Nonlinear Effects in Asymmetric Catalysis

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Abstract: Seemingly unusual phenomena may occur in asymmetric catalysis involving partially resolved ligands. Deviations from linearity (between the ee of the ligand and the ee of the product) are possible, and various cases are considered using simplified models. The fundamental features are highlighted in models taking into account diastereomeric associations inside (model 1) or outside (model 2) the catalytic cycle. Various cases found experimentally are considered.

Introduction

Asymmetric syntheses are necessarily performed with the help of a chiral auxiliary, which is used in stoichiometric or catalytic amounts, according to the reaction type. Many efficient asymmetric syntheses are now known, with ee's often higher than 90%.[2] Usually the chiral auxiliary is a compound taken or derived from the chiral pool of natural products (e.g., terpenes, amino acids, alkaloids, ...) or is prepared by resolution of a racemic mixture. Whenever possible, the chiral auxiliary is used as enantiomerically pure material, with the intention of maximizing the enantiomeric yield of the asymmetric synthesis. However, in some instances, exploratory experiments are performed with auxiliaries having ee < 100%, since they come from a tedious resolution or are prepared from the enantiomerically impure natural compounds (e.g., certain terpenes). The enantioselectivity of the asymmetric synthesis (EE_{prod}) is usually correlated to the enantiomeric excess of the chiral auxiliary (ee_{aux}) by eq 1.

$$EE_{prod} = EE_0 ee_{aux} \quad (1)$$

In eq 1 EE_0 stands for the enantiomeric excess of the product when using an enantiopure chiral auxiliary.[3]

Equation 1 allows calculation of EE_{prod} (the extrapolated enantiomeric yield), for any enantiomeric excess of the chiral auxiliary. It is based on the hypothesis of a linear correlation between the enantiomeric excess of the product of the asymmetric synthesis and ee_{aux}. In 1986 with Agami's group, we criticized the foundations of this classical hypothesis and described the first three examples of nonlinear correlations in asymmetric synthesis.[4] Since that time, additional examples have appeared in the literature.[5-12] We proposed the expression "nonlinear effect" (abbreviated here as NLE) to define departure from proportionality between the ee of the product and the ee of the chiral auxiliary.[13] In Figure 1 the three possibilities of correlation between EE_{prod} and ee_{aux} are schematized: the linear correlation (straight line 1), the "positive" nonlinear effect (curve 2) and the "negative" nonlinear effect (curve 3), using nomenclature proposed independently by us (Zhao, S. H. Thesis, Orsay, 1987) and by Mikami.[8c]

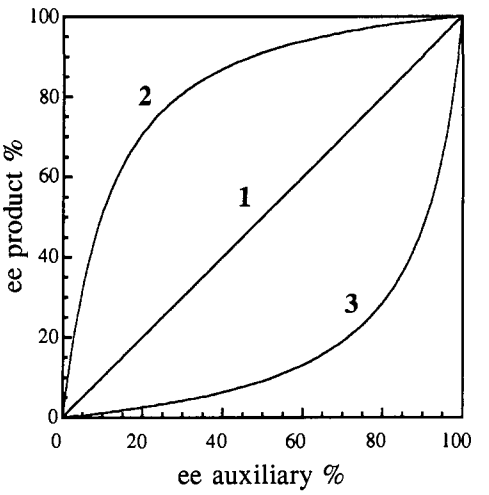

Figure 1. The general situations (curves 1–3) relating the ee of a chiral auxiliary to the ee of product.

We wish to consider here the specific situation of asymmetric

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(2) (a) *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1982–1985; Vol. 1–5. (b) *Catalysis in Asymmetric Synthesis*; Ojima, I., Ed.; VCH: New York, 1993. (c) *Asymmetric Catalysis in Organic Synthesis*; Noyori, R., Ed.; J. Wiley: New York, 1994.

(3) In eq 1 and following equations the enantiomeric excesses are taken with values between 0 and 1. An arbitrary sign is given to ee for a given enantiomer. In this paper, the graphs are standardized with positive values for both product and chiral auxiliary of a given experiment.

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

(5) (a) Oguni, N.; Matsuda, Y.; Kaneko, T. *J. Am. Chem. Soc.* **1988**, *110*, 7877–7878. (b) Hayashi, M.; Matsuda, T.; Oguni, N. *J. Chem. Soc., Perkin Trans. 1* **1992**, 3135–3140.

(6) Kitamura, N.; Okada, S.; Suga, S.; Noyori, R. *J. Am. Chem. Soc.* **1989**, *111*, 4028–4036. See also: Noyori, R.; Kitamura, M. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 49–59.

(7) Iwasawa, N.; Hayashi, Y.; Sakurai, H.; Narasaka, K. *Chem. Lett.* **1989**, 1581–1584.

(8) (a) Terada, M.; Mikami, K.; Nakai, T. *J. Chem. Soc., Chem. Commun.* **1990**, 1623–1624. (b) Mikami, K.; Terada, M.; Narisawa, S.; Nakai, T. *Synlett* **1992**, 255–265. (c) Mikami, K.; Terada, M. *Tetrahedron* **1992**, *48*, 5671–5680. (d) Terada, M.; Mikami, K. *J. Chem. Soc., Chem. Commun.* **1994**, 833–834. (e) Mikami, K.; Motoyama, Y.; Terada, M. *J. Am. Chem. Soc.* **1994**, *116*, 2812–2820. (f) Mikami, K.; Motoyama, Y.; Terada, M. *Inorg. Chim. Acta* **1994**, *222*, 71–75.

(9) (a) Bolm, C. *Tetrahedron: Asymmetry* **1991**, *2*, 701–704. (b) Bolm, C.; Schlingloff, G.; Harms, K. *Chem. Ber.* **1992**, *125*, 1191–1203. (c) Bolm, C.; Ewald, M.; Felder, M. *Chem. Ber.* **1992**, *125*, 1205–1215. (d) Bolm, C.; Müller, J.; Schlingloff, G.; Zehnder, M.; Neuburger, M. *J. Chem. Soc., Chem. Commun.* **1993**, 182–183.

(10) Tanaka, K.; Matsui, J.; Kawabata, Y.; Suzuki, H.; Watanabe, A. *J. Chem. Soc., Chem. Commun.* **1991**, 1632–1634.

(11) (a) Rossiter, B. E.; Miao, G.; Swingle, N. M.; Eguchi, N.; Hernández, A. E.; Patterson, R. G. *Tetrahedron: Asymmetry* **1992**, *2*, 231–234. (b) Sasai, H.; Suzuki, T.; Itoh, N.; Shibasaki, M. *Tetrahedron Lett.* **1993**, *34*, 851–854. (c) Komatsu, N.; Hashizume, M.; Sugita, T.; Uemura, S. *J. Org. Chem.* **1993**, *58*, 4529–4533. (d) Keck, G. E.; Krishnamurthy, D.; Grier, M. C. *J. Org. Chem.* **1993**, *58*, 6543–6544. (e) Evans, D. A.; Nelson, S. G.; Gagné, M. R.; Muci, A. R. *J. Am. Chem. Soc.* **1993**, *115*, 9800–9801. (f) Zhou, Q. L.; Pfaltz, A. *Tetrahedron* **1994**, *50*, 4467–4478. (g) Barnhart, R. W.; Wang X.; Noheda, P.; Bergens, S. H.; Whelan, J.; Bosnich, B. *Tetrahedron* **1994**, *50*, 4335–4346.

(12) (a) Vries, A. H. M. de; Jansen, J. F. G. A.; Feringa, B. L. *Tetrahedron* **1994**, *50*, 4479–4491. (b) Faller, J. W.; Parr, J. *J. Am. Chem. Soc.* **1993**, *115*, 804–805.

(13) Horeau and Guetté discussed in 1974 the importance of diastereomeric interactions of a mixture of enantiomers, especially to account for some unusual physical properties such as cases of nonequivalence between optical purity and enantiomeric excess.[14] Wynberg and Feringa pointed out in 1976 the possibility of different chemical behavior (rates and product distributions) of an enantiopure compound and the corresponding racemic mixture in the absence of chiral reagent.[15]

(14) Horeau, A.; Guetté, J. P. *Tetrahedron* **1974**, *30*, 1923–1931.

(15) Wynberg, H.; Feringa, B. *Tetrahedron* **1976**, *32*, 2831–2834.

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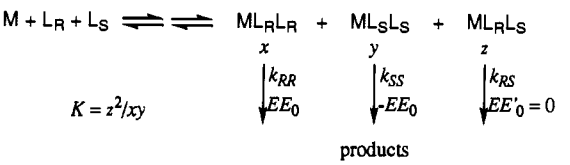


Figure 2. Simplified model of a catalytic reaction using a chiral ligand L (ML_2 system). x, y, and z are the relative concentrations of the three catalytic species at the steady state.

catalysis, using simplified models which could be helpful in analyzing experimental data.

