Kinetic Resolution When the Chiral Auxiliary Is Not Enantiomerically Pure: Normal and Abnormal Behavior

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Abstract: Kinetic resolutions with enantioimpure chiral auxiliaries (reagents or catalysts) are considered, and a kinetic treatment for various rate laws is described. A useful parameter, the apparent stereoselectivity factor, is defined and correlated to the enantiomeric excess of the chiral auxiliary. Deviations from the regular laws are possible (asymmetric amplification or depletion). These anomalies have their origins in the same phenomena that cause nonlinear effects in enantioselective catalysis. Asymmetric amplifications have been experimentally observed.

Introduction

Kinetic resolutions (KR) by nonenzymatic[1] or enzymatic methods[2] are well documented processes. They are based on the partial transformation of a racemic starting material (*R*, *S*) into an achiral product P or a chiral product (P_R, P_S), as depicted in Figure 1 where k_1 and k_2 represent pseudo-first-order rate constants.

The efficiency of a kinetic resolution is characterized by the rate constant ratio $k_{rel} = k_1/k_2 = s$ (*s* is the stereoselectivity factor,[1] also called the *E* factor[2] in enzymatic reactions).[3] The stereoselectivity factor *s* may be calculated by eqs 1 or 2, where *c* stands for conversion ($0 \leq c \leq 1$) while ee_{sm} and ee_{prod} ($0 \leq ee_{sm}, ee_{prod} \leq 1$) are the enantiomeric excesses of recovered starting material and product, respectively.[1] The *s* factor is equal to the rate ratio at initial conversion of the racemic mixture.

$$s = \frac{k_1}{k_2} = \frac{\ln[(1 - c)(1 - ee_{sm})]}{\ln[(1 - c)(1 + ee_{sm})]} \tag{1}$$

$$s = \frac{k_1}{k_2} = \frac{\ln[1 - c(1 + ee_{prod})]}{\ln[1 - c(1 - ee_{prod})]} \tag{2}$$

The evolution of ee_{sm} and ee_{prod} as a function of conversion, for a set of fixed *s* values, gives curves which can be found in refs 1, 2, and 4. For convenience the *s* factor is taken as >1.

(1) Kagan, H. B.; Fiaud, J. C. Kinetic Resolution. In *Topics in Stereochemistry*; Eliel, E. L., Wilen, S. H., Eds.; John Wiley & Sons: New York, 1988; Vol. 18, pp 249−330.
(2) Sih, C. J.; Wu, S. H. Resolution of Enantiomers via Biocatalysis. In *Topics in Stereochemistry*; Eliel, E. L., Wilen, S. H., Eds.; John Wiley & Sons: New York, 1989; Vol. 19, pp 63−125.
(3) It is interesting to draw a parallel between enantioselective synthesis and KR. In both processes the desired selectivity may be expressed by a rate ratio (k_{rel}). If the $\Delta\Delta G_{298}^{\ddagger}$ of the two competing transition states is 2.72 kcal mol⁻¹ ($k_{rel} = 99$), then in both cases the product may have the satisfactory value of $ee_{prod} = 98\%$. In an enantioselective synthesis this value will stay constant during the whole course of the reaction, while in a KR it is achieved only at low conversion then it progressively decreases, simultaneously the ee of the reisolated starting material (ee_{sm}) increases. The higher k_{rel} is, the higher is the increase of ee_{sm} with conversion.
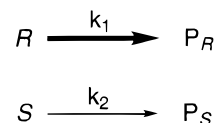
Figure 1. Kinetic resolution of a racemate to give a chiral product ($k_1 > k_2$); when an achiral product P is formed, hence P = P_R = P_S.

With $k_1 > k_2$ in eq 1, ee_{sm} refers to an excess of (*S*)-enantiomer of residual substrate, whereas with eq 2 ee_{prod} refers to the enantiomeric excess of the product derived from the (*R*)-enantiomer. In other words we arbitrarily label the fast-reacting enantiomer as (*R*), while the (*S*)-enantiomer is the slow-reacting species.

Equations 1 and 2 apply only to cases where the reaction is first order with respect to substrate and any order with respect to the co-reactants or catalysts.[1] The case where the reaction is second order with respect to substrate is discussed in the section on kinetic treatment.

Kinetic resolution can also lead to chiral products with an additional chiral unit (e.g., reduction of a racemic ketone) and/or products derived from functionalization at various sites in the molecule (e.g., the Baeyer−Villiger oxidation of a racemic ketone to give a mixture of two isomeric lactones). This complex situation has been discussed.[5] The stereoselectivity factor *s* can still be obtained using eq 1 but cannot easily be extracted from eq 2 since ee_{prod} is not definable due to the multiple chiral products.

In *asymmetric synthesis* the chiral auxiliary (connected to the reagent or catalyst) is sometimes only partially resolved (with $ee_{aux} < 1$), affording a reaction product with ee_{prod} lower than the ee of the product (ee_{max}) obtained with the enantiopure chiral auxiliary. The usual assumption of proportionality between ee_{prod} and ee_{aux} allows the calculation of the maximum value (ee_{max}) of the enantiomeric excess of the product.[6]

The linear correlation between ee_{prod} and ee_{aux} may not, however, always be assumed. Nonlinear behavior was discov-

(4) Martin, V. S.; Woodard, S. S.; Katsuki, T.; Yamada, Y.; Ikeda, M.; Sharpless, K. B. *J. Am. Chem. Soc.* **1981,** *103,* 6237−6240.
(5) (a) El Baba, S.; Poulin, J. C.; Kagan, H. B. *Tetrahedron* **1984,** *40,* 4275−4284. (b) Kagan, H. B. *Croat. Chem. Acta* **1996,** *69,* 669−680.
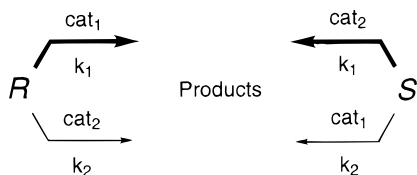(6) Calculation uses the following equation: $ee_{prod} = ee_{max}ee_{aux}$.

