present a variety of opportunities in a relatively unexplored area.

### Experimental Section

Samples of *R,R*-**1** and *S,S*-**1** were prepared as previously described.<sup>15a,30</sup> Racemic **1** was prepared in two ways, either from racemic 1,2-cyclohexanediamine by a procedure identical with that used to make the enantiomerically pure **1**,<sup>15a,30,31</sup> or from a mixture of *R,R*-**1** and *S,S*-**1**. (When the latter mixtures were used in HKR reactions, control

experiments exhibited no significant enantiomeric excess in epoxides reisolated from reactions taken to high conversion.) Enantiomeric excesses for 1-pentene oxide and styrene oxide were determined by NMR using Eu(hfc)<sub>3</sub> as shift reagent in CDCl<sub>3</sub>.

**Hydrolytic Kinetic Resolution of Styrene Oxide: Example Procedure.** A solution containing 3% enantiomeric excess of *R,R*-**1** was prepared from 9.9 mg (0.015 mmol) of *R,R*-**1** and 5.9 mL of a 0.079 M stock solution of racemic **1** in THF. After mixing for 1 min, 2.1 mL (18.4 mmol) of styrene oxide and 1.8 mL (101 mmol) of deionized water were added to the catalyst mixture with continued stirring. After 2.5 h the percent conversion was determined to be 91% from NMR integration of the epoxide peak at  $\delta$  2.79 versus a diol hydroxyl peak at  $\delta$  2.50. The reaction mixture was then poured into a flask containing 25 g of silica gel and 50 mL of hexanes. After swirling the red hexanes solution was gravity-filtered, and its volume reduced on a rotary evaporator. The unreacted epoxide was then reisolated by chromatography on a 0.5 cm  $\times$  8 cm silica gel column using hexanes as the eluent.

Reactions of 1-pentene oxide employed an analogous procedure except that the unreacted 1-pentene oxide was reisolated by a vacuum transfer, drying with Na<sub>2</sub>SO<sub>4</sub>, and fractional distillation.

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