

Practical Consequences of Non-Linear Effects in Asymmetric Synthesis

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Dedicated to Professor J.-F. Normant on the occasion of his 65th birthday.

Abstract: The fundamental principles of non-linear effects (NLE) are reviewed. Particular emphasis is placed on the case of asymmetric amplification, since it allows one to perform useful chemistry with a non-enantiopure chiral auxiliary. A strong asymmetric depletion in a catalytic reaction may lead to an underestimation of the actual enantioselectivity of the fully resolved ligand. The study of NLE's is also proving useful as a mechanistic tool in asymmetric catalysis. Similar concepts may be extended to chiral reagents or to kinetic resolution.

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1. What is a Non-Linear Effect in Asymmetric Synthesis?

Keywords: asymmetric amplification; asymmetric catalysis; asymmetric synthesis; chiral auxiliary; non-linear effects

A chiral auxiliary (in catalytic or stoichiometric amount) is necessary for the control of the formation of a new chiral unit (asymmetric center, atropoisomers, etc.). The chiral auxiliary may be directly taken

from the chiral pool (alkaloids, menthol, etc.) or derived from a natural product. It can also be obtained by total synthesis as a racemic mixture which is subsequently resolved. In both approaches it may sometimes be difficult to obtain the enantiomerically pure chiral auxiliary, even if a natural product is the starting material (for example, many terpenes are not enantiopure). It is then tempting to use a chiral auxiliary of a given enantiomeric excess (ee_{aux}), and to measure the ee of the corresponding product (ee_{prod}). The ee of the product (ee_{max}) formed with a chiral auxiliary of 100% ee can then be calculated by correcting for the ee of the chiral auxiliary:

$$ee_{max} (\%) = (ee_{prod}/ee_{aux}) \times 100.$$

Equation 1 is an equivalent equation in which the three ee 's are considered for simplicity to have absolute values ≤ 1 .

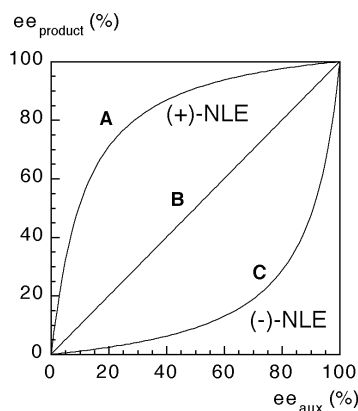
$$ee_{prod} = ee_{max} \times ee_{aux} \quad (1)$$

Equation 1 means that there is a linear relationship between ee_{prod} and ee_{aux} .^[1,2] This classical equation was used by many early practitioners of asymmetric synthesis. It can be rigorously established. For that purpose the only assumption required is that mixtures of various amounts of the enantiomeric auxiliaries will provide, in the same relative amounts, two asymmetric syntheses with identical rates, but giving products of opposite absolute configurations.^[5] The general validity of Equation 1 has been questioned by Izumi and Tai.^[4] In 1986, we demonstrated for the first time that deviations from Equation 1 may indeed occur in asymmetric catalysis.^[6] These deviations were named "non-linear effects" (NLE) to illustrate that the curves $ee_{prod} = f(ee_{aux})$ are no longer the straight lines defined by Equation 1. A positive non-linear effect [(+)-NLE] characterizes situations such as that of curve A in Scheme 1, demonstrating that the product is of a higher ee than the value given by the straight line B. A negative non-linear effect [(-)-NLE] corresponds to curves of type C, where the prod-

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ucts are of lower ee than expected. The terms asymmetric amplification^[7] and asymmetric depletion^[5] are currently used as synonyms of (+)- and (-)-NLE, respectively.



Scheme 1. The various possible relationships between enantiomeric excesses of the product (ee_{product}) and of the chiral auxiliary (ee_{aux}).