Figure 2. Kinetic resolution of a racemate under the influence of a chiral catalyst to give a chiral product ($k_1 > k_2$). Cat$_1$ and cat$_2$ represent the two enantiomers of the catalyst.

ered by us in 1986 in various asymmetric catalytic reactions.[7] The nonlinear effects (NLEs) were defined as positive or negative when giving rise to amplification or depletion of ee with respect to linearity. Many examples of NLEs have subsequently been found.[8] We have proposed some models to account for this behavior,[11] and extended mechanistic investigations have been carried out by Noyori et al. in the catalytic addition of diethylzinc to benzaldehyde.[12] NLEs find their roots in the formation of diastereomeric species in situ, both active or inactive as catalysts, when one shifts from the use of enantiomerically pure chiral auxiliaries to partially enantiomerically enriched ones. Consequently, one can also expect to find some unusual features of *enantioimpure* chiral catalysts or reagents in *kinetic resolution*. In this article we describe the expected behavior of the rate constant ratio when the chiral auxiliary is a mixture of enantiomers,[13] as well as experimental results showing, in some cases, a deviation from this normal behavior.

Competitive Reactions Involved with Enantioimpure Catalysts. In Figure 2 the set of the four competitive reactions involving the enantiomeric catalysts cat$_1$ and cat$_2$ are indicated. k_1 and k_2 stand for pseudo-first-order rate constants while cat$_1$ and cat$_2$ refer to the total and fixed concentrations of the two enantiomeric catalysts. We shall label cat$_1$ the catalyst giving a reaction faster on the (R)-substrate than on the (S)-substrate, as a consequence $k_1 > k_2$ (hence $k_1/k_2 > 1$). Due to mirror symmetry, the reaction with the catalyst cat$_2$ will be faster on the (S)-enantiomer (rate constant k_1) than on the (R)-enantiomer (rate constant k_2). The same stereoselectivity factor will operate, but in favor of the (S)-enantiomer. In conclusion, when the catalyst in a KR is a mixture of enantiomers, the four reactions involve *only two rate contants* (k_1 and k_2). The intrinsic stereoselectivity factor $k_{rel} = k_1/k_2 = s$ is the basic parameter for discussing KR, whatever the ee is of the catalyst. We shall see below how corrections for the ee of the catalyst (ee$_{aux}$) may be done.

(7) Puchot, C.; Samuel, O.; Duñach, E.; Zhao, S.; Agami, C.; Kagan, H. B. *J. Am. Chem. Soc.* **1986**, *108*, 2353−2357.

(8) For some reviews on NLE in catalysis see refs 9 and 10.

(9) Avalos, M.; Babiano, R.; Cintas, P.; Jimenez, J. L.; Palacios, J. C. *Tetrahedron: Asymmetry* **1997**, *8*, 2997−3017.

(10) Girard, C.; Kagan, H. B. *Angew. Chem.* **1998**, *110*, 3088−3127. Girard, C.; Kagan, H. B. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2922−2959.

(11) Guillaneux, D.; Zhao, S. H.; Samuel, O.; Rainford, D.; Kagan, H. B. *J. Am. Chem. Soc.* **1994**, *116*, 9430−9439.

(12) (a) Kitamura, M.; Okada, S.; Noyori, R. *J. Am. Chem. Soc.* **1989**, *111*, 4028−4036. (b) Yamakawa, M.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 6327−6335. (c) Kitamura, M.; Suga, S.; Oka, H.; Noyori, R. *J. Am. Chem. Soc.* **1998**, *120*, 9800−9809.

(13) To our knowledge, the first discussion of the effect of the enantiomeric purity of a chiral catalyst on KR is in the review of Micheau et al. on the various ways to amplify small enantiomeric excesses, and where some calculations were briefly mentioned (pseudo-first-order reactions).[14] After the completion of our work Ismagilov published a mathematical description of KRs when catalyst and substrate are enantiomerically impure.[15] Our approach, mainly devoted to catalytic reactions on racemic substrates, is different from refs 14 and 15, since its aim is to discuss deviations with respect to the predictions given by a classical kinetic treatment.

Kinetic Treatment

Two cases will be considered. The first includes reactions involving *chiral catalysts* that are either first order or nth order ($n \neq 1$) with respect to racemic substrates and chiral catalysts (these two cases will be considered separately). The second includes kinetic resolutions using *chiral reagents*.

In the following discussion only kinetic resolutions with *substrate recovery* are considered.

Catalytic Reaction. When a mixture of enantiomeric catalysts cat$_1$ and cat$_2$ (assumed to be fully independent from each other) reacts with a racemic mixture, the following two equations can be written, by considering the four competitive reactions in Figure 2. These equations give the rate of consumption of substrate, assuming a kinetic law where the reaction is of nth order with respect to catalyst, of pth order with respect to racemic substrate, and of qth order with respect to reagent (not indicated in Figure 2).

$$-\frac{d[R]}{dt} = k_1[\text{cat}_1]^n[R]^p[\text{reagent}]^q + k_2[\text{cat}_2]^n[R]^p[\text{reagent}]^q$$

$$-\frac{d[S]}{dt} = k_2[\text{cat}_1]^n[S]^p[\text{reagent}]^q + k_1[\text{cat}_2]^n[S]^p[\text{reagent}]^q$$

The ratio of rates simplifies greatly since the concentrations of achiral reactants (here reagent) cancel out. The equations obtained below apply to reactions of any order with respect to the reagent.

$$\left(-\frac{d[R]}{dt}\right)\bigg/\left(-\frac{d[S]}{dt}\right) = \left(\frac{k_1[\text{cat}_1]^n + k_2[\text{cat}_2]^n}{k_2[\text{cat}_1]^n + k_1[\text{cat}_2]^n}\right)\left(\frac{[R]}{[S]}\right)^p \quad (3)$$

Let us define as s' the first fraction of the above relationship:

$$s' = \frac{k_1[\text{cat}_1]^n + k_2[\text{cat}_2]^n}{k_2[\text{cat}_1]^n + k_1[\text{cat}_2]^n} \quad (4)$$

The quantity s' is a constant since k_1, k_2, cat$_1$, and cat$_2$ are constant during the course of the reaction, provided the catalyst is not modified by the products.[16] We propose to define s' as the *apparent stereoselectivity factor* of a KR, while $s = k_1/k_2$ is the *intrinsic stereoselectivity factor*.

The apparent stereoselectivity factor s' is a function of s and also depends on the ee of catalyst [(ee$_{aux}$ = (cat$_1$ − cat$_2$)/(cat$_1$ + cat$_2$)]. When the catalyst is enantiopure (cat$_2$ = 0), then s' becomes equal to s.