Model 1

ML_2 System. In our previous publication[4] we briefly discussed a model for asymmetric catalysis which is based on a fast ligand exchange between *reactive species involving two chiral ligands* (L_R, L_S), for example around a metallic center M (Figure 2). The discussion is identical for ML_2 or $(ML)_2$ systems. We assumed a steady state for complexes ML_RL_R, ML_SL_S, and ML_RL_S (in amounts x, y, and z respectively) and a last irreversible step with pseudo-first order constants k_{RR}, k_{SS} ($k_{RR} = k_{SS}$), and k_{RS} (these apparent rate constants include absolute rates and equilibrium constants), assuming a zero order dependence with respect to the substrate. Racemic product is formed from the meso catalyst, while enantiomeric products are obtained from the two homochiral complexes. It was then easy to calculate (details in supplementary material) the ee of the resulting product (EE_{prod}) in the above model; eq 2 has been obtained.[4]

$$EE_{prod} = EE_0 ee_{aux} \frac{1+\beta}{1+g\beta} \qquad (2)$$

In eq 2 two basic parameters were introduced: β expresses the *relative amounts* of the meso and homochiral complexes ($\beta = z/(x+y)$) while g defines the *relative reactivities* of the meso and homochiral catalysts ($g = k_{RS}/k_{RR}$). EE_0 stands for the enantiomeric excess of the product when an enantiopure chiral auxiliary is used. If $\beta = 0$ (no meso catalyst) or $g = 1$ (identical reactivities of meso and homochiral catalysts), eq 2 simplifies into eq 1, and there is a linear correlation. In all the other cases, the correcting factor $(1+\beta)/(1+g\beta)$ in eq 2 is not equal to 1, and a nonlinear correlation necessarily occurs. To get a "positive nonlinear effect" with EE_{prod} larger than predicted by eq 1, one needs a correcting factor >1. This condition is achieved each time $g < 1$ (meso complex less reactive than the homochiral complexes). A "negative nonlinear effect" occurs for $g > 1$. Calculations apply even if some of the ligands remain unbound with an enantiomeric excess ee_{aux}. Model 2 will apply to cases where there is a change in the initial ee (ee_{aux}) of the chiral ligand.

We want to show here that eq 2 allows us to compute the curves $EE_{prod} = f(ee_{aux})$. For that purpose it is necessary to know the distribution between the three complexes of the scheme in Figure 2, as a function of the initial ee (ee_{aux}). One hypothesis is to assume a fast ligand exchange before the final irreversible step of the catalytic cycle. One can then discuss the ligand distribution in the equilibrium between the three complexes described in Figure 2, as a function of a parameter $K = z^2/xy$, which becomes the equilibrium constant if the distribution of complexes is close to the thermodynamic equilibrium (as in the Curtin–Hammett conditions). The ratio β of meso and homochiral complexes is given by formula 3 (see details on calculation in supplementary material).

$$\beta = \frac{-K\,ee_{aux}^2 + \sqrt{-4K\,ee_{aux}^2 + K(4 + K\,ee_{aux}^2)}}{4 + K\,ee_{aux}^2} \qquad (3)$$

EE_{prod} can be expressed as a function of K, by the combined use of eqs 2 and 3.

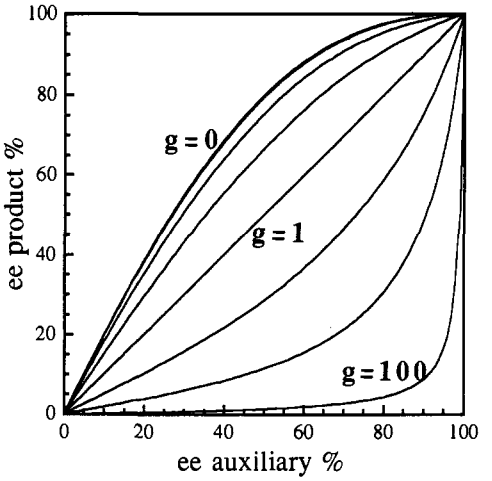


Figure 3. Computer-drawn from eq 4 with g = 0, 0.01, 0.1, 0.33, 1, 3, 10, and 100 (statistical distribution of ligands in ML_2 complexes).

In the particular case where there is a *statistical distribution of ligands* between the three complexes, their relative amounts are in the proportions $x/y/z = (1 + ee_{aux})^2/(1 - ee_{aux})^2/2(1 + ee_{aux})(1 - ee_{aux})$. $K = z^2/xy$ becomes equal to 4.

Equation 3 allows us to calculate the value of β in that case: $\beta = (1 - ee_{aux}^2)/(1 + ee_{aux}^2)$. The general equation 2 is then transformed into eq 4, which gives the variations of EE_{prod} as a function of ee_{aux} and g.

$$EE_{prod} = EE_0 ee_{aux} \frac{2}{1 + g + (1-g)ee_{aux}^2} \qquad (4)$$

There is always a nonlinear correlation, unless $g = 1$. The maximum departure from linearity in "positive" NLE is obtained when $g = 0$ (no reactivity of the meso complex). Computer-drawn curves for several g values are plotted in Figure 3. Equation 5 correlates EE_{prod} and ee_{aux} for the statistical distribution of ligands and no reactivity of the meso complex ($g = 0$).

$$EE_{prod} = EE_0 ee_{aux} \frac{2}{1 + ee_{aux}^2} \qquad (5)$$

When there is *no statistical distribution of ligands* ($K \neq 4$), one must use eqs 2 and 3. Curves are given in Figure 4 for K = 9 and 2500 (predominance of the meso complex). A general trend is clearly apparent: the highest positive NLE ("amplifying effect", as proposed by Oguni[5]) is reached when $g = 0$. The amplification is especially important if one combines small g and large K (low reactivity and high relative concentration of meso complex). Conversely the curves dip strongly ("depressing effect") for $g \gg 1$.

We tried to compare curves of Figures 3 and 4 with some experimental data. A reasonable fit was obtained with the curve previously given for Sharpless asymmetric oxidation of geraniol[4] (**1**) (Scheme 1) by taking $g = 0.35$ and $K = 1000$ (Figure 5a). These data mean that, in the present model, the titanium complex of meso composition is less reactive ($k_{RS}/k_{RR} \approx 1/3$) and more abundant in the equilibrium of Figure 2 ($K = 1000$) than the homochiral complex. This interpretation is in agreement with the Sharpless mechanism of asymmetric epoxidation, which indicates the intervention of a dimeric complex, introducing two tartrate units in the active species.[16]

We investigated the asymmetric epoxidation of allylic alcohol (*E*)-**3**, using 1 equiv of the Sharpless reagent Ti(O-i-Pr)$_4$ + (*R*,*R*)-DET (1:1) in dichloromethane at −20 °C (Scheme 2). Epoxide

(16) Finn, M. G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1991**, *113*, 113–126.

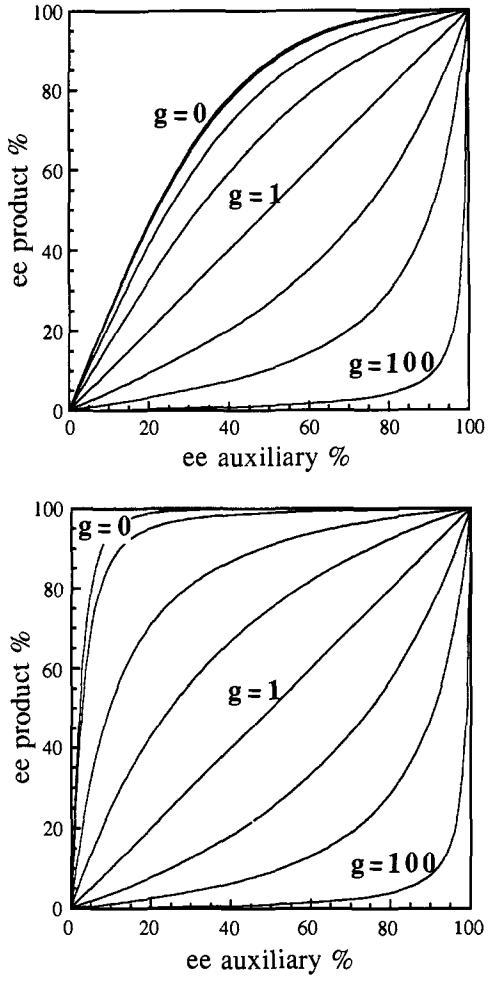


Figure 4. (a) Computer-drawn from eqs 2 and 3 with $K = 9$ and $g = 0, 0.01, 0.1, 0.33, 1, 3, 10$, and 100 (nonstatistical distribution of ligands in ML_2 complexes). (b) Computer-drawn from eqs 2 and 3 with $K = 2500$ and $g = 0, 0.01, 0.1, 0.33, 1, 3, 10$, and 100 (nonstatistical distribution of ligands in ML_2 complexes).