In our 1986 paper, we presented one case of asymmetric amplification (Sharpless epoxidation of geraniol) and two cases of asymmetric depletion (sulfide oxidation and proline-catalyzed intramolecular aldol reaction). Since that time, many examples of NLE have been discovered in a wide variety of reactions. Some reviews have been published.^[8–12] Asymmetric amplification has been specifically reviewed in refs.^[5,13]

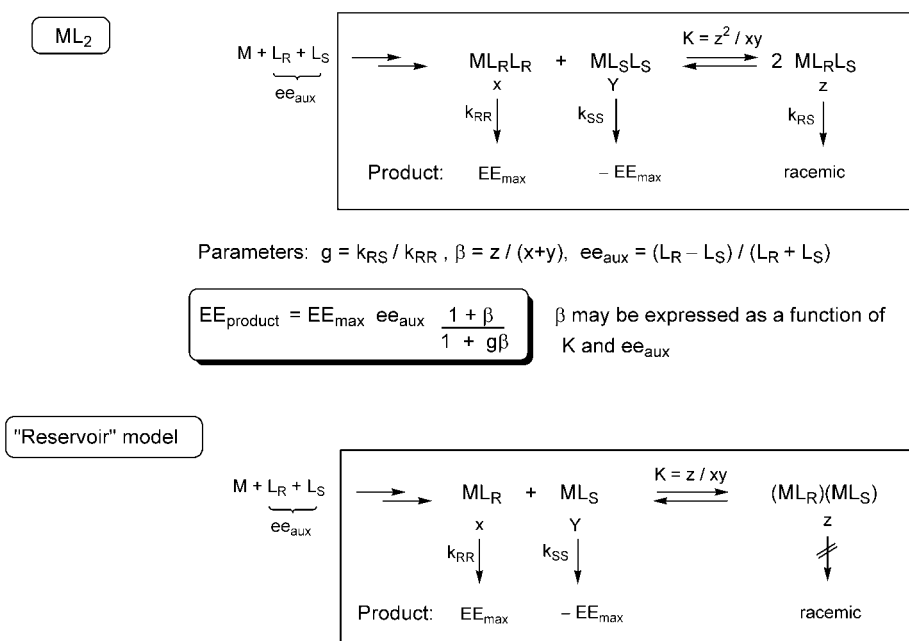
2. The Conditions for Observing a Non-Linear Effect in Enantioselective Catalysis

Two enantiomeric catalytic systems give rise to exactly the same distribution of products (but of opposite absolute configuration) and with identical reaction rates. The reason for this is the mirror-image relationships existing between the two systems.

When two enantiomeric catalysts are mixed in various amounts, the prediction of the enantiomeric purity of the products is easy, provided that the mixing does not introduce additional interactions between the enantiomeric systems. In this ideal behavior, simple additivity rules will give rise to Equation 1 (linearity). A deviation from ideal behavior must generate diastereomeric species that are not present in the homochiral systems with, as a possible consequence, a deviation from linearity. In the kinetic framework, the non-ideal behavior will introduce new reaction paths and may change the kinetics from those defined with the enantiopure catalysts.

Let us clarify these points by considering a metal complex bearing two ligands (L) symbolized as ML_2 . The corresponding enantiopure complexes with chiral ligands (L_R or L_S) may be of the type ML_RL_R or ML_SL_S . If the ligand has some enantiomeric excess (ee_{aux}), a heterochiral (*meso*) complex ML_RL_S may be created in addition to the two homochiral complexes ML_RL_R and ML_SL_S . The *meso*-complex is a diastereomer of the two homochiral complexes, it will give a racemic product and its catalytic activity may be very different to that exerted by the homochiral complexes. It will introduce a perturbation which cannot be predicted from the simple knowledge of the behavior of the homochiral catalysts. In such cases a deviation from Equation 1 can occur, giving a non-linear effect. The perturbation arises from the “heterochiral marriage” of the two enantiomeric auxiliaries, either inside (*vide supra*) or outside the catalytic cycle. For example, a monomeric catalyst ML_R may be in equilibrium with an inactive dimer $(ML_R)_2$. When the ligand is not enantiomerically pure, the mixed dimer $(ML_R)(ML_S)$ may also be formed. The latter is a newcomer which disturbs the predictions. One extreme case is a heterochiral complex of very high stability with respect to the homochiral dimers; it stores some racemic ligand and, consequently, increases the ee of the active monomeric catalyst (*vide infra*).