The apparent stereoselectivity factor can be expressed as a function of ee$_{aux}$ and s (eq 5), reciprocally s can be expressed as a function of s' (eq 6), as explained in the Supporting Information.

$$s' = \frac{s(1 + \text{ee}_{aux})^n + (1 - \text{ee}_{aux})^n}{(1 + \text{ee}_{aux})^n + s(1 - \text{ee}_{aux})^n} \quad (5)$$

$$s = \frac{s'(1 + \text{ee}_{aux})^n - (1 - \text{ee}_{aux})^n}{(1 + \text{ee}_{aux})^n - s'(1 - \text{ee}_{aux})^n} \quad (6)$$

Using the definition of s' (eq 6) we can rewrite eq 3 as eq 7

(14) de Min, M.; Levy, G.; Micheau, J. C. *J. Chim. Phys.* **1988**, *85*, 607−608.

(15) Ismagilov, R. F. *J. Org. Chem.* **1998**, *63*, 3772−3774.

(16) Alberts, A. H.; Wynberg, H. *J. Am. Chem. Soc.* **1989**, *111*, 7265−7266.

$$\left(-\frac{d[R]}{dt}\right)\Big/\left(-\frac{d[S]}{dt}\right) = s'\left(\frac{[R]}{[S]}\right)^{p} \tag{7}$$

Integration of eq 7 is easy (see Supporting Information). Only two cases need to be considered: $p = 1$ or $p \neq 1$. This integration allows the elimination of time as a parameter and it gives a relationship between the enantiomers (R) and (S). To simplify the results one can use the enantiomeric excess of recovered starting material (ee$_{sm}$), defined as $(S - R)/(S + R)$, since we assume (vide supra) that the (S)-enantiomer is the slower-reacting species. We also considered the conversion c as another useful parameter ($c \leq 1$).

(i) The reaction is first order with respect to substrate: Integration of eq 7 where s' is a constant (for a fixed value of ee$_{aux}$) gives eq 8

$$s' = \frac{\ln[(1 - c)(1 - ee_{sm})]}{\ln[(1 - c)(1 + ee_{sm})]} \tag{8}$$

(ii) The reaction is any order ($p \neq 1$) with respect to substrate: Integration of eq 7 where s' is constant (for a fixed value of ee$_{aux}$) and $p \neq 1$ gives eq 9

$$s' = \frac{(1 - c)^{1-p}(1 - ee_{sm})^{1-p} - 1}{(1 - c)^{1-p}(1 + ee_{sm})^{1-p} - 1} \tag{9}$$

Discussion. The combined use of eq 5 (which depends only on the order with respect to catalyst) and eq 8 or 9 (according to the order with respect to substrate) allows us to discuss all the possible situations arising in kinetic resolution. Apparent stereoselectivity factor s' (for a given ee$_{aux}$) can be determined by measuring ee$_{sm}$ and the conversion c in a KR experiment. This determination uses eq 8 or 9. Then eq 6 will allow the calculation of the intrinsic stereoselectivity factor s. It is interesting to point out that all the above results are independent of the order with respect to an achiral reagent. The variation of s' as a function of the ee of catalyst is independent of the order with respect to substrate but depends on the order with respect to the catalyst (eq 5). Equations 8 and 9 are independent of reaction order with respect to the catalyst and allow experimental determination of s for a given ee$_{aux}$.

The relationships for $s = f(ee_{sm},c,ee_{aux})$ in the case of reactions of first order with respect to substrate and to catalyst, first order with respect to substrate and second order with respect to catalyst, second order with respect to substrate and first order with respect to catalyst, and second order with respect to substrate and catalyst are given by eqs 12–15, respectively (Supporting Information). These relationships were obtained by elimination of s' between eq 5 and eq 8 or 9, leaving the general eqs 10 and 11 (Supporting Information) for reactions of first order and second order with respect to substrate, respectively. The introduction, in eqs 10 and 11 of the proper values of order n with respect to catalyst allows us to obtain eqs 12–15. It is then possible to draw the curves ee$_{sm}$ = $f(c,s,ee_{aux})$ for all the desired situations. Some examples are given below.

Graphical Representation. Figures 3 and 4 show the variation of ee$_{sm}$ as a function of conversion for reactions of first and second order with respect to substrate, respectively (by fixing $s = 10$ in both cases and giving several values of ee$_{aux}$). In these two cases we considered reactions of first order with respect to catalyst ($n = 1$ in eq 5). As usual in a KR the enantiomeric excess of the recovered starting material increases continuously with conversion for a given ee of the auxiliary. The effect of ee$_{aux}$ is also easily seen.[17]
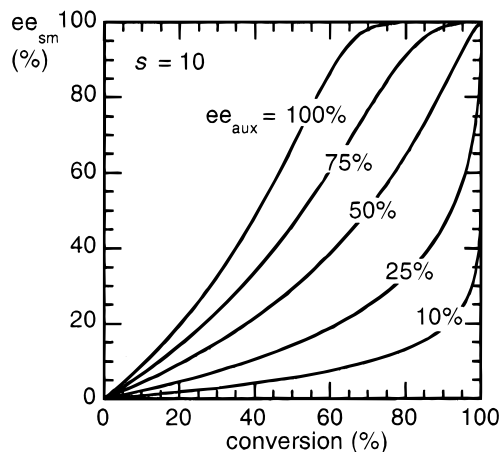

Figure 3. Variation of ee$_{sm}$ with conversion c for reaction first order with respect to substrate and to catalyst. Curves are calculated with $s = 10$ for different ee$_{aux}$ values (using eq 12, see Supporting Information).
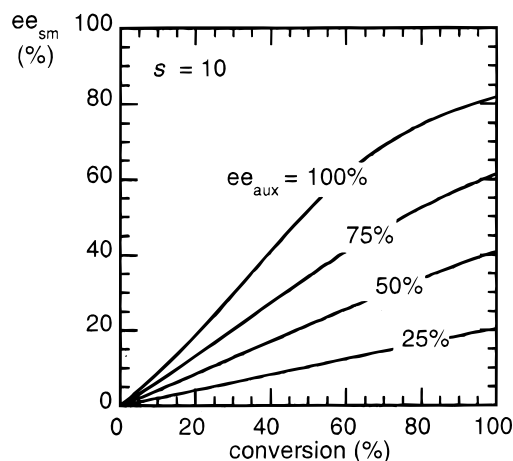

Figure 4. Variation of ee$_{sm}$ with conversion, for reaction of second order with respect to substrate and first order with respect to catalyst. Curves are plotted with $s = 10$ for different ee$_{aux}$ values (using eq 14, see Supporting Information).