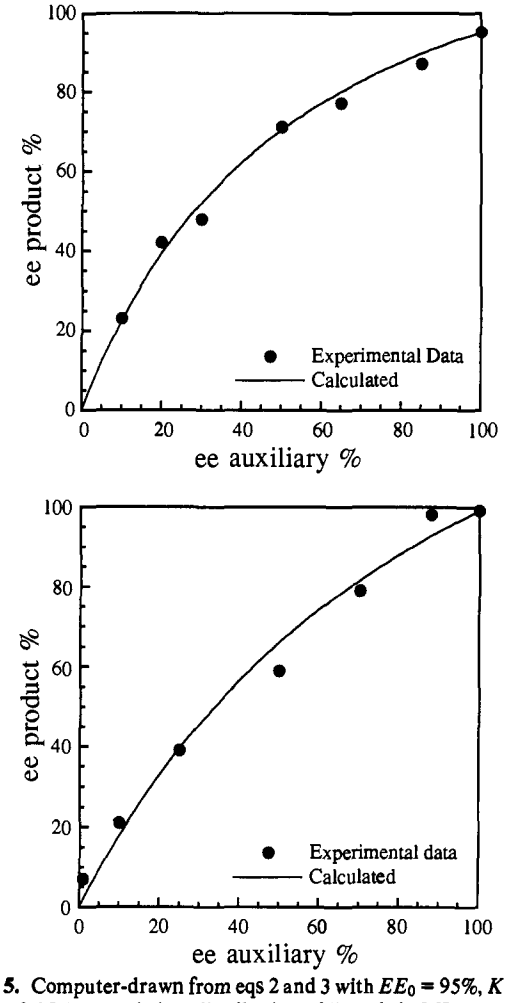
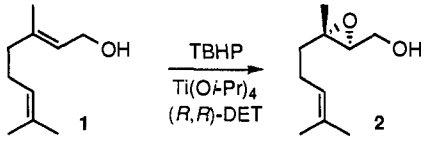
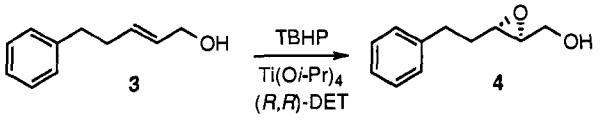


Figure 5. Computer-drawn from eqs 2 and 3 with $EE_0 = 95\%$, $K = 1000$, and $g = 0.35$ (nonstatistical distribution of ligands in ML_2 complexes). Experimental data from ref 4 (Sharpless epoxidation of geraniol). (b) Computer-drawn from eqs 2 and 3 with $EE_0 = 99\%$, $K = 1000$, and $g = 0.5$ (nonstatistical distribution of ligands in ML_2 complexes). Experimental data from ref 4 (Sharpless epoxidation of (*E*)-3).

Scheme 1



Scheme 2



4 is obtained with >98% ee (measured by ^1H NMR on Mosher esters). When the same experiment was repeated with DET of various ee's, an amplification as for geraniol epoxidation was observed (Figure 5b). One finds $g = 0.5$ and $K = 1000$.

The experimental curve[4] (negative NLE till $ee_{aux} = 70\%$ and then linearity) for the asymmetric oxidation of methyl *p*-tolyl sulfide (**11**) in the presence of a water-modified Sharpless reagent[17] is not reproduced by any of the curves of Figures 3 and 4. The nonlinear effect observed in an asymmetric aldolization of **5** catalyzed by (*S*)-proline[18] is out of the scope of the present model, it has been discussed and interpreted by Agami *et al.* on the basis of a kinetic treatment[19] (*vide infra*).

Enantioselective 1,4-addition of cuprates bearing chiral β-amino alcohols to cyclo enones recently provided additional examples of nonlinear effects.[10,11a] Rossiter postulated the formation of dimeric organocuprates and assumed a statistical distribution of readily exchangeable ligands and no reactivity for the meso complex, and there was a good fit between observed enantioselectivities and calculations,[11a] these calculations being very similar to those obtained by the use of eq 5 (simplified ML_2 system with statistical distribution of ligands and no reactivity of meso complex).

The complex ML_RL_S has been assigned a *meso* structure, producing a racemic product. One can envisage a *chiral* ML_RL_S complex if coordination of chiral ligands creates a new chiral unit on the metal (see ref 20 for the significance of chiral metals in asymmetric catalysis). For example, precursors (labile racemic mixture or achiral complex M) will be sequentially transformed into M_SL_R and then $M_SL_RL_S$. Heterochiral complexes $M_RL_RL_S$ and $M_SL_SL_R$ are here enantiomers, notwithstanding each complex has a racemic composition of ligands. Of course the homochiral complexes $M_RL_RL_R$ and $M_SL_SL_S$ will also have a chiral unit on the metal M. Figure 6 shows the general scheme, with four pairs of enantiomers having each their own reactivities and selectivities (k_i and EE_i).

By taking the same hypotheses as above (fast exchange of ligands, formation of products from competitive irreversible

(17) Pitchen, P.; Duñach, E.; Deshmukh, M. N.; Kagan, H. B. *J. Am. Chem. Soc.* **1984**, *106*, 8188–8193.
(18) Agami, C. *Bull. Soc. Chim. Fr.* **1988**, 499–507.
(19) Agami, C.; Puchot, C. *J. Mol. Catal.* **1986**, *38*, 341–343.
(20) Brunner, H. *Acc. Chem. Res.* **1979**, *12*, 250–257.

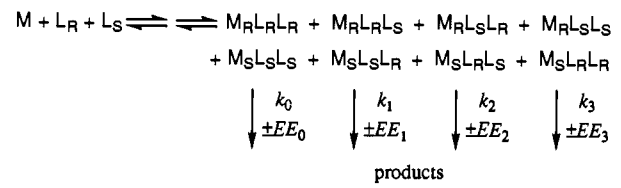


Figure 6. Simplified model of a catalytic reaction using a chiral ligand L (M^*L_2 system).

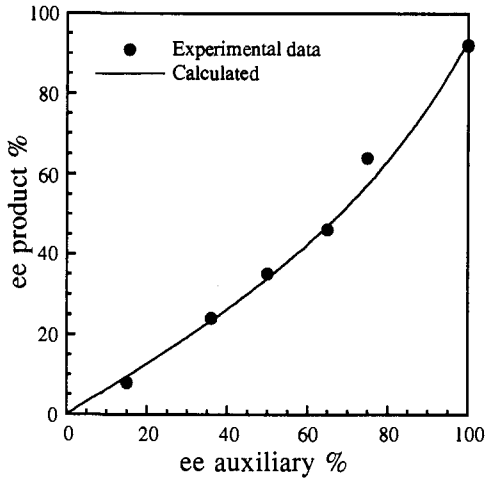
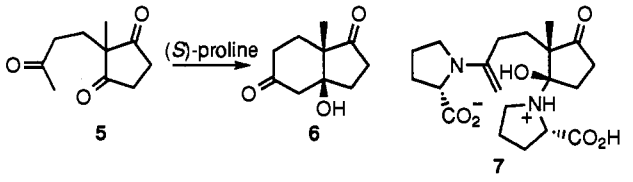


Figure 7. Computer-drawn from eq 4 with $EE_0 = 93\%$ and $g = 2$ (statistical distribution of ligands in M^*L_2 complexes with induction of chirality at the center M by the first ligand). Experimental data from ref 4 (proline-catalyzed aldolization).

Scheme 3



pseudo-first-order reactions) one calculates the enantiomeric excess of products as a function of parameters linking the relative amounts of the eight stereoisomers and of their selectivities and relative reactivities. The expressions are actually the same as for the ML_2 system (see supplementary material): the equation obtained from the combined use of eqs 2 and 3 will still apply here, the only difference lying in the definition of parameters K, g, and EE_0.

The formation of hydrindanone **6** (Scheme 3) by asymmetric aldolization catalyzed by proline[18] gives a negative NLE,[4] which was interpreted by Agami *et al.* with a kinetic model,[19] based on the fact that the reaction is second-order with respect to proline. The authors proposed that asymmetric cyclization occurs through complexes of the general structure **7**. A first proline molecule gives a chiral enamine, and a second proline molecule (absolute configuration not important) mediates a proton transfer (general base catalysis) leading to ketol **6**. The kinetic analysis reproduced the experimental data. The model in Figure 6 is mechanistically related to **7**: in $M_RL_RL_S$, M now represents the substrate, while L_R is the first proline molecule involved in the enamine formation. In that particular case, where the configuration of M is correlated to the configuration of the first ligand, one finds (see supplementary material) that the expressions are strictly the same as in the ML_2 case. And since the configuration of the second proline does not interfere,[19] one can assume a statistical distribution of ligands and use eq 4. The experimental curve can be simulated (Figure 7) by taking $EE_0 = 93\%$ (ee of **6** found experimentally when using enantiopure proline[11,12]). Taking $g = 2$ gives a good fit. This value is exactly the value found by the authors ($k_{homo}/k_{hetero} = 0.50$) in their kinetic analysis, which is equivalent to the present model.[19]

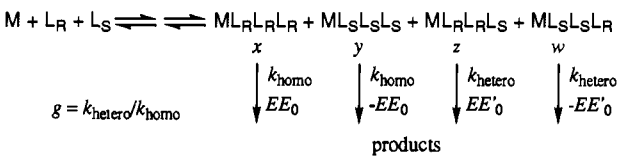


Figure 8. Simplified model of a catalytic reaction using a chiral ligand L (ML_3 system). x, y, z, and w are the relative concentrations of the four complexes at the steady state.