There are innumerable examples of kinetic schemes which may introduce non-linearity. They share in common some additional pathways or equilibria by respect to the reactions carried out with the enantiopure catalysts, building up new diastereomeric species.

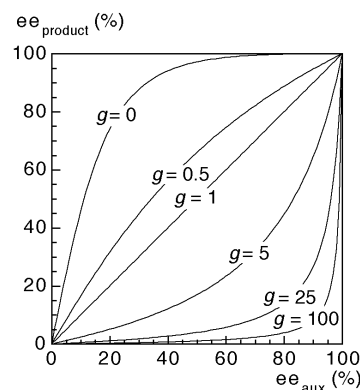


Scheme 2. Two models for explaining non-linear effects, where M stands for a metal and L for a ligand.

If the catalyst is modified by the product (autoinduction processes^[14,15]), additional complications will occur which, in principle, should give rise to non-linearity. This aspect, as well as asymmetric autocatalytic reactions,^[13] will not be discussed here.

3. Some Simple Models of NLE in Enantioselective Catalysis

Let us assume that an active catalyst is of the type ML_2 . It is possible to derive a simple kinetic scheme, by considering the three competing catalysts ML_RL_R , ML_SL_S , and ML_RL_S which are in equilibrium.^[16] The main features of ML_2 systems are indicated in Scheme 2. The calculated curves (ML_2 model) when there is a non-statistical distribution of ligands ($K = 64$) are reproduced in Scheme 3. If the *meso*-complex is unreactive ($g = 0$), this provides the maximum asymmetric amplification, while a very reactive *meso*-complex ($g = 100$, for example) gives rise to a strong (–)-NLE. Linearity is observed for the case of $g = 1$ (equal reactivity of heterochiral and homochiral catalysts). The second model of Scheme 2 involves the formation of the one-ligand complexes (ML_R and ML_S), which are the active catalysts, in equilibrium with the three inactive dimers ($(\text{ML}_R)_2$, $(\text{ML}_S)_2$, and $(\text{ML}_R)(\text{ML}_S)$). Strong asymmetric amplification may occur if the equilibrium favors the heterochiral dimer (with respect to the homochiral dimers) which acts as a trap for ligands of racemic composition, hence the name “reservoir effect” for this model. Computation can be done after fixing some parameters as the equilibrium constants.



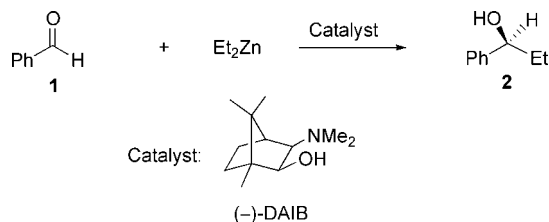
Scheme 3. Curves for $\text{ee}_{\text{product}} = f(\text{ee}_{\text{aux}})$ computed with the formula in the ML_2 model (Scheme 2). Equilibrium constant $K = 64$, g ($k_{\text{meso}}/k_{\text{homochiral}}$) ranging from 0 to 100.

4. Comparison of the Sizes of Asymmetric Amplifications

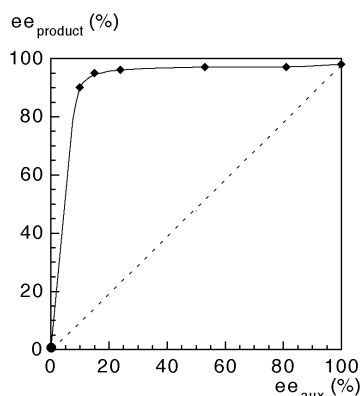
Let us consider the reaction of diethylzinc with benzaldehyde catalyzed by the β -amino alcohol **1** (DAIB) (Scheme 4). This reaction, studied by Noyori et al. in 1989, displays a superb asymmetric amplification (Scheme 5).^[17] The enantiopure DAIB provided 98% ee in alcohol **2**. When DAIB is only of 21% ee, the recovered product is of 96% ee!