Comparison of the curves in Figures 3 and 4 shows an interesting feature. In Figure 3 (first order with respect to substrate) the recovered substrate tends to be close to 100% ee for high conversions (whatever the value of ee$_{aux}$), while in Figure 4 (second order with respect to substrate) ee$_{sm}$ tends toward a limit ee$_{sm}$ = $(s - 1)/(s + 1)$ for the enantiopure catalyst, as calculated from eq 14. Calculations show that the value of ee$_{sm}$ for the final point is proportional to ee$_{aux}$. The lower efficiency of KR (with enantiopure catalysts) of reactions which are second order with respect to substrate in comparison to first order has already been noticed,[18] and can be seen by a comparison of the curves in Figures 3 and 4.

The curves in Figures 3 and 4 ($s = 10$) are modified if one moves from first order to second order with respect to catalyst ($n = 2$), which can be found in the Supporting Information.

Another useful analysis of the influence of the ee$_{aux}$ on the efficiency of a KR is to plot the apparent stereoselectivity factor s' as a function of ee$_{aux}$ by using eq 5. In Figure 5 cases of reactions which are first order with respect to catalyst and any order with respect to substrate are given for an intrinsic stereoselectivity factor $s = 10$.

(17) Equation 5 when $n = 1$ and some curves derived from it were briefly mentioned by Micheau et al.[14]

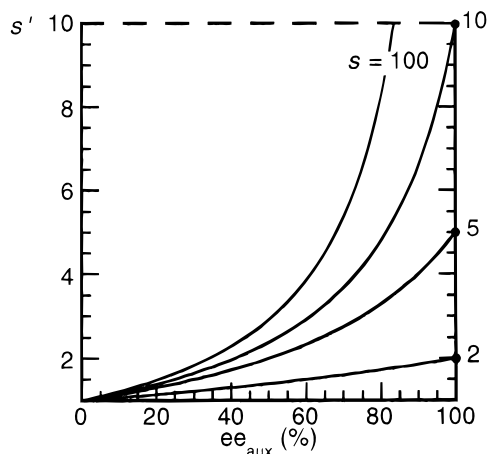(18) Sepulchre, M.; Spassky, N.; Sigwalt, P. *Isr. J. Chem.* **1976–77**, *15*, 33–38.

Figure 5. The dependence of the apparent stereoselectivity s' on ee_{aux} with fixed s values of 100, 10, 5, and 2. The curves were calculated using eq 5, for any order with respect to substrate and for first order with respect to catalyst (eq 5, $n = 1$).

To determine the intrinsic stereoselectivity factor ($s = k_1/k_2$), which is the key parameter in the set of reactions described in Figure 2, one may proceed via either calculation (eq 6, using the proper value of order n together with a number of s' and ee_{aux} values) or by comparing the computed curves of Figure 5 (defined by s, with the measured s' and ee_{aux} values). Formulas for s as a function of ee_{sm}, ee_{aux}, and c for all the combinations of first order and/or second order with respect to substrate and/or catalyst are given by eqs 11−15 in the Supporting Information.

The apparent stereoselectivity factor s' defined by eq 5 is not linearly correlated to enantiomeric excess of the chiral auxiliary (ee_{aux}).

In the Supporting Information are also reported calculations and equations for asymmetric catalysis obtained if the enantiomeric excess of the product is considered (ee_{prod}) instead of ee_{sm} or if the initial substrate is not racemic ($ee_o \neq 0$).

Chiral Reagents. We shall consider here only reactions which are first order with respect to both racemic substrate and a stoichiometric chiral reagent. This situation is described by the set of four competitive reactions in Figure 6.

The relative rate ratio of the overall reaction on the (R)- and (S)-enantiomers is equal to:

$$\frac{-\dfrac{d[R]}{dt}}{-\dfrac{d[S]}{dt}} = \frac{[R][k_1 Z^* + k_2 \bar{Z}^*]}{[S][k_2 Z^* + k_1 \bar{Z}^*]}$$

which gives:

$$\frac{-\dfrac{d[R]}{dt}}{-\dfrac{d[S]}{dt}} = \frac{s Z^* + \bar{Z}^*}{Z^* + s \bar{Z}^*} \frac{[R]}{[S]} = s' \frac{[R]}{[S]}$$

The apparent stereoselectivity factor s' is defined by an equation similar to eq 4 ($n = 1$) where the two enantiomers of the reagent are involved rather than the two enantiomers of the catalyst. Consequently s' is no longer a constant since the concentration of the chiral reagent will vary with conversion. One cannot apply calculations similar to those used in catalysis. To determine the enantiomeric excess of the substrate (as well as those of the chiral reagent) it is necessary to solve the following four
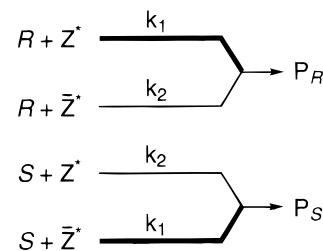

Figure 6. Kinetic resolution of a racemic mixture under the influence of a stoichiometric chiral reagent ($k_1 > k_2$). Z* and $\bar{Z}$* stand for chiral reagents of opposite configuration.
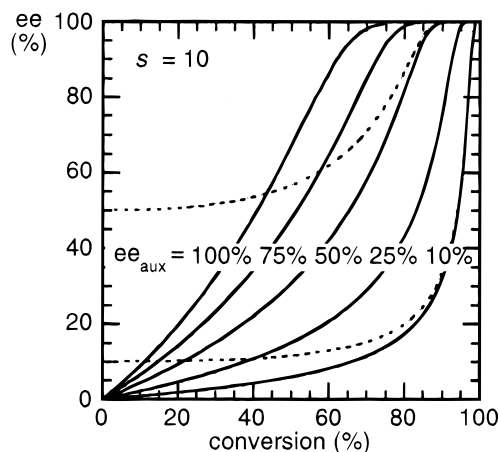

Figure 7. Enantiomeric excess of reisolated substrate (ee_{sm}) in KR with chiral reagent and $s = 10$. Initial conditions: equimolar amounts of racemic substrate and chiral reagent with initial ee_{aux} varying from 100% to 10%. The curves were calculated by using the Runge−Kutta approximation (see text). Ee_{sm}: solid curves; $ee_{reagent}$ (initially of 50% ee and 10% ee): dashed curves.

differential equations:

$$-\frac{d[R]}{dt} = k_1[R][Z^*] \qquad -\frac{d[R]}{dt} = k_2[R][\bar{Z}^*]$$

$$-\frac{d[S]}{dt} = k_2[S][Z^*] \qquad -\frac{d[S]}{dt} = k_1[S][\bar{Z}^*]$$

This problem has been studied by Ugi et al. by computation using the Runge−Kutta approximation.[19] These authors, in a pioneering study, analyzed the case of a racemic mixture in the presence of 1 equiv of a chiral reagent (ee_{aux}).