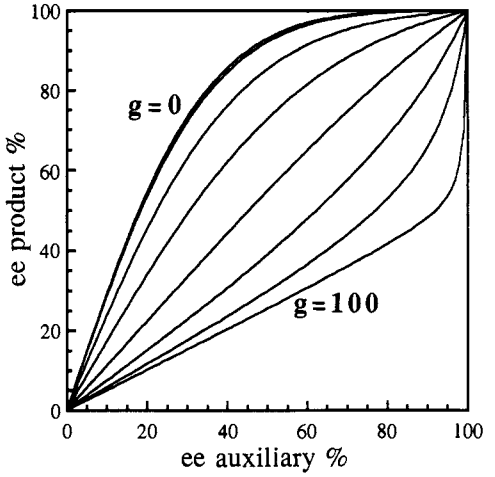


Figure 9. Computer-drawn from eq 6 with $EE_0 = 100\%$, $EE'_0 = 50\%$, and $g = 0$, 0.01, 0.1, 0.33, 1, 3, 10, and 100 (statistical distribution of ligands in ML_3 complexes).

All the equations developed in this section for ML_2 systems (Figure 2) also apply to cases where ML_RL_R, ML_SL_S, and ML_RL_S complexes dissociate *irreversibly* (with or without intervention of a reactant) leading to ML_R and ML_S complexes which appear then at the last irreversible step of the catalytic cycle (see supplementary material).

ML_3 System. One can also envisage ML_3 (or $(ML)_3$) complexes as the catalytic species. At least four entities are involved: $ML_RL_RL_R$, $ML_SL_SL_S$, $ML_RL_RL_S$, and $ML_SL_SL_R$. Heterochiral complexes are never achiral, contrary to the ML_2 case. Optically active product is generated simultaneously from homochiral and heterochiral complexes (Figure 8). Calculation of EE_{prod} as a function of ee_{aux} is very difficult. The analytical expressions are complicated, but it is possible to get general expressions (*vide infra*, in the conclusion). A simplification occurs if one assumes a *statistical distribution* of the chiral ligands between the four complexes. Equation 6 is obtained (see supplementary material).

$$EE_{prod} = EE_0 ee_{aux} \frac{3 + 3g\,EE'_0/EE_0 + (1 - 3g\,EE'_0/EE_0)ee_{aux}^2}{1 + 3g + 3(1-g)ee_{aux}^2} \quad (6)$$

In this equation, EE_0 and EE'_0 stand for enantiomeric excess of the product obtained using homochiral and heterochiral complexes (of 100% ee), respectively, and g is defined as in the ML_2 case, as the ratio of the pseudo-first-order rate constants of heterochiral and homochiral complexes.

In Figure 9 some curves are drawn for selected combinations of g and EE'_0/EE_0 ($EE'_0/EE_0 < 1$). The influence of these two parameters is clearly demonstrated: the bigger the ratio EE'_0/EE_0 and the lower the value of g, *the higher* the curve is located. In Figure 9 we chose to keep $EE'_0/EE_0 < 1$. This hypothesis means that the homochiral complex (*e.g.*, $ML_RL_RL_R$) gives an enantioselectivity higher than the heterochiral complex.

Another likely possibility has to be considered: the heterochiral complex is more enantioselective than the homochiral complex

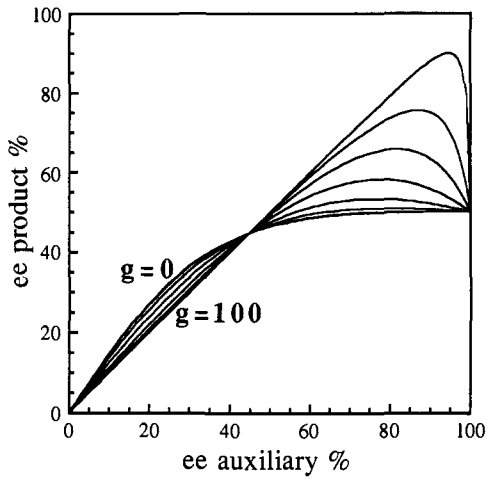


Figure 10. Computer-drawn from eq 6 with EE_0 = 50%, EE'_0 = 100%, and g = 0, 0.01, 0.1, 0.33, 1, 3, 10, and 100 (statistical distribution of ligands in ML_3 complexes).

($EE'_0/EE_0 > 1$). Computed curves for various g values show two situations. When $g < 1$ (higher catalytic activity of homochiral complex), the curves are not very different from the curves described in the previous case, with a continuous increase until EE_0 (enantioselectivity corresponding to the use of enantiomerically pure ligand).

An interesting situation occurs for high values of g (very reactive heterochiral complex). EE_{prod} can take *values much larger for partially resolved ligand than for enantiomerically pure ligand*! For example one obtains a product of 90% ee (if ee_{aux} = 95%) instead of 50% ee (if ee_{aux} = 100%) for the following set of data: g = 100, EE_0 = 50%, EE'_0 = 100% (Figure 10). The location of the maximum is strongly correlated to g. A very reactive heterochiral complex will give a curve close to a straight line between 0 and EE'_0 (see Figure 10), it is upon approaching ee_{aux} = 100% that the curve drops sharply to EE_0. It has never been pointed out that a chiral auxiliary can be more efficient in asymmetric synthesis when not enantiomerically pure, and to our knowledge, there is no precedent in literature for this case.[21]

We wanted to explore experimentally such a possibility. In order to be successful one needs to fulfill three conditions:

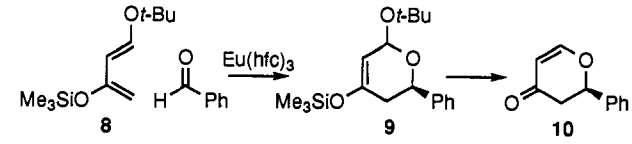
(i) One must find a catalyst with more than two ligands.

(ii) The heterochiral catalyst must be more reactive than the homochiral catalyst.

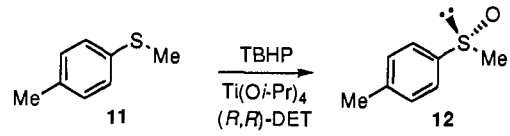
(iii) The enantioselectivity of the heterochiral catalyst must be higher than that of the homochiral catalyst.

Such conditions are quite restrictive, especially conditions ii and iii, which are hard to predict. Even condition i is not obvious, since there are only a few examples in the literature of a catalyst retaining three ligands during the whole catalytic cycle.[23] We selected the asymmetric hetero-Diels–Alder reaction catalyzed by the chiral Lewis acid ($Eu(hfc)_3$). This reaction has been studied by Danishefsky *et al.*[25a] Siloxy diene **8** reacts with benzaldehyde in the presence of 1% $Eu(hfc)_3$ to produce cycloadduct **9**, which was transformed to **10** (50% ee) (Scheme 4). We reinvestigated this reaction by using (+)-$Eu(hfc)_3$ of various enantiomeric

Scheme 4



Scheme 5



excesses. The chemical yield is excellent, but there is no departure whatever from linearity (see the Experimental Section). A suitable system remains to be found.

ML_4 System. We will consider now the case where there are four chiral ligands in a ML_4 complex (or in $(ML)_4$ systems). This generates five possible complexes: $M(L_R)_4$, $M(L_S)_4$, $M(L_R)_3L_S$, $M(L_S)_3L_R$, and $M(L_R)_2(L_S)_2$. We will consider $M(L_R)_2(L_S)_2$ as a meso complex and assume no additional stereoisomers involving the metal center. If there is a *statistical distribution of ligands* between the five complexes, then their relative concentrations are easy to calculate. It is possible to derive eq 7 (see supplementary material), which expresses EE_{prod} as a function of ee_{aux}.

$$EE_{prod} = \frac{8EE_0 ee_{aux}\left[1 + ee_{aux}^2 + 2g(1 - ee_{aux}^2)EE'_0/EE_0\right]}{(1 + ee_{aux})^4 + (1 - ee_{aux})^4 + 8g(1 - ee_{aux}^4) + 6f(1 - ee_{aux}^2)^2} \quad (7)$$

Introduced in this equation are the relative reactivities g and f of the two heterochiral complexes (with respect to $M(L_R)_4$) as well as the enantioselectivities EE_0 and EE'_0 given by the enantiopure homochiral and heterochiral complexes (the meso complex will give a racemic product). The ML_4 system in principle applies to asymmetric oxidation of sulfides by *t*-BuOOH in the presence of $Ti(O\text{-}i\text{-}Pr)_4$/diethyl tartrate/$H_2O$ = 1/2/1 used in stoichiometric[17] or catalytic amounts (Scheme 5).[26] In the oxidation of methyl *p*-tolyl sulfide, a strong negative NLE has been found[4] up to ee_{aux} = 70%, after which linearity was regained. This could be evidence for a dimeric titanium complex (with four diethyl tartrate ligands), which should be exhibited by ML_4 complexes, since none of the curves computed for the case ML_2 exhibit such a behavior. The above equation did not reproduce the dissymetrical experimental curve, possibly because there is not a statistical distribution of ligands, but a good fit has been found (Figure 11) using the general formulas (see supplementary material) with the following set of parameters: EE_0 = 85% (enantioselectivity of the reaction performed with enantiopure ligand), K = 200 (=$[M(L_R)_3L_S]^2/[M(L_R)_4][M(L_R)_2(L_S)_2]$), EE'_0 = 10%, g = 0.45 (predominance of a fairly active and poorly selective heterochiral catalyst), K' = 1000 (=$[M(L_R)_2(L_S)_2]^2/[M(L_R)_3L_S][M(L_S)_3L_R]$), and f = 0.25 (large predominance of a poorly active meso catalyst).