Without asymmetric amplification the product is expected to be of only 20.6% ee ($98 \times 21\%$). The extent of asymmetric amplification can be expressed by the ratio $\text{ee}_{\text{prod}}/\text{ee}_{\text{linear}} = 97/19.4 = 4.9$. We suggested instead the use of the $\text{er}_{\text{prod}}/\text{er}_{\text{linear}}$ ratio in or-

der to obtain a better picture of the amplification. Here one calculates $er_{\text{prod}} = 49.0$ and $er_{\text{linear}} = 1.5$, giving an amplification of 32.6. The index of amplification is very appropriate when ee_{prod} and ee_{linear} are over 90%, making it difficult to estimate the amplification. For example, if $ee_{\text{prod}} = 99\%$ instead of $ee_{\text{linear}} = 97\%$, one calculates $ee_{\text{prod}}/ee_{\text{linear}} = 1.02$ and $er_{\text{prod}}/er_{\text{linear}} = 16.1$ respectively. The latter value is more realistic for the situation. In a recent review, we compared the asymmetric amplifications of various reactions by selecting the maximum asymmetric amplifications of each curve.^[5] The highest values presently known range between 10 and 32.



Scheme 4. Addition of diethylzinc catalyzed by (-)-DAIB.^[17]



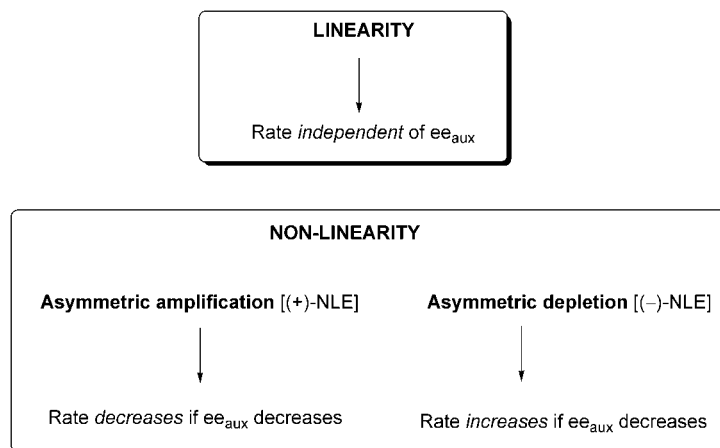
Scheme 5. An example of asymmetric amplification [(+)-NLE]: the reaction in Scheme 4.

5. Rates and Non-Linear Effects in Asymmetric Catalysis

New diastereomeric species may be generated if the chiral auxiliaries are non-enantiopure. As a direct consequence, this modifies the overall reaction rate (in comparison to that of the enantiopure system), as pointed out first by Blackmond.^[18] This is easily understandable by looking at the models of Scheme 2. In the ML_2 model, an asymmetric amplification means a low reactivity and a high amount of the heterochiral catalyst, hence a lowering of the global reactivity in comparison to a mixture of homochiral catalysts. The bonus given by the (+)-NLE has to be paid by a deficit, the decrease in the catalytic activity. The same conclusion is reached for the ML model with dimerization (Scheme 2). The decrease of the amount of ligand available for the monomeric catalysts consequently lowers the quantity of catalytic species in respect to the reference systems with enantiopure ligands. The general relationship between the rates and the enantiomeric excesses of the chiral auxiliary are represented in the Scheme 6.