We reinvestigated this situation with the aim of comparing the influence of ee_{aux} on ee_{sm} in various cases of KR by using the same format of curves. Figure 7 shows curves for a reaction that is first order with respect to the racemic substrate for several values of ee_{aux} of the chiral reagent. The ee of reagent and the ee of recovered substrate both increase during the reaction. This is an example of mutual kinetic resolution.[1] At 60% conversion, for example, the substrate (initially racemic in composition) has reached 37% ee and the reagent (initially of 50% ee) has increased its ee to 58%. At 90% conversion both remaining substrate and reagent are of very high ee (close to 99%).

When the ee of the initial chiral reagent approaches 100%, then the classical case of KR, first order with respect to racemic substrate and any order with respect to the reagent or catalyst (giving eq 1), is reached.

In the Supporting Information is shown a comparison of two KRs of a racemic mixture ($s = 10$), run with a chiral reagent

(19) Brandt, J.; Jochum, C.; Ugi, I. *Tetrahedron* **1977**, *33*, 1353−1363.
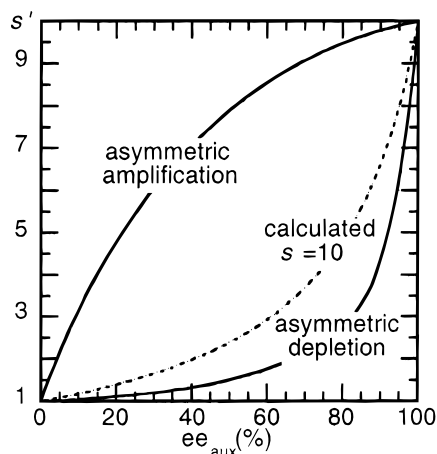
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Figure 8. Asymmetric amplification and depletion of the apparent stereoselectivity factor s' in kinetic resolution. Dashed curve: calculated for reactions first order with respect to catalyst (eq 5, $n = 1$) with $s = 10$.

Figure 9. Variation of s' with ee_{binol} in the kinetic resolution of the racemic sulfoxide **1b** (solid curve)[22] and the calculated behavior (dashed curve) for a system with "normal" behavior (eq 5, $n = 1$, $s = 2.5$). Kinetic resolution of **1a** (Figure 10A) (solid curve) and the calculated "normal" behavior (dashed curve) (eq 5, $n = 1$, $s = 2.8$), $ee_{aux} = ee_{DET}$.

(initially of 50% ee) or with a chiral catalyst (of 50% ee). In both cases the reaction is first order with respect to the substrate, to the reagent, and to the catalyst. At a given conversion (for example 80%), the ee of the reisolated substrate ($ee_{sm} = 90\%$) is significantly higher using a chiral reagent than for the reaction with a chiral catalyst ($ee_{sm} = 70\%$). This reflects the fact that the chiral reagent continuously improves its ee by mutual kinetic resolution (vide supra), compared to the chiral catalyst that maintains a constant enantiomeric excess during the whole course of the reaction.

Abnormal Behavior in Kinetic Resolution

If the chiral auxiliary is affected by diastereomeric associations in the reactive and/or unreactive species (catalyst or reagent in large excess) the previous calculations will necessarily be perturbed by the introduction of a new reactive species or by modification of the initial ee_{aux}. The deviation of the observed $ee_{sm} = f(\text{conversion}, ee_{aux})$ or of the observed apparent rate ratio s' from the expected curves may reflect an improved or a poorer kinetic resolution. We propose to characterize these two types of behavior by the expressions "asymmetric amplification" and "asymmetric depletion". For example, let us consider the KR in Figure 3. Using our knowledge of KR with enantiopure catalyst (showing $s = 10$), the curve for $ee_{aux} = 50\%$ has been computed. If the experimental curve for $ee_{aux} = 50\%$ is above the expected curve it will reflect an asymmetric amplification, since the actual KR is improved. An experimental curve below the computed one will indicate an asymmetric depletion. The same definitions apply to the apparent stereoselectivity factor. Figure 8 shows the calculated curve of $s' = f(ee_{aux})$ when $s = 10$ (reaction first order with respect to both sustrate and catalyst), with some curves of asymmetric amplification or asymmetric depletion. The roots of the phenomenon are the same as those of nonlinear effects in aymmetric synthesis,[9,10] but because of the shapes of the theoretical curves, one can no longer use the expression nonlinear effect for a departure from the normal behavior.

There are few examples in the literature of data for KRs performed with a partially resolved chiral auxiliary. The first case can be traced to early reports of mutual kinetic resolution[1] where one of the reactants was used as a racemic mixture. This situation was accidentally studied by Horeau et al. in 1974 in his method for the assignment of the absolute configuration of alcohols by the kinetic resolution of α-phenylbutyric anhy-
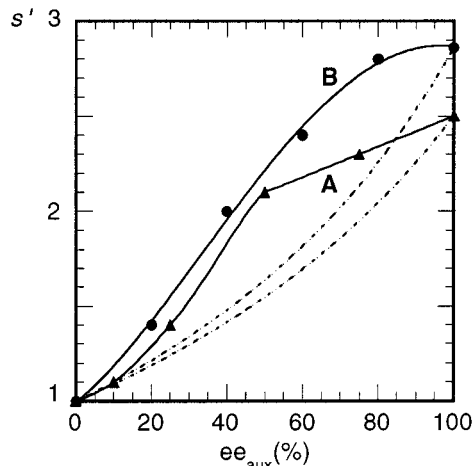
dride.[20] Occasionally the alcohols were the products of asymmetric synthesis and were partially enantiomerically enriched. From the data given in various papers[20,21] one may conclude normal behavior for KR following the Horeau method.

A more recent report is the investigation by Uemura et al. in 1993.[22] These authors studied the asymmetric oxidation of racemic sulfoxides catalyzed by a chiral titanium−binaphthol complex (100% ee). A stereoselectivity factor $s = 2.5$ was measured in the kinetic resolution of racemic methyl p-tolyl sulfoxide **1b**. Kinetic resolution with 1,1′-binaphthol of decreasing ee gave a decrease in the apparent rate ratio s'. The authors correctly described the results as an asymmetric amplification, but seem to refer to the normal situation as a linear one. In Figure 9, for curve A we have drawn the actual normal behavior using eq 5 ($n = 1$) with $s = 2.5$. The amplification is indeed better than believed by the authors.