It is interesting to point out that a double-shape curve is apparent from experimental data given by Tanaka *et al.*[10] for the 1,4-

(21) An analogy can be found in biological activities of insect pheromones[22] where sometimes the optimum activity is correlated to enantiomeric excesses lower than 100%.

(22) Mori, K. *Tetrahedron* **1989**, *45*, 3233–3298.

(23) Oxovanadium(V) trialkoxides of chiral or racemic alcohols were recently prepared.[24] It was found that homochiral complexes ($L_RL_RL_R$ or $L_SL_SL_S$ composition) are significantly more stable than heterochiral complexes ($L_RL_RL_S$ or $L_SL_SL_R$ composition). Exchange of ligands was observed in solution, it is a slow process on the NMR time scale. Asymmetric catalysis with these systems has not yet been reported.

(24) Crans, D. C.; Chen, H.; Felty, R. A. *J. Am. Chem. Soc.* **1992**, *114*, 4543–4550.

(25) (a) Bednarski, M.; Maring, C.; Danishefsky, S. *Tetrahedron Lett.* **1983**, *24*, 3451–3454. (b) Maruoka, K.; Itoh, T.; Shirasaka, T.; Yamamoto, H. *J. Am. Chem. Soc.* **1988**, *110*, 310–312.

(26) Zhao, S.; Samuel, O.; Kagan, H. B. *Tetrahedron* **1987**, *43*, 5135–5144.

(27) For some references on the aggregation of alkali metal compounds in solution and their reactivity, see: (a) Williard, P. G.; Salvino, J. M. *J. Org. Chem.* **1993**, *58*, 1–3. (b) Edwards, A. J.; Hockey, S.; Mair, F. S.; Raithby, P. R.; Snaith, R.; Simpkins, N. S. *J. Org. Chem.* **1993**, *58*, 6942–6943.(c) Gilchrist, J. H.; Collum, D. B. *J. Am. Chem. Soc.* **1992**, *114*, 794–795. (d) Sato, D.; Kawasaki, H.; Shimada, I.; Arata, Y.; Okamura, K.; Date, T.; Koga, K. *J. Am. Chem. Soc.* **1992**, *114*, 761–763. (e) Reich, H. J.; Medina, M. A.; Bowe, M. D. *J. Am. Chem. Soc.* **1992**, *114*, 11003–11004. (f) Krom, J. A.; Streitwieser, A. *J. Am. Chem. Soc.* **1992**, *114*, 8747–8748. (g) Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1624–1654.

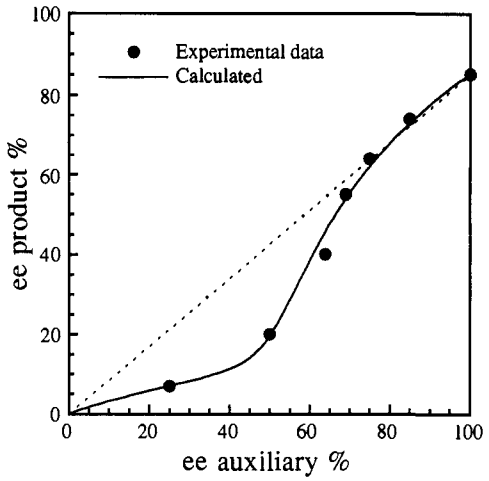


Figure 11. Computer-drawn for the ML_4 system with $EE_0 = 85\%$, $EE'_0 = 10\%$, $K = 200$, $K' = 1000$, $g = 0.45$, and $f = 0.25$. Experimental data from ref 4 (asymmetric oxidation of methyl *p*-tolyl sulfide).

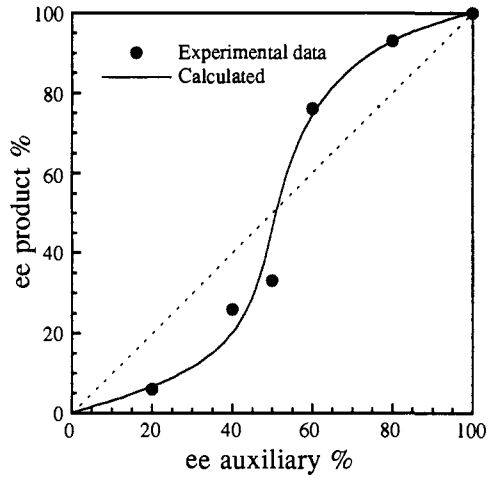


Figure 12. Computer-drawn for the ML_4 system with $EE_0 = 100\%$, $EE'_0 = 50\%$, $K = 1000$, $K' = 1$, $g = 0.25$, and $f = 2$. Experimental data from ref 10 (asymmetric synthesis of muscone).

addition of a chiral cuprate and plotted in Figure 12, where there is also a simulation using the general formulas with $EE_0 = 100\%$, $EE'_0 = 50\%$, $K = 1000$, $K' = 1$, $g = 0.25$, and $f = 2$.

The ML_4 system is expected to be found for aggregation involving organolithium species.[27] In this context it is important to recall that Rautenstrauch[28] showed that enantiomerically pure or racemic camphor is reduced to borneol or isoborneol (by potassium in liquid ammonia) with different stereoselectivities. The borneol/isoborneol ratio as well as the ee of each alcohol is not linearly related to the ee of camphor.[28] This has been explained as being due to disproportionation between ketyl pairs, involving four K^+ and four chiral ketyls.[28] ML_4 complexes are analogous to the molecular assembly of four ketyl species.

Model 2. The "Reservoir Effect"

If a partially resolved chiral ligand is involved in a catalytic system, one can always expect some complications when diastereomeric complexes are formed, either *in the catalytic cycle* (see model 1) or *at its periphery*. The properties of these complexes are not predicted from the behavior of complexes prepared from enantiomerically pure ligands.

Starting from 1 mol of chiral ligand (with ee = ee_{aux}), we call α the fraction which is engaged in various complexes not directly involved in the catalytic cycle. If the enantiomeric excess of the

(28) Rautenstrauch, V.; Mégard, P.; Bourdin, B.; Furrer, A. *J. Am. Chem. Soc.* **1992**, *114*, 1418–1428.

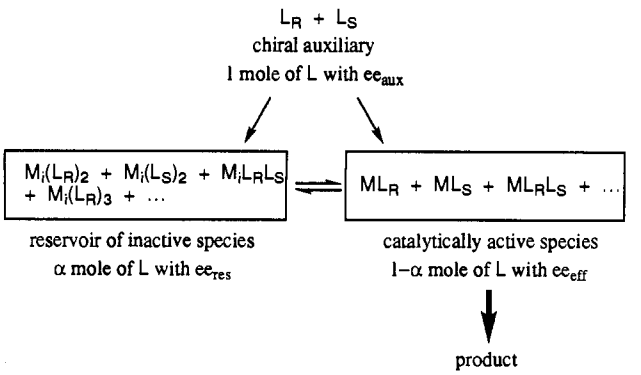


Figure 13. Storage of ee different from the initial ee_{aux} (reservoir effect).

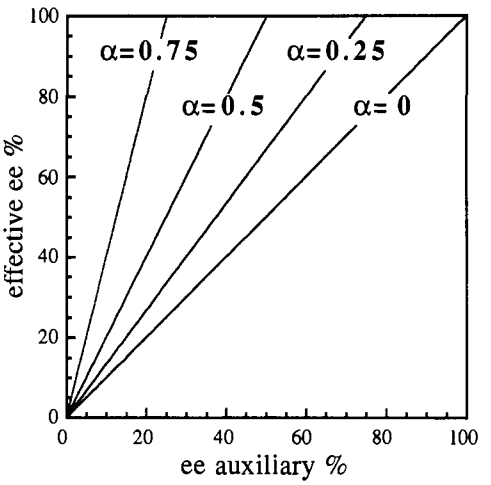


Figure 14. Computer-drawn from eq 8 (reservoir effect) with $ee_{res} = 0\%$ and $\alpha = 0$, 0.25, 0.5, and 0.75.

total amount of ligands engaged in the above unproductive complexes (called ee_{res}) is different from the initial ee_{aux}, this will change the ee of the ligand engaged in the catalytic cycle. One can say that part of the ee is stored in a reservoir (unproductive complexes). This reservoir effect modifies the ee of the ligand available to the catalyst: ee_{aux} is transformed into an effective ee, named ee_{eff}. The scheme in Figure 13 summarizes these definitions. It is easy to relate the partition of enantiomeric excess ee_{aux} of 1 mol of a compound between two samples ee_{res} and ee_{eff} of relative amounts α and $1 - \alpha$. One obtains eq 8.

$$ee_{eff} = \frac{ee_{aux} - \alpha ee_{res}}{1 - \alpha} \qquad (8)$$

A graphical representation of ee_{eff} as a function of ee_{aux} is given in Figure 14, for various α and ee_{res}. Enhancements of ee are possible for some combinations of ee_{res} and α. For example, if one starts from 50% ee ($ee_{aux} = 50\%$) and if 40% of the material ($\alpha = 0.4$) is stored in the reservoir in a racemic composition ($ee_{res} = 0\%$), one recovers 60% ($1 - \alpha = 0.6$) with ee of 83% ($ee_{eff} = 83\%$). An increase in ee_{eff} occurs if one removes ee_{res} lower than ee_{aux}; the reverse effect will result if $ee_{res} > ee_{aux}$.

