Nonlinear Effects in Asymmetric Catalysis: A Personal Account

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Dedicated to Professor R. Noyori for his fundamental contributions to organic chemistry and asymmetric catalysis.

Abstract: The discovery of nonlinear effects (NLE) is recalled, and the main features of NLE are described. The origin of the nonlinear effects is discussed. The asymmetric amplification is especially considered. The concept on nonlinear effects has been extended to pseudo-enantiomeric catalysts, to chiral reagents and to kinetic resolution. The use of NLE as a mechanistic tool is underlined.

Key words: asymmetric amplification, asymmetric catalysis, asymmetric depletion, asymmetric synthesis, chiral auxiliary, nonlinear effects

1 Introduction

This article does not intend to detail the area of nonlinear effects for which already exist many review articles in journals or books.[1-7] I would like to explain how we entered in that field, and what were the early investigations as well as the main subsequent developments.

I became involved in asymmetric catalysis in the late sixties, when we developed the use of C_2-symmetric chiral diphosphines such as (–)-diop **1**.[8,9] We also looked at some monophosphines, which gave much less enantioselective catalysts than camp **2**.[10] At that time I considered what could be the behaviour of a rhodium catalyst with a non-enantiopure ligand. I suspected some complications for the monodentate phosphines, since two ligands are involved possibly giving rise to diastereomeric catalysts.[11] We checked that with diop **1** of 50% ee the asymmetric hydrogenation of (*Z*)-*N*-acetyl-dehydrophenylalanine gave *N*-acetylphenylalanine with exactly half of the value observed with enantiopure diop (40% ee versus 80% ee). We envisaged to investigate the behaviour of some non-enantiopure monophosphines, but the project was stopped because of lack of easily available enantioselective monophosphines. However, I remained convinced that the accumulation of chiral ligands in a catalyst should sometimes give unpredictible results if the initial material is not enantiopure. I worked until 1968 in the laboratory of Prof. Horeau in College of France, and I kept contact with him later, then I was aware of the literature dealing with diastereomeric associations in solution. For example Horeau clearly demonstrated that optical purity (measured by polarimetry) and enantiomeric excess (measured by any reliable method) are not always equivalent.[13] The departure to linearity occurs when the solvent favours autoassociations of the chiral solute. This has been well established with 2-ethyl 2-methyl succinic acid, which gave an important deviation to linearity in chloroform (because of diastereomeric aggregate formation). Uskokovic et al. discovered that the nmr spectrum of dihydroquinine racemic or enantiopure are not identical, because of diastereomeric solute-solute interactions.[14] Horeau and Guetté discussed in details in 1974 the diastereomeric interactions in solution between enantiomers.[15] In 1976 Wynberg and Feringa demonstrated that some diastereoselective reactions can give a different stereochemical outcome if the substrates are not enantiomerically pure.[16] The authors called this effect "antipodal interaction effect", it is related to non-bonded interactions.