We have studied the KR of racemic methyl phenyl sulfoxide **1a** in the presence of a titanium reagent (1 equiv) based upon a combination of Ti(O*i*-Pr)$_4$/(*R,R*)-diethyl tartrate (DET)/*i*-PrOH (1:4:4) that we have recently described (Figure 10A).[23] The stereoselectivity factor s is 2.8 (measured for $ee_{DET} = 100\%$). The hyperbolic curve computed from eq 5 is below the experimental curve, showing a strong asymmetric amplification in this kinetic resolution (Figure 9, curve B).

We have also investigated the KR of a reaction known to give rise to asymmetric amplification in enantioselective syntheses. We studied the KR of racemic 2-phenylpropanal **3** by addition of Et$_2$Zn catalyzed by (*R*)-(−)-3,3-dimethyl-1-piperidinobutan-2-ol (PDB) as described by Oguni et al.[24] (Figure 10B). The experimental results (Figure 11) clearly show an asymmetric amplification in the KR of **3** with a measured s of 4.5 in this case.

To support the calculations leading to eq 5 we investigated one case of KR where the chiral catalyst was known not to give rise to nonlinear effects in enantioselective reactions. Hence

(20) Horeau, A. In *Stereochemistry Fundamentals and Methods*; Kagan, H. B., Ed.; Thieme Verlag: Stuttgart, 1977; Vol. 3, pp 51−94.

(21) Horeau, A. *Bull. Soc. Chim. Fr.* **1967**, 117−124.

(22) Komatsu, N.; Hashizume, M.; Sugita, T.; Uemura, S. *J. Org. Chem.* **1993**, *58*, 7624−7626.

(23) Brunel, J. M.; Luukas, T. O.; Kagan, H. B. *Tetrahedron: Asymmetry* **1998**, *9*, 1941−1946.

(24) Hayashi, M.; Miwata, H.; Oguni, N. *J. Chem. Soc., Perkin Trans. 1* **1991**, 1167−1171.
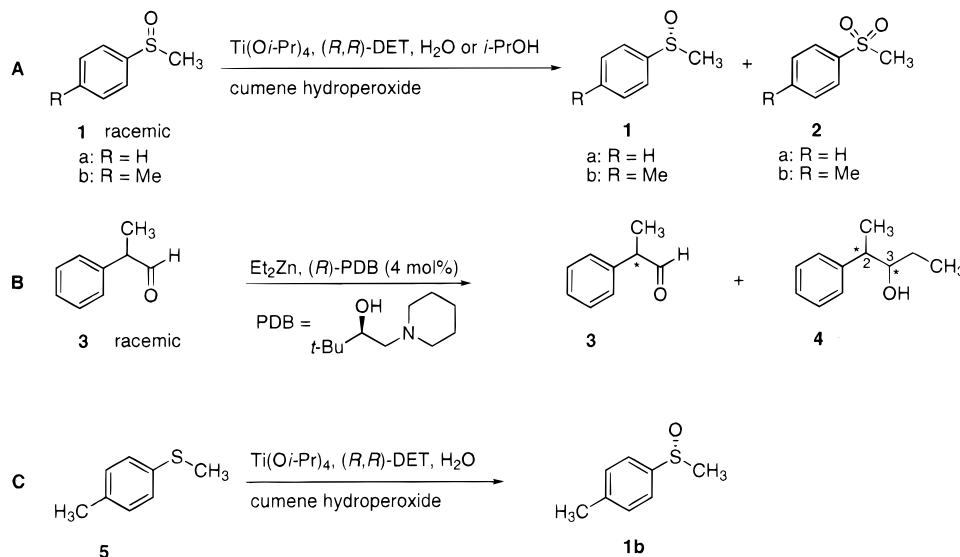
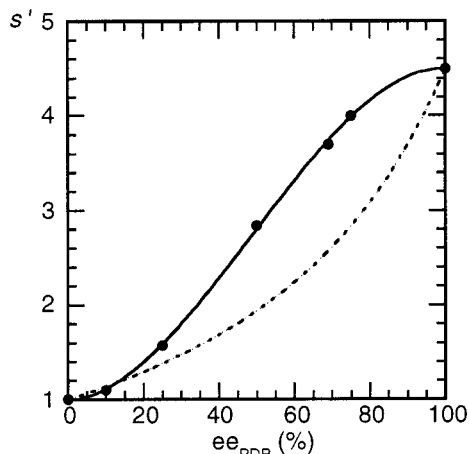**Figure 10.** Examples of kinetic resolution.

Figure 11. Kinetic resolution of racemic 2-phenylpropanal (**3**) with PDB (Figure 10B): experimental values (●, solid curve); reference curve (dashed) calculated using eq 5 ($n = 1$).
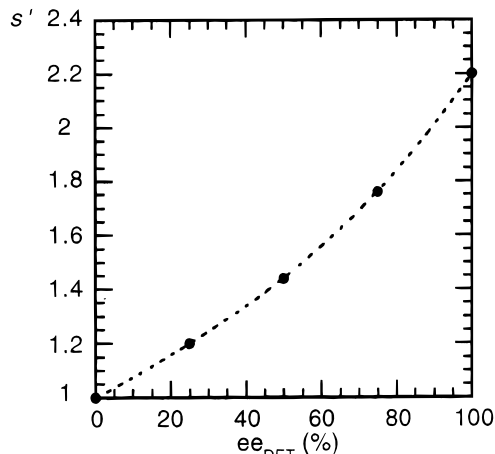

Figure 12. Kinetic resolution of racemic sulfoxide **1b** (Figure 10A) displaying an absence of asymmetric amplification or asymmetric depletion (see text): experimental values (●); reference curve (dashed) calculated using eq 5, $n = 1$ with $s = 2.2$.

in a KR it should also provide no departure from the normal hyperbolic behavior.

For this purpose, we studied the asymmetric oxidation of methyl *p*-tolyl sulfide into sulfoxide **1b** (Figure 10C) using cumene hydroperoxide (CHP) in the presence of 1 equiv of the combination Ti(O*i*-Pr)$_4$/(*R,R*)-diethyl tartrate (DET)/H$_2$O (1:2:1) prepared under well-defined conditions.[25] We first repeated this experiment and demonstrated again the perfect linearity between the ee of the product sulfoxide **1b** and ee of the catalyst (data in the Experimental Section). Using the same conditions the KR of racemic sulfoxide **1b** was then investigated. The stereoselectivity factor has a value of 2.2. The variation of the apparent stereoselectivity factor s' coincides well with the curve calculated for normal behavior (Figure 12). This is good confirmation of the validity of eq 5 in describing normal behavior for KRs which are first order with respect to catalyst.