The curves of Figure 14 are obtained by the simple application of eq 8 (taking all the ee's < 1), and assuming a mechanism fixing $ee_{res} = 0\%$. How can such a reservoir be established? One can envisage several possibilities. For example, an aggregation process can occur before, or in parallel to, the establishment of the steady state in the catalytic cycle. Dimerization or oligomerization of alcoholates (or of organometallics) is a classical process. If the chiral auxiliary is involved in an alcoholate (as the alcohol component or as a ligand of the metal center), it can be stored in part in catalytically inactive polymeric species while complexes of low aggregation numbers will behave as the catalyst or as the

catalyst precursor. A change of the initial enantiomeric excess ee_{aux} will occur only if the reservoir stores $ee_{res} \neq ee_{aux}$; this occurs when the resting species are diastereomeric entities involving at least two chiral ligands. The simplest way to store a racemic mixture is to produce a heterodimer *in situ* (meso compound) which is thermodynamically stable and kinetically inactive. The storage of enantiomerically pure material in a reservoir (ee_{res} = 100%) independently of ee_{aux} also needs special situations. One possibility is the intervention of an additional chiral unit, giving an *in situ* kinetic resolution into inactive species. A related example has been reported by Brown *et al.*[29] in asymmetric hydrogenation. These authors realized *in situ* the highly efficient kinetic resolution of racemic diphosphines by addition of 0.5 equiv of an iridium complex of menthyl *N*-acetyl dehydrophenylalanine. A limited amount of $(RhClCOD)_2$ is then added to the solution for the complexation of the free diphosphine, giving a chiral catalyst as efficient as the one prepared from enantiomerically pure diphosphine. The iridium complex remains in solution and is catalytically inactive; it behaves as the reservoir. Yamamoto also used a limited amount of 3-bromocamphor to resolve *in situ* a racemic organoaluminum complex, which then catalyzed a hetero-Diels–Alder reaction with 82% ee.[30] Faller *et al.* developed a related strategy (called chiral poisoning) to generate an enantioselective catalyst from a racemic chiraphos/rhodium complex.[12b]

Comparison of Simulated Curves with Experimental Data

The various equations that we developed (*vide supra*) gave an opportunity to compare experimental data with some mechanistic scenarios. Of course a given experimental curve sometimes can be fitted with several models, and only a detailed kinetic investigation will provide all features of the mechanism and of the origin of the NLE.

The nonlinear effect observed in asymmetric epoxidation of allylic alcohols (Figure 5a,b) does not fit the curves of Figure 14. This does not mean that a reservoir effect (storage of meso complex) has to be fully excluded; perhaps ee_{res} is not fixed and is correlated to ee_{aux} and α. Obviously ML_2 or $(ML)_2$ models are good and simple approximations (as indicated in Figure 5a,b), although other models can be used.

The catalyzed 1,2 or 1,4 asymmetric addition of organozincs has been studied very much during the last five years and has provided examples of strong positive NLE.[5,6,9,12] Indicated in Figures 15 and 16 are results reported by Noyori[6] and Oguni[5] in catalyzed addition of diethylzinc to benzaldehyde using β-amino alcohols as catalyst precursors (DAIB and PDB, respectively). Noyori *et al.* described a detailed mechanistic study of this type of reaction and concluded that the origin of the amplification lies mainly in the formation of dinuclear zinc complexes deriving from the chiral β-amino alcohol used (DAIB).[6] The meso dimer is thermodynamically favored and is also unreactive compared to the chiral dimer. This latter is easily dissociated and reacts with Et_2Zn and benzaldehyde. A more accurate picture will then be to take into account models 1 and 2, with the modification of model 1 where there is an irreversible dissociation of one ligand from ML_2 giving the catalytic complex ML. Hence we considered the model ML_2 with a final irreversible dissociation to ML (Figure 17).

Calculations (see supplementary material) led to the same equations as for the ML_2 system (eqs 2 and 3).

If one applies formula 8 (with ee_{res} = 0%) to the experimental data of Figures 15 and 16, one finds α = 0.88 and α = 0.87, respectively. Better fits are obtained by using eqs 2 and 3 (ML_2 case, with a large predominance of inactive meso complex: K = 5000 and g = 0.01 for Figure 15, and K = 4000 and g = 0.015 for Figure 16).

(29) Brown, J. M.; Maddox, P. J. *Chirality* **1991**, *3*, 345–354.
(30) Maruoka, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1989**, *111*, 789–790.

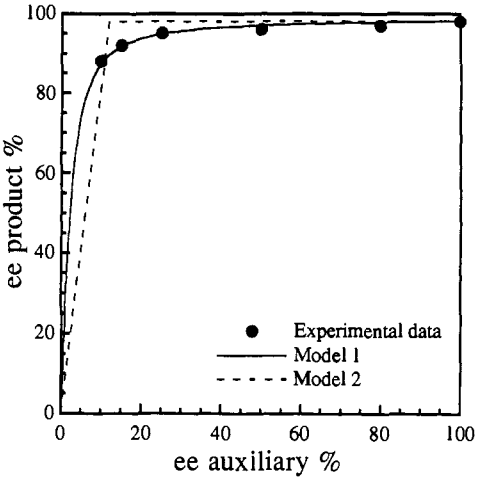


Figure 15. Computer-drawn from eq 8 with EE_0 = 98%, ee_{res} = 0%, and α = 0.88 (dashed line) and from eqs 2 and 3 with EE_0 = 98%, K = 5000, and g = 0.01 (nonstatistical distribution of ligands in ML_2 complexes) (solid line). Experimental data from ref 6 (catalyzed addition of Et_2Zn on benzaldehyde).

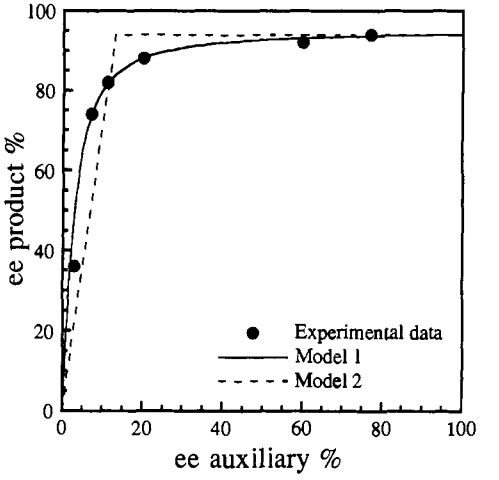


Figure 16. Computer-drawn from eq 8 with EE_0 = 94%, ee_{res} = 0%, and α = 0.87 (dashed line) and from eqs 2 and 3 with EE_0 = 94%, K = 4000, and g = 0.015 (nonstatistical distribution of ligands in ML_2 complexes) (solid line). Experimental data from ref 5a (catalyzed addition of Et_2Zn on benzaldehyde).

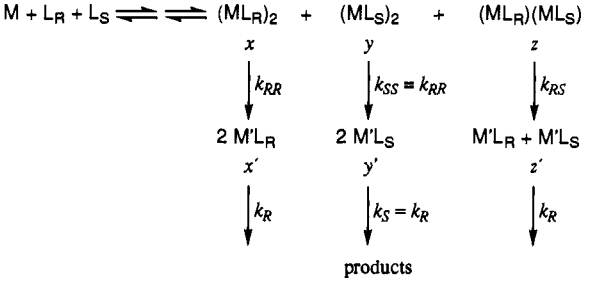


Figure 17. Simplified model of the ML_2 system with final dissociation to ML (irreversible step).

The 1,4-addition of diethylzinc to chalcone is catalyzed by a nickel complex and some chiral β-amino alcohols, and a strong positive nonlinearity has been found by Bolm.[9] This has been interpreted as a reservoir effect involving nickel complexes bearing two chiral β-amino alcohols. Here is also a good fit is obtained by using model 1 (ML_2), where the meso complex is abundant and of very low reactivity (Figure 18).

Feringa also described nonlinear effects in the 1,4-addition of organozincs or Grignard reagents catalyzed by chiral Ni(II) or Zn(II) complexes.[12] An ene reaction catalyzed by a chiral

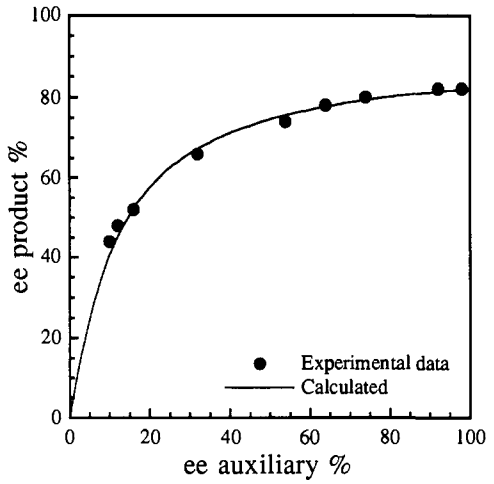


Figure 18. Computer-drawn from eqs 2 and 3 with $EE_0 = 82\%$, $K = 1000$, and $g = 0.1$ (nonstatistical distribution of ligands in ML_2 complexes). Experimental data from ref 9a (Et_2Zn addition on benzaldehyde).