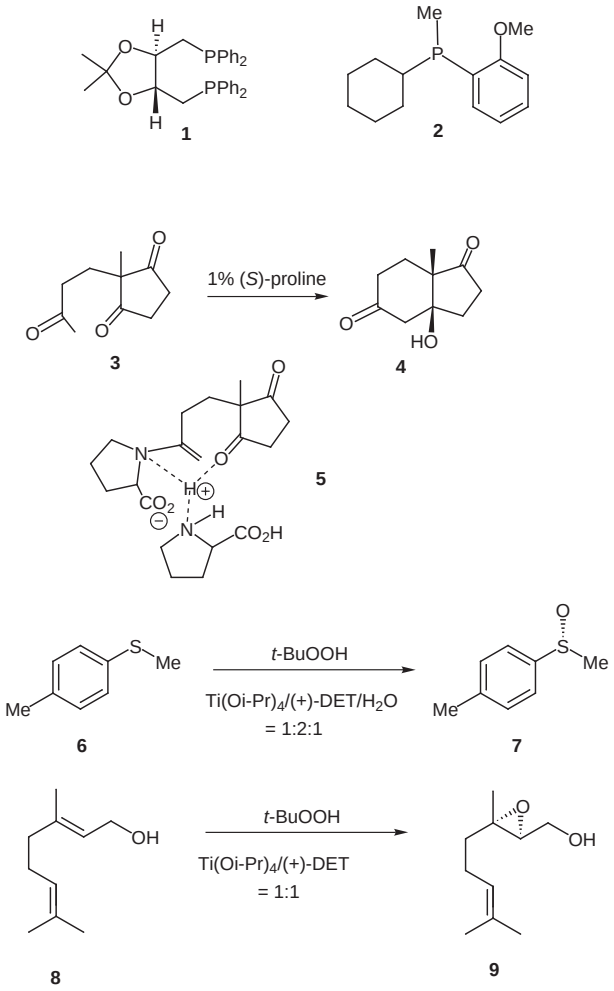
In 1985 I was invited by Prof. Agami to give a seminar in Université Paris VI. After my lecture I discussed with Prof. Agami, and he tell me that he was investigating the mechanism of the Hajos-Parrish-Wiechert aldol cyclisation of triketone **3** into ketol **4**.[17,18] The mechanistic details were unknown at that time. The Agami group interestingly discovered that the reaction was second-order with the catalyst.[19,20] This means that two proline molecules were presumably involved in the reaction, as described for **5**. I suggested to use non-enantiopure proline to get an additional indication of the participation of two proline molecules. The experiments were quickly done, showing values of ee for ketol **4** lower than expected by applying the usual rule eq. 1 which relates ee of product (ee_{prod}) and ee of auxiliary (ee_{aux}).

$$ee_{prod} = ee_{max}\ ee_{aux}$$

Equation 1

In eq. (1) ee_{max} is the ee value of product observed by using enantiopure catalyst.

Simultaneously, we investigated the asymmetric sulfoxidation **6** → **7** by changing the enantiomeric excess of diethyl tartrate.[21] There was a significant departure to linearity, especially when DET was below 70% ee. The sulfoxide **7** had an ee much lower than that calculated from eq. 1. Finally the Sharpless epoxidation of geraniol **8** was checked and gave an epoxide **8** of higher ee than predicted from eq. 1. We decided with Prof. Agami to write a joint paper which was published in 1986[25] (see section 2).