Conclusion

The normal behavior of a chiral catalyst (when enantiomerically impure) in the kinetic resolution of a racemic mixture has been discussed, and the main kinetic equations defined, covering

most of the cases concerning reaction orders with respect to substrate and catalyst. The most convenient parameters to handle in the equations are the enantiomeric excesses of the recovered starting material (ee$_{sm}$) and the catalyst (ee$_{aux}$), the conversion (*c*), and the intrinsic stereoselectivity factor $s = k_{rel}$.[26] The apparent stereoselectivity factor s' is a useful piece of information when discussing KRs, since it has been mathematically related to ee$_{aux}$ and s, and it is easily available from experiments using eq 8 or eq 9. Using the set of equations and curves established for the various important kinetic scenari (orders with respect to subtrate and catalyst) one can calculate the intrinsic stereoselectivity factor s when the enantiopure catalyst is not available.

The differences between KRs involving a chiral catalyst or a chiral reagent have been outlined. When diastereomeric species can be generated inside or outside the catalytic cycle one may suspect some deviations from the expected curve relating apparent stereoselectivity factor s' and ee$_{aux}$. Asymmetric amplification or asymmetric depletion may be found as for

(25) Diter, P.; Duetsch, M.; Kagan, H. B. *J. Org. Chem.* **1995**, *60*, 8086–8088.

(26) The general formulas when the initial starting material is already enantioenriched (ee$_o \neq 0$) and/or when one considers the enantiomeric excess of the product (ee$_{prod}$) instead of ee$_{sm}$ are given in the Supporting Information.

Enantioimpure Chiral Auxiliaries

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nonlinear effects in asymmetric catalysis.[27,29] A modeling of the abnormal behavior in KR (asymmetric amplification or depletion) has been performed and will be reported soon.[31] Kinetic resolution has been carried out on two types of reactions (oxidation of racemic sulfoxides and diethylzinc addition on hydratropaldehyde). We found evidence for both abnormal behavior (asymmetric amplification) and normal behavior, according to the nature of the catalyst. Kinetic resolution itself is a way to amplify chirality by means of a partial conversion of a racemic mixture. It is interesting to note that superimposition of an asymmetric amplification in a KR leads to an overall double amplification of chirality.[32]

Experimental Section

The curves in the various schemes were computed by Mathematica and Excel and graphics were obtained using Kaleida Graph. All the reactions were performed under an argon atmosphere using standard Schlenk techniques. The Schlenks and stirring bars were oven dried.

Measurements of ee's were made by HPLC analyzed on a Spectroseries P100 pump module with a Spectroseries UV100 detector and a Daicel Chiralcel OD-H column. Measurements of ee's by chiral GC were made on a Fisons GC9000 series gas chromatography with an ASTEC B-PM (β-cyclodextrin, permethylated) 50 m column. Determinations for conversions were made on a Fisons GC8000 series gas chromatograph with a J&W Scientific DB-1 30 m column. Column chromatography was performed using silica gel 60 Å (35−70 μm) purchased from SDS.

Chemicals. Dichloromethane was distilled from calcium hydride. Diethyl tartrate and titanium tetraisopropoxide were distilled using a Vigreux column before use. The commercially available cumene hydroperoxide (80% in cumene alcohol) was purchased from Aldrich and used without purification. The active free peroxide was determined by iodometric titration. Racemic sulfoxides were prepared as described by Ali et al.[33] The synthesis of (−)-PDB has been previously described by Oguni et al.[24] Hexane was distilled from sodium benzophenone ketyl under argon. Diethylzinc and 2-phenylpropanal were purchased from Fluka and the latter was distilled before use.

Kinetic Resolution of Sulfoxide 1a. Ti(O-*i*Pr)$_4$ (0.20 mL, 0.71 mmol) was added dropwise to a stirred solution of (*R,R*)-DET (0.49 mL, 2.85 mmol) in 8 mL of CH$_2$Cl$_2$ at 20 °C. The resulting solution was stirred for 20 min then 2-propanol (0.22 mL, 2.85 mmol) was added dropwise over 30 s. After being stirred for an additional 20 min a solution of sulfoxide **1a** (100 mg, 0.7 mmol) in 2 mL of CH$_2$Cl$_2$ was added in one portion. On completion of the addition stirring was stopped and the reaction cooled to −24 °C. After 20 min CHP, precooled to −24 °C (0.13 mL, 0.86 mmol), was added. The reaction was quenched after 16−20 h by pouring into a solution of ferrous sulfate heptahydrate (1 g, 5.4 mmol) and citric acid (330 mg, 1.6 mmol) in water (15 mL). Ether (20 mL) and 1,4-dioxane (7 mL) were added and the resulting biphasic mixture was vigorously stirred for 15 min. The phases were separated and the aqueous phase washed with ether (3 × 15 mL). The

organic phases were combined and vigorously stirred with NaOH (15 mL, 2 M) solution for 1 h. After separation of the phases the aqueous phase was washed with ether (3 × 15 mL). The organic extracts were combined, dried (MgSO$_4$), and evaporated to dryness to give the crude product. The crude product was purified by column chromatography (eluent: ethyl acetate) to give enantiomerically enriched sulfoxide **1a**. The sulfoxide was analyzed by HPLC on a Chiralcel OD-H column (eluent: hexane:2-propanol (98:2); flow rate: 0.5 mL/min; λ: 254 nm; R_t-(*R*): 28.2 min; R_t-(*S*): 38.2 min).

Kinetic Resolution of Sulfoxide 1b. Ti(O-*i*Pr)$_4$ (0.41 mL, 1.5 mmol) was added dropwise to a stirred solution of (*R,R*)-DET (0.5 mL, 3.0 mmol) in 5 mL of CH$_2$Cl$_2$ at 20 °C. The resulting solution was stirred for 20 min then water (27 μL, 1.5 mmol) was added dropwise over 45 s. After being stirred for an additional 20 min stirring was stopped and the reaction cooled to −24 °C. After 20 min a solution of sulfoxide **1b** (230 mg, 1.5 mmol) in 1 mL of CH$_2$Cl$_2$ and CHP, precooled to −24 °C (0.44 mL, 3.0 mmol), were added. The reaction was quenched after 16−48 h by pouring into a solution of ferrous sulfate heptahydrate (1 g, 5.4 mmol) and citric acid (330 mg, 1.6 mmol) in water (15 mL). Ether (15 mL) and 1,4-dioxane (7 mL) were added and the resulting biphasic mixture was vigorously stirred for 15 min. The phases were separated and the aqueous phase washed with ether (3 × 15 mL). The organic phases were combined and vigorously stirred with NaOH (15 mL, 2 M) solution for 1 h. After separation of the phases the aqueous phase was washed with ether (3 × 15 mL). The organic extracts were combined, dried (MgSO$_4$), and evaporated to dryness to give the crude product. The crude product was purified by column chromatography (eluent: ethyl acetate) to give enantiomerically enriched sulfoxide **1b**. The sulfoxide was analyzed by HPLC on a Chiracel OD-H column (eluent: hexane:2-propanol (98:2); flow rate: 0.5 mL/min; λ: 254 nm; R_t-(*R*): 28.9 min; R_t-(*S*): 33.9 min).