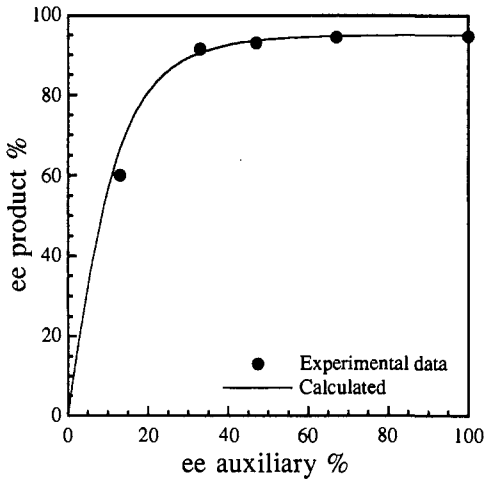


Figure 19. Computer-drawn from eqs 2 and 3 with $EE_0 = 95\%$, $K = 150$, and $g = 0$ (nonstatistical distribution of ligands in ML_2 complexes). Experimental data from ref 8a–d (catalyzed ene reaction).

titanium complex (prepared from 1,1-binaphthol) showed a remarkable positive nonlinear effect[8] (Figure 19). The reaction studied in detail is the condensation of α-methylstyrene on methyl glyoxylate.

It was established by Mikami and Nakai that two dimeric titanium complexes are generated in solution, the meso complex is stable, while the homochiral dimer dissociates easily (especially at low concentrations), giving the monomeric complex which is the active catalyst.[8] The nonlinear effect increases with a decrease in the catalyst concentration, which is the reverse of what was observed in catalyzed organozinc additions. A reservoir is also clearly operating here, but simulation by the ML_2 model with a large amount of inactive meso complex gave a better fit than an exclusive reservoir effect.[7]

Summary and Conclusion

Nonlinear effects discovered in 1986[2] are now frequently observed.[4-12] They can occur in asymmetric catalysis whenever some associations of chiral ligands occur directly or indirectly *outside* and/or *inside* the catalytic cycle. The diastereomeric associations produce a new situation (compared to enantiopure ligands) that is able to give departures from the usual linear correlation expressed by eq 1.

In the above situation, we made a clear-cut distinction between two models: model 1 (ML_n systems) and model 2 (reservoir effect).[31] In practice, these two extreme cases may merge or *combine together*. For example, we can say that the reservoir effect also exists inside the catalytic cycle when some diastereomeric complexes at the steady state are inactive or slightly active with respect to other species. Consider the ML_2 system (Figure 2) with eq 2 which gives the ee of the reaction product. If we have a catalytically inactive meso complex ($g = 0$), eq 2 is transformed into

$$EE_{prod} = EE_0 ee_{aux}(1 + \beta)$$

The same expression can be derived from eq 8 (reservoir effect) if one considers that the homochiral complex catalyzes formation of products with linear correlation (eq 1) while the meso complex is a dormant species (reservoir). By combining eqs 1 and 8 (taking $ee_{res} = 0\%$) one obtains

$$EE_{prod} = EE_0 ee_{aux}/(1 - \alpha) = EE_0 ee_{aux}(1 + \beta), \quad \text{since } \beta = \alpha/(1 - \alpha)$$

The more general situation will be the one where model 1 and model 2 act simultaneously. It is beneficial to increase first the ee of the ligand by a reservoir effect and to then increase it again according to model 1. Of course opposite effects should also be observed. The recent report of Faller on "chiral poisoning" seems to constitute a case of cooperation of both models, since the chiral poison first partially resolved the racemic chiraphos–rhodium complex, which by itself has been shown to give a positive nonlinear effect.[12b] An interesting conclusion of our studies on model 1 is the prediction that in some systems a partially resolved ligand should give a *higher* enantioselectivity (hyper-(+)-NLE) than the enantiopure ligand (bell-shape curve). This unconventional way to optimize an optical yield has to be considered seriously: it has some chance of occurring with ML_n systems ($n > 2$). Our study on model 1 also shows that double-shape curves are possible (Figure 12, ML_4 system), as recently found experimentally.[10]

NLE can be used as already pointed out,[4] as a mechanistic tool. For example, Seebach found that a chiral titanium diolate acts as an enantioselective catalyst for Et_2Zn addition to benzaldehyde (99% ee). There is a perfect linear correlation, in agreement with the hypothesis of a monomeric species in solution.[36] On the other hand, when there is a NLE (positive or negative), the shape of the curve can be informative about some of the species present in the solution (*vide supra* in the section Model 1). As mentioned above, Mikami and Nakai found that chlorotitanium–(*R*,*R*)-1,1′-binaphthoxide complex is an excellent catalyst for some ene reactions.[8b] There is a strong positive NLE

(31) Model 1 has been developed with some hypotheses, which are summarized: (i) There is no unbound chiral auxiliary, or the unbound fraction has its ee equal to ee_{aux}. (ii) The fraction of the active species ML_n (by respect to the total amount of complexes in the catalytic cycle) is the same for all the competitive catalytic cycles. (iii) The K parameter is assumed to be independent of ee_{aux} (this is true if the composition of the reactive complexes corresponds to the thermodynamic equilibrium or for a statistical distribution of ligands in the complexes). (iv) The number of isomeric ML_n complexes was taken equal to $n - 1$, with a meso structure for the complexes having a racemic composition in ligands. In specific cases additional stereoisomerism should increase the number of complexes. (v) The more general situation where catalysis occurs simultaneously by ML_{n-i} and ML_n complexes has not been considered, but it can be similarly treated. (vi) It is assumed that there is no modification of the catalysts by the product, as is sometimes observed.[32-35]

(32) Wynberg, H. *Chimia* **1989**, *43*, 150–152.

(33) (a) Alberts, A. H.; Wynberg, H. *J. Am. Chem. Soc.* **1989**, *111*, 7265–7266. (b) Alberts, A. H.; Wynberg, H. *J. Chem. Soc., Chem. Commun.* **1990**, 453–454.

(34) (a) Soai, K.; Niwa, S.; Hori, H. *J. Chem. Soc., Chem. Commun.* **1990**, 982–983. (b) Soai, K.; Hayase, T.; Shimada, C.; Isobe, K. *Tetrahedron: Asymmetry* **1994**, *5*, 789–792.

(35) (a) Danda, H.; Nishikawa, H.; Otaka, K. *J. Org. Chem.* **1991**, *56*, 6740–6741. (b) It is interesting to point out that in the above reference a catalyst derived from two different chiral components may give a product of slightly higher ee than the two initial ee's.

(36) Schmidt, B.; Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1321–1323.

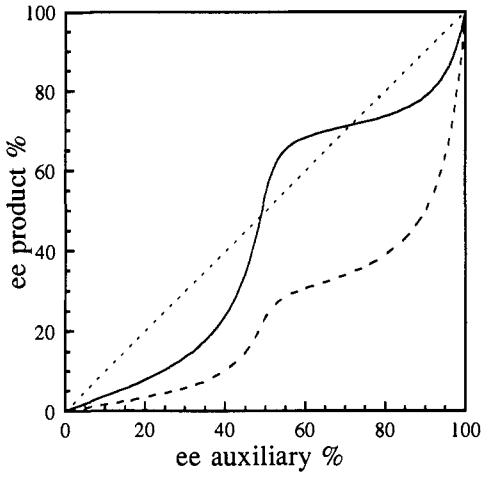


Figure 20. Computer-drawn for the ML_4 system with $EE_0 = 100\%$, $EE'_0 = 70\%$ (curve a, solid line) and 30% (curve b, dashed line), $K = 1000$, $K' = 1$, $g = 10$, $f = 100$. The dotted line symbolizes the linear correlation.

(Figure 19), and the authors analyzed the curve taking into account dimeric and trimeric species.[8c]

The general case of a mixture of ML_n species has been mathematically treated (see supplementary material). In this treatment the same hypotheses and parameters were retained as in the above ML_2, ML_3, and ML_4 cases, namely, relative reactivities (k_n) and relative distributions (x_n). A general equation allows one to analyze various cases and to find some features of the curves $EE_{prod} = f(ee_{aux})$. For example, the slopes of the curves for $ee_{aux} = 0\%$ and $ee_{aux} = 100\%$ are given by simple expressions. It is also possible to calculate the maximum number of intersections of the curve $EE_{prod} = f(ee_{aux})$ with the line $EE = EE_0 ee_{aux}$. This number is equal to $n - 2$. It means that intersection is impossible in the ML_2 case, while ML_3 and ML_4 will give rise to a maximum of one and two intersections, respectively. We checked this prediction for ML_4; in Figure 20 is indicated curve a, which exhibits such a behavior.