Scheme 1

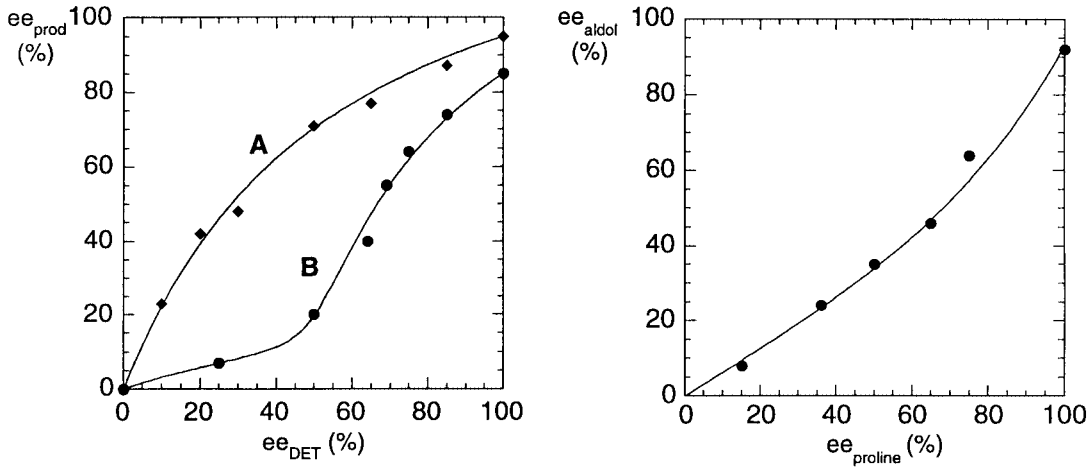
2 Nonlinear effects

The three curves obtained in the 1986 paper are reproduced in Scheme 2. The departure to the straight line computed by eq. 1 is significant, although not very high. However it was enough to clearly show a breaking of the proportionality rule as described by eq. 1. In conclusion there are three possibilities of curves when plotting ee_{prod} versus ee of chiral auxiliary (ee_{max}), as indicated in Scheme 3. We soon introduced a vocabulary to define the departure to the linearity in the graph $ee_{prod} = f(ee_{aux})$. The curve above the straight line was said to characterise a positive nonlinear effect, abbreviated as (+)-NLE. This is to recall that the size of the enantiomeric excess (in absolute sense) is higher than the value calculated by eq. 1 ($|ee_{prod}| > |ee_{linear}|$]. When the curve is below the straight line ($|ee_{prod}| < |ee_{linear}|$], the phenomenon was called negative nonlinear effect [(–)-NLE]. We used this vocabulary since 1987[26], we learned that Mikami et al. independently proposed the same convention.[27] For conveniency we draw the graphs as indicated in Scheme 3, whatever are the absolute configurations of the product or of the chiral auxiliary.[28]

After our 1986 paper, there were no other reports in that area, until a publication of Oguni et al. in 1988 which described a strong positive nonlinear effect in the addition of diethylzinc on benzaldehyde catalyzed by PDB **12** (Scheme 4).[30] The authors proposed to use the expression "asymmetric amplification" as synonymous of (+)-NLE. We later similarly introduced the expression "asymmetric depletion" as equivalent to (–)-NLE.[29] In 1989, R. Noyori et al. published an important paper where the formation of **11** was catalysed by DAIB **13**.[31] The size of the asymmetric amplification was impressive : for example **13** of 15% ee gave product **11** in 95% ee, not too far from the maximum value of 98% ee with the enantiopure catalyst. The paper also afforded some mechanistic investigations allowing to discuss of the origin of the nonlinear effect (*vide*

Biographical Sketch

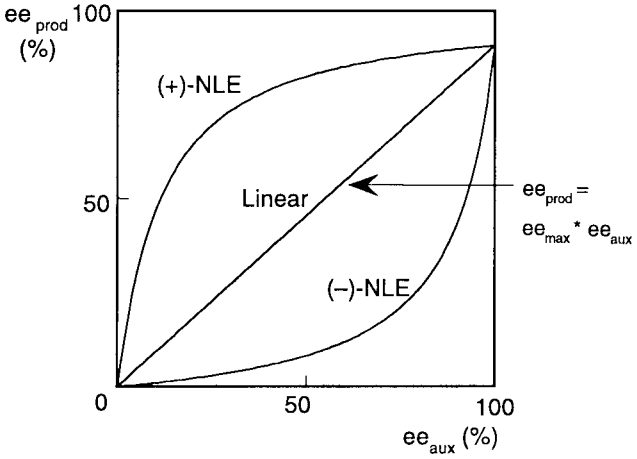
Henri B. Kagan was born in Boulogne-Billancourt, France in December 1930. He graduated from Sorbonne and Ecole Nationale Supérieure de Chimie de Paris in July 1954. He got a PhD in College de France in 1960 (Paris) under the supervision of Dr J. Jacques. After his PhD he became research associate with professor A. Horeau in College de France. In 1965 he was research associate at University of Texas, Austin (Pr T. Mabry). In 1967 he became professor in Université Paris-Sud, where he is emeritus professor since 1999. He is member of the french Academy of Sciences. He was the supervisor of 60 PhD and 60 postdoctoral fellows. He developed researches in various area of organic synthesis and stereochemistry. His current research interests are mainly related to new aspects of asymmetric catalysis. He has been the recipient of various awards and distinctions over the years, including the 2001 Wolf Prize in Chemistry shared with Profs R. Noyori and K. B. Sharpless.



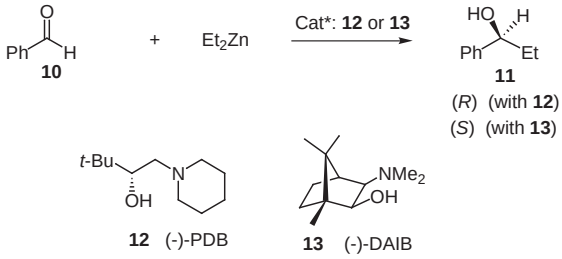
A: asymmetric epoxidation into **9**
B: asymmetric sulfoxidation into **7**

asymmetric aldol formation (**4**)