6. Non-Linear Effects Involving Chiral Reagents

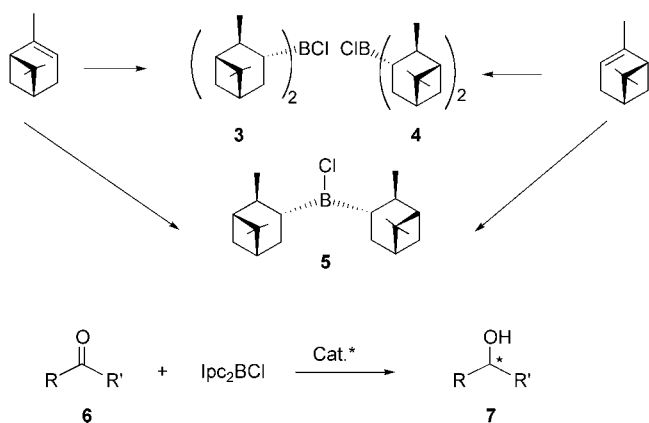
The concepts underlying the non-linear effects in asymmetric catalysis may apply with some modifications to enantioselective reactions involving a chiral reagent. A chiral reagent is prepared or derived from a chiral auxiliary. If the reagent is synthesized from several chiral units (for example $LiAlH_4 + 3 R^*OH$) or if it undergoes a dimerization, then one enters into situations quite similar to those depicted in Scheme 2. The difference lies in the fact that the chiral species are no longer in a fixed concentration (as usual for catalytic species), their amounts decrease with the extent of



Scheme 6. Relations between reaction rates and the presence or absence of non-linear effects.

conversion of the substrate. A chiral reagent involving several units of enantiopure chiral auxiliaries will be a mixture of diastereomers of different reactivities. Then, the more reactive species will react first and, as a consequence, one may observe a change of ee_{prod} with conversion, unless there is a large excess of reagent.

A good illustration of this situation is the asymmetric reduction of ketones by Ipc_2BCl , the reagent developed by Brown et al.^[19] A research group at Merck used this chloroborane of various enantiopurities for the preparation of an alcohol which is the key intermediate in the synthesis of a specific leukotriene antagonist.^[20–22] The authors found a strong asymmetric amplification, especially if ee_{prod} is measured at the early stages of the reaction.^[22] Independently, we performed similar studies on acetophenone, with similar conclusions.^[23,24] We observed an asymmetric amplification when Ipc_2BCl was prepared from non-enantiopure α -pinene, while there is linearity if the two isomers, (+)- Ipc_2BCl and (–)- Ipc_2BCl of 100% ee each, are mixed in various proportions. This has been interpreted as an absence of interconversion between homochiral reagents (**3**, **4**) and *meso*-reagent (**5**) during the ketone reduction (Scheme 7). The asymmetric amplification originates from the sluggishness of the *meso*- Ipc_2BCl **5** with respect to the two homochiral reagents, which are of higher ee than the initial α -pinene. The principle is very similar to those depicted in enantioselective catalysis, as exemplified in Scheme 2 (ML_2 model or reservoir effect for ML dimerization).



Scheme 7. Asymmetric reduction of ketones by Ipc_2BCl prepared from α -pinene of various enantiomeric excesses.

7. Mechanistic Applications of Non-Linear Effects

In asymmetric catalysis it is important to optimize the enantioselectivity in the transformation of a given substrate, by a fine tuning of the structure of the catalyst and of the experimental conditions. For that purpose some knowledge about the reaction mechanism

may be very useful. In just this context the study of non-linear effects is emerging as a simple and additional mechanistic tool.

The presence of (+)- or (–)-NLE is a good argument for some complexity in the kinetic scheme, with the formation of species containing several ligands giving rise to diastereomers. Often, the aggregation of a complex may be detected by a (+)-NLE coming from heterodimers or heterooligomers of low reactivity.^[17,25,26] Reactions which are second-order in catalyst may also give rise to (–)-NLE (as in asymmetric aldol reaction)^[6,27,28] or (+)-NLE (as in asymmetric *meso*-epoxide opening).^[29]

A non-linear effect coupled with some kinetic data may give rise to a significant insight into the mechanistic scheme of a catalytic system. For this purpose several rate laws have been elaborated, based on alternative mechanisms. Then, the simulation of the curves $ee_{\text{prod}} = f(ee_{\text{aux}})$ and $\text{rates} = f(ee_{\text{aux}})$ may be compared with the experimental data, allowing one to retain the hypothesis that gives the better fit.^[30,31]

In catalytic reactions where no NLE is observed, it is difficult to draw any conclusions. The linearity may reflect the monomeric character of all the ML complexes. It may also be the result of an aggregation of ML complexes or formation of ML_2 complexes, with parameters providing linearity. For example, the ML_2 system (Scheme 2) gives linearity if the *meso*-complex has the same reactivity as the homochiral complexes ($g = 1$), or if the *meso*-complex is not formed ($\beta = 0$). Similar conclusions have been drawn for dimers $(\text{ML})_2$ derived from ML monomers.