Catalytic Oxidation of Sulfide 5 (NLE Studies). Ti(O-*i*Pr)$_4$ (0.81 mL, 3.0 mmol) was added dropwise to a stirred solution of (*R,R*)-DET (1.0 mL, 6.0 mmol) in 9 mL of CH$_2$Cl$_2$ at 20 °C. The resulting solution was stirred for 20 min then water (54 μL, 3.0 mmol) was added dropwise over 90 s. After being stirred for an additional 20 min a solution of sulfide **5** (0.4 mL, 3.0 mmol) in 1 mL of CH$_2$Cl$_2$ was added in one portion. On completion of the addition stirring was stopped and the reaction cooled to −24 °C. After 20 min CHP, precooled to −24 °C (0.89 mL, 6.0 mmol), was added. The reaction was quenched after 16−20 h by pouring into a solution of ferrous sulfate heptahydrate (3 g, 10.8 mmol) and citric acid (1 g, 4.8 mmol) in water (30 mL). Ether (20 mL) and 1,4-dioxane (15 mL) were added and the resulting biphasic mixture was vigorously stirred for 15 min. The phases were separated and the aqueous phase washed with ether (3 × 20 mL). The organic phases were combined and vigorously stirred with NaOH (15 mL, 2 M) solution for 1 h. After separation of the phases the aqueous phase was washed with ether (3 × 20 mL). The organic extracts were combined, dried (MgSO$_4$), and evaporated to dryness to give the crude product. The crude product was purified by column chromatography (eluent: ethyl acetate) to give sulfoxide **1b**. The sulfoxide was analyzed as previously described above. (*R,R*)-DET of ee$_{aux}$ = 100%, 75%, 50%, and 25% gave **1b** with ee values of respectively 83.8%, 64.0%, 40.5%, and 22.0%.

Kinetic Resolution of Racemic Aldehyde 3 with (−)-PDB. Naphthalene (100 mg), to act as an internal standard, was added to a stirred solution of (−)-PDB (0.15 mmol) in 15 mL of dry, degassed hexane. The solution was cooled to 0 °C and diethylzinc (8.2 mmol) was added in one portion. The temperature was allowed to rise to 17 °C over 30 min then cooled to −20 °C. Racemic 2-phenylpropanal **3** (7.45 mmol) was added dropwise and stirring was continued for an additional 16−20 h. HCl (20 mL, 1 M) was added and the resulting mixture was extracted with ether (3 × 35 mL). The organic extracts were combined, dried (MgSO$_4$), and evaporated to dryness. The components of the residue were isolated using flash chromatography (eluent 12:1 *n*-hexane:ethyl acetate). The ee values of the diastereomers of 2-phenylpentan-3-ol **4** were determined by GC analysis on a chiral B-PM column (R_t-*anti*: 151 min (2*R*,3*S*), 154 min (2*S*,3*R*); R_t-*syn*: 171 min (2*S*,3*S*), 174 min (2*R*,3*R*); isotherm 100 °C).

The unreacted aldehyde **3** was reduced with an excess of LiAlH$_4$ (28 mg, 0.74 mmol) in diethyl ether (5 mL) to give (*S*)-2-phenylpro-

(27) For definition of indexes of asymmetric amplification in asymmetric catalysis see the discussion in ref 28.

(28) Kagan, H. B.; Fenwick, D. R. Asymmetric Amplification. In *Topics in Stereochemistry*; Denmark, S., Ed.; John Wiley & Sons: New York, 1999; Vol. 22, pp 257−296.

(29) The rate dependency with ee$_{aux}$ has been discussed by D. Blackmond for ML$_n$ models in asymmetric catalysis,[30a] and for kinetic implications of NLEs in asymmetric synthesis.[30b] The same concepts should apply to kinetic resolution.

(30) (a) Blackmond, D. *J. Am. Chem. Soc.* **1997**, *119*, 12934−12939. (b) Blackmond, D. *J. Am. Chem. Soc.* **1998**, *120*, 13349−13353.

(31) Luukas, T. O.; Girard, C.; Fenwick, D.; Kagan H. B. Manuscript in preparation.

(32) For ee$_{aux}$ values <1 the *s*′ or ee$_{sm}$ values can be higher than expected, but never higher than the final value of *s* or ee$_{max}$ (for ee$_{aux}$ = 1). As predicted for (+)-NLEs in asymmetric catalysis (see ref 11), one may envisage *s*′ or ee$_{sm}$ values *higher* than *s* or ee$_{max}$ for ee$_{aux}$ < 1. There are, as yet, no described examples of such situations. We are presently investigating these cases by both modeling and experiment.[31]

(33) Ali, M.; Stevens, W. *Synthesis* **1997**, 764−768.

panol (100 mg, 100%). The ee of (*S*)-2-phenylpropanol was determined by GC analysis on a chiral B-PM column (R_t-(*R*): 119 min; R_t-(*S*): 123 min; isotherm 105 °C).

Due to slight racemization of aldehyde **3** during the workup the stereoselectivity factor was determined more accurately by considering the enantiomeric excess of products (ee$_{prod}$) using eq 2. The two peaks corresponding to the diastereomers generated from (*R*)-**3** are combined. Similarly the two peaks related to the reaction of (*S*)-**3** are combined. The ratio of the above areas (products obtained from (*R*)-**3**/products obtained from (*S*)-**3**) is equal to the enantiomeric ratio, er$_{prod}$, from which ee$_{prod}$ can be calculated.

Supporting Information Available: Detailed calculations for formulas giving the apparent stereoselectivity factor as a function of conversion and ee$_{sm}$ or ee$_{prod}$ with various reaction orders are shown; similar calculations for intrinsic stereoselectivity factor are given; results, for a number of examples, of the application of these formulas are represented graphically; the apparent stereoselectivity factor is plotted as a function of er$_{aux}$; and the script to perform Runge−Kutta approximations with Mathematica (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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