Scheme 2 Early examples of nonlinear effects[25]



Scheme 3



Scheme 4

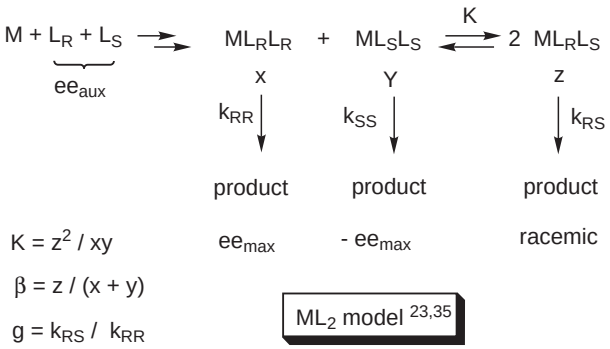
3 About the origin of nonlinear effects

My personal perception of the abnormal behaviour connected with the use of non-enantiopure auxiliaries was the possible occurrence of diastereomeric species, not present in the enantiopure system.

The simple model, based on organometallic chemistry, that we soon envisaged, was symbolised as ML_2 (M and L stand for metal and ligand, respectively). It is indeed quite common to find a catalyst involving two chiral ligands. A mathematical model was then devised, assuming reaction rates first-order with substrate and catalyst.[25] The model was later extended as ML_n ($n \leq 4$).[35] The key feature is the involvement of a heterochiral (*meso*) catalyst which can compete with the homochiral catalyst, and make the enantiomeric excess of the product worst with respect to the ee (ee_{linear}) as calculated by eq. 1. The reverse possibility is to see the heterochiral catalyst fully unreactive, paving the road to catalysis by the homochiral catalyst of higher ee than the initial ee_{aux}. The increase of enantiomeric excess for the acting catalyst comes from the removal of some racemic ligand, trapped into the unreactive *meso* complex. The calculations on the ML_2 model involving an

infra). Narasaka et al. observed in 1989 a (+)-NLE in a Diels-Alder reaction catalysed by a titanium/binol Lewis acid, at low ee_{aux} the reaction medium was not homogeneous because of the precipitation of some titanium complexes.[32] In 1990 Mikami and Nakai used a titanium-binol catalyst in the glyoxylate-ene reaction, they observed a substantial asymmetric amplification.[33] After 1990 an increasing number of publications noticed or studied nonlinear effects. We published a large review article in 1998 entitled "Nonlinear effects in asymmetric synthesis and stereoselective reactions: ten years of investigations". In this article over 90 references directly connected to NLE have been collected.[1] A broad array of reactions have been shown to display NLEs, usually in the presence of an organometallic chiral catalyst. Organic catalysts are also able to lead to NLEs, as already mentioned above with proline, but until now only few examples are known.[34]

equilibrium between the three complexes, used as parameters the relative reactivity expressed by $k_{rel} = k_R/k_S = g$ and the equilibrium constant K. A useful parameter for the calculations is the relative amount β of heterochiral versus homochiral complexes (Scheme 5).



Scheme 5

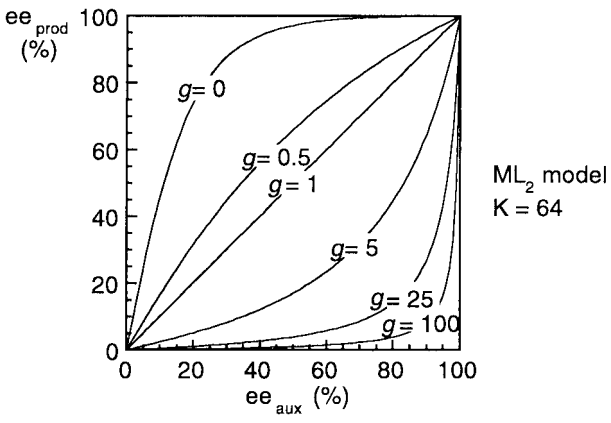
Using the simple kinetic scenario in Scheme 5 it was possible to establish eq. 2 between ee_{prod}, ee_{aux}, g, and β. In this equation ee_{max} stands for the enantiomeric excess of the product when the chiral auxiliary is enantiomerically pure.