In enantioselective reactions involving a chiral reagent (*vide supra*), the study of the NLE at various conversions combined with a kinetic model may lead to useful predictions for applications. This had been highlighted by Blackmond who studied the kinetic aspects of the asymmetric reduction of ketones by Ipc_2BCl . She analyzed the data $ee_{\text{prod}} = f(ee_{\alpha\text{-pinene}})$ obtained at low conversion, when the reagent is prepared from enantiomerically impure α -pinene.^[30,31] The data were used to calculate the enantioselectivities at high conversions for various $ee_{\alpha\text{-pinene}}$, giving a good fit with the experimental values. The ML_2 model indicated that the *meso*-reagent was produced from α -pinene in a higher than statistical distribution, and that it has 10% of the reactivity of homochiral species ($g = 0.1$). This discussion is well supported by the recent work of Sowa et al., which established the *in situ* initial *meso/dl* distribution of the three reagents (**3**, **4**, and **5**).^[32] These studies allow us to safely predict what excess of Ipc_2BCl prepared from non-enantiopure α -pinene has to be used to achieve high enantioselectivities at a satisfactory reaction rate. Such an approach should be of wide applicability in asymmetric stoichiometric syntheses using non-enantiopure chiral auxiliaries.

8. Synthetic Applications

Non-linearity is the consequence of the complexity of the catalytic system or of the chiral reagent. Synthetic organic chemists must be careful about the presence of a *negative non-linear effect*. Let us consider a (–)-NLE which gives rise to an asymmetric depletion of 20 ($er_{\text{prod}}/er_{\text{linear}} = 20$). If the enantiopure catalyst generates a product in 99% ee ($ee_{\text{max}} = 0.99$), one expects for a ligand of 98% ($ee_{\text{aux}} = 0.98$) a product of $ee_{\text{linear}} = 0.99 \times 98\% = 97.0\%$, meaning $er_{\text{linear}} = 65.6$. The asymmetric depletion of 20 will instead give a product of $er_{\text{prod}} = 65.6/20 = 3.28$ ($ee_{\text{prod}} = 53.2\%$). Such a modest enantioselectivity for a chiral auxiliary of 98% ee does not reflect its high efficiency ($ee_{\text{max}} = 99\%$) when enantiopure. It could be misleading if the chiral auxiliary is easy to upgrade by crystallization. It also shows that a strong (–)-NLE can “kill” the development of some chiral auxiliaries, even if available in high enantiopurities.

On the contrary, a *positive non-linear effect* (asymmetric amplification) may provide a way to upgrade a chiral auxiliary of mediocre enantiopurity. In the previous example, let us replace the asymmetric depletion of 20 by an asymmetric amplification of equivalent size (20). A ligand of 20% ee will give a product of 93.5% ee ($er_{\text{prod}} = 29.8$) instead of $ee_{\text{linear}} = 19.8\%$ ($99 \times 0.20\%$).

9. Concluding Remarks

Non-enantiopure chiral auxiliaries may be worthy of consideration in stoichiometric or catalytic enantioselective synthesis when they are associated with an asymmetric amplification. Some kinetic investigations help to predict the best experimental conditions beneficial both to a high enantioselectivity and a convenient reaction rate.

The presence of a non-linear effect is a factor that can be used to analyze a mechanism or to gain some information about the state of the catalyst or of the reagent (for example, their aggregation state). The reaction rate dependence on enantiomeric excess of the chiral auxiliary is also useful to consider.

Asymmetric amplification is a beneficial situation which may allow one to use non-enantiopure chiral auxiliaries, while high asymmetric depletions may be detrimental to enantioselective reactions run with chiral auxiliaries of high ee's.

Finally, the concepts that form the foundations of non-linear effects may be extended to kinetic resolutions,^[35–35] or to mixtures of diastereomeric catalysts (although with some modifications).^[36–39]

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