Triple-shape curves may also be computed in the ML_4 system (Figure 20, curve b), and such behavior has been found recently by Pfaltz *et al.*[11f]

The general equation also allows us to predict that a higher enantioselectivity may occur for partially resolved ligands (see Figure 10). This is always possible except for the ML_2 system. The mathematical treatment established that an inversion of absolute configuration of the product may occur, the reactions performed with enantiopure or partially resolved ligand giving products with opposite absolute configurations. One could even find a case where the enantiopure auxiliary ($ee_{aux} = 100\%$) generates a homochiral catalyst producing a racemic product ($EE_0 = 0\%$) while heterochiral complexes are enantioselective. This means that the line $EE_0 ee_{aux}$ is now horizontal in the graphs previously discussed.

A positive nonlinear effect could be useful in asymmetric autocatalytic reactions, namely, reactions where the product is involved in the generation of catalytic species. In the above discussion we did not consider that the product interacts with the ML_n species to generate new catalysts. In the special case where the product is also the same as the initial catalyst, then the amplification of ee can occur during the course of the reaction. Wynberg gave the first examples of related systems which can be considered as prebiotic models of propagation of optical activity on earth.[32,33] A few additional cases of asymmetric autocatalysis were described.[34,35] These results also underline the importance of the product formation which can give rise to mixed aggregates with some of the reactants, possibly influencing the course of the reaction itself.[6,27,32-38]

Much emphasis has been put on positive nonlinear effects since the amplification is synthetically beneficial. However, negative nonlinear effects should be important to consider. If a strong negative nonlinearity is present ("depressing effect" such as in Figure 3, $g = 100$), wrong conclusions could be formulated if one uses a ligand coming from the incomplete resolution of a racemic mixture. Indeed, here a trace of the undesired enantiomer will considerably lower the enantioselectivity of the asymmetric catalyst. We are currently looking for such a situation as well as examining other aspects of nonlinear effects, which remain of interest for both fundamental and applied chemistry.[39,40,42]

Experimental Section

General. All reactions were performed in freshly dried and distilled solvents. The yields cited refer to crude products unless otherwise stated. (*E*)-5-Phenyl-2-penten-1-ol (**3**) was prepared according to a modified published procedure.[44] In the asymmetric syntheses, the commercial (+)- and (−)-DET were of 99% ee. The (+)-MTPCl was prepared from commercial (+)-MTPA of 99% ee (oxalyl chloride and catalytic DMF in dichloromethane (DCM) at room temperature). The (+)-MTPCl was distilled once prior to use. The ee determinations were performed in C_6D_6 at 250 MHz. The (+)- and (−)-Eu(hfc)$_3$ were purchased from Aldrich.

The curves in the various schemes were computed by Excel and graphics obtained with KaleidaGraph. When there is a curve with experimental data, this curve has been adjusted by using the proper equations and set of parameters (in order to visually get a good fit).

Sharpless Epoxidation of Allylic Alcohol (*E*)-3. (−)-(1*S*,2*R*)-2,3-Epoxy-5-phenylpentan-1-ol (4). To a stirred solution of Ti(O-*i*-Pr)$_4$ (*ca.* 2.0 mmol) in dry DCM (15 mL) was added (+)-(*R*,*R*)-DET (1.1 equiv) *via* a syringe, under argon at −20 °C. After 5 min, to the stirred pale yellow solution was added a solution of **3** (1.0 equiv) in DCM (5.0 mL) dropwise, the temperature being maintained at −20 °C. To the resultant solution was added *t*-BuOOH (2 equiv of a *ca.* 3.3 M solution in anhydrous toluene), and the reaction mixture was transferred to a freezer (−18 °C) overnight.

The reaction was transferred to a −20 °C bath and treated with tartaric acid (1.67 equiv of a 1.6 M solution in water). The aqueous layer was seen to freeze. After 1 h at −20 °C, the reaction mixture was allowed to warm to room temperature, during which time the phases separated.

(37) Seebach, D.; Amstutz, R.; Dunitz, J. D. *Helv. Chim. Acta* **1981**, *64*, 2622–2626.

(38) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543–2549.

(39) Most of the equations developed above can apply to stoichiometric reactions where a chiral reagent has several ligands or gives rise to aggregation.[27] For example, the behavior of reagents of the ML_2 or $(ML)_2$ type with fast ligand exchange is described by eqs 2–5, and the complexes of Figure 2 represent the reagent and not catalytic species. This approach has already been considered here with the 1,4-addition of chiral cuprates[11] (see, in text, ML_2 systems). If there is no exchange of ligands for ML_2 or $(ML)_2$ systems the various diastereomeric reagents (whose distribution can change with ee_{aux}) will react at different rates. One expects a change of ee_{prod} as long as the reaction proceeds. Nonlinearity can be discussed meaningfully only for a reaction with a stoichiometric amount of the chiral reagent and a quantitative conversion. When the reagent is in large excess the diastereomeric composition will be independent of the reaction extent, allowing one to use eqs 2–5.

(40) The nonlinear effects are the consequence of the formation of diastereomeric species (by complexation or aggregation). If for a given system species of homochiral composition are produced, only full linearity is expected. There are no general trends allowing one to predict the distribution between diastereomeric species. For example, in metal complexes cases are known where the homochiral complexes are the most stable[23,41] or where there are no differences between homochiral and heterochiral complexes.[41]

(41) (a) Kurganov, A. A.; Ulanovskii, I. L.; Ponomareva, T. M.; Davankov, V. A. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1988**, *37* (7), 1537–1539; *Bull. Acad. Sci. USSR, Div. Chem. Sci. (Engl. Transl.)* **1988**, *37* (7), 1357–1360. (b) Boyle, T. J.; Eilerts, N. W.; Heppert, J. A.; Takusagawa, F. *Organometallics* **1994**, *13*, 2218–2229.

(42) Diastereoselective reactions and kinetic resolutions should also be perturbed by the same phenomena which are at the origin of nonlinear effects in enantioselective reactions. We are currently investigating this area. For a recent report on kinetic resolution in the asymmetric oxidation of sulfoxides, see ref 43.

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

(44) Nuñez, M. T.; Martín, V. S. *J. Org. Chem.* **1990**, *55*, 1928–1932.

The aqueous layer was removed, and the organic layer washed with water and brine. The organic layer was dried ($MgSO_4$) and evaporated. The crude epoxy alcohol was dissolved in ether (15 mL) and treated with NaOH (3.0 equiv of a 1 M solution in water) at 0 °C for 30 min. The aqueous layer was removed and the organic layer washed with saturated aqueous $NaHCO_3$, water, and brine. The organic layer was dried ($MgSO_4$) and evaporated to give **4** as a colorless oil, whose odor revealed slight contamination with unreacted *t*-BuOOH.

The epoxy alcohol was used crude in all further experiments; ^1H NMR indicated it generally to be ≥95% pure. A sample of the pure epoxy alcohol was distilled bulb-to-bulb ($bp_{0.3}$ 180 °C).

$[\alpha]_D^{20} = -33.3$ ($c = 4.22$, $CHCl_3$).

Measure of the Enantiomeric Excess of 4. ^1H NMR analysis of crude epoxy acetate (prepared by acetylation of **4**) in $CDCl_3$ and C_6D_6 (observation of the acetate CH_3 protons), in the presence of various quantities of (+)-Eu(tfc)$_3$, were unsuccessful in determining the enantiomeric excesses.

The ee of **4** was measured through formation of Mosher esters with (+)-MTPCl.[38] ^{19}F NMR analyses of Mosher esters in $CDCl_3$ or C_6D_6 (observation of the C-1′ fluorines) were unsuccessful in determining the enantiomeric excesses. ^1H NMR analysis of crude Mosher esters in C_6D_6 (integration of the C-3 protons) allowed direct measurement of the enantiomeric excesses.

Catalytic Asymmetric Hetero-Diels–Alder Reaction. Reaction was performed according to Danishefsky *et al.*[25a] using as catalyst Eu(hfc)$_3$ of various ee. The samples of catalyst were prepared by mixing weighed amounts of the two enantiomers, giving the following values of specific rotations ($c = 1$, $CHCl_3$): $[\alpha]_D = +135.5°$; $[\alpha]_D = +70.5°$; $[\alpha]_D = +31.5°$. These samples correspond to estimated ee's of 86%, 45%, and 20%, respectively.

A representative experiment is as follows: 5 mmol of benzaldehyde (0.5 g) and 5.5 mmol (1.2 g) of (triethylsilyl)oxy diene **8** were kept in 10 mL of chloroform with 0.05 mmol (60 mg) of Eu(hfc)$_3$ for 48 h at room temperature. Then 0.5 mL of CF_3CO_2H was added, and the reaction medium was stirred for 2 h at room temperature. After workup and flash chromatography on silica gel (ether/hexane = 1/3) one recovered 600–650 mg of pure enone **10** (71-75% yield). The ee was measured by specific rotation in chloroform ($c = 1$), taking $[\alpha]_D = -108°$ ($c = 1$, $CHCl_3$) as the maximum specific rotation of **10**.[25b] Results are as follows:

$[\alpha]_D$ catalyst	+135.5°	+70.5°	+31.5°
ee (%) of (*R*)-(−)-**10**	36	19.7	8.4

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Supplementary Material Available: Detailed calculations for model 1 in the general case of a mixture of ML_n complexes and in the particular cases M^*L_2 and ML_2 with dissociation to ML (chirality centered on M induced through complexation) (15 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.