$$ee_{prod} = ee_{max}\, ee_{aux}\, (1+\beta) / (1+g\beta)$$

Equation 2

Eq. 2 collapses into eq. 1 (linearity) when β = 0 (absence of *meso* catalyst) or if g = 1 (same intrinsic reactivities of homochiral and heterochiral complexes). We named ee_{linear} the value of ee_{prod} obtained from eq. 1. If the *meso* complex is the fast catalyst (g > 1), then $(1+\beta)/(1+g\beta) < 1$, whatever is the relative amount of β. It results that $ee_{prod} < ee_{max}\, ee_{aux} = ee_{linear}$, characterising a (–)NLE. If the heterochiral complex is slower than the homochiral complex (g < 1) it will generate an asymmetric amplification [(+)-NLE]. The maximum asymmetric amplification will occur for g = 0, meaning a fully unreactive *meso* complex. Under that circumstance, eq. 2 gives $ee_{prod} = ee_{linear}(1+\beta)$. The larger is the relative amount of heterochiral complexes, the highest is the asymmetric amplification. In eq. 2 it is possible to express β as a function of ee_{aux} and K, and then to compute curves $ee_{prod} = f(ee_{aux})$ for given values of g and K. In Scheme 6 is represented the example of curves obtained for K = 64. The statistical distribution of L_R and L_S between the complexes occurs for K = 4, accumulating less *meso* complex than for K = 64.

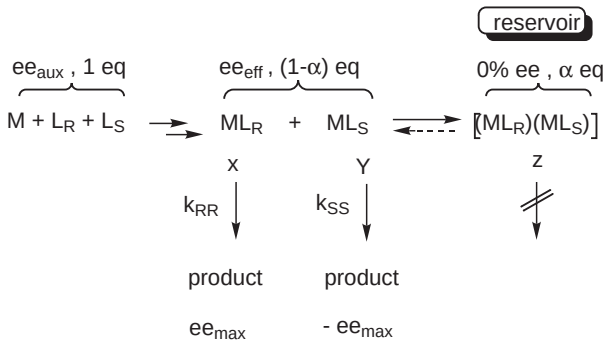
The mechanistic studies of R. Noyori et al. on the addition of diethylzinc on benzaldehyde catalysed by DAIB **13** (Scheme 4) gave some light on the origin of the asymmetric amplification in this reaction.[31,36,37] The key factor is the formation of a zinc alcoholate of **13**, which dimerises



Scheme 6

into a stable unreactive heterochiral *meso* dimer. Kinetic studies favoured the alkyl transfer on the carbonyl group within a dinuclear zinc species involving only one chiral ligand. Then the asymmetric amplification is clearly explained by the enhancement of the enantiomeric excess of the chiral ligand which is present in the reactive zinc complex. It gives an alternate mechanism for asymmetric amplification to the one we proposed in the ML_2 model, but the bases remain similar : an amplification of the enantiomeric excess of the ligand involved in the catalytic species thanks to a mechanism allowing to store some amount of racemic ligand out of the catalytic cycle [monomeric complex ML_RL_S or dimeric complex $(ML_R)(ML_S)$]. In 1994 we formalised the case where inactive complexes of racemic composition are involved, calling it the "reservoir" mechanism (Scheme 7).[35] In the same paper we computed by the ML_n model (n > 2) many fancy curves, especially multi-shape curves. Simultaneously we looked for some experimental evidences in literature. For example, the 1,4-addition of a methylcuprate on an enone gave rise to an asymmetric synthesis of muscone in presence of a β-aminoalcohol.[38] A NLE study provided data displaying a (+)-NLE at high ee_{aux} and a (–)-NLE at low ee_{aux}, with a crossing of the straight line around ee = 50%. We were able to simulate this curve by a formal ML_4 model, our interpretation being the involvement of dimers of dimers accounting for the 4 chiral ligands[35] (for a recent discussion on this case see ref. 39). One type of curve that we predicted by the ML_n model (n ≥ 3) is the possibility that an enantiopure catalyst with mediocre enantioselectivity can give rise to a better enantioselectivity by decreasing the enantiopurity of the ligand.[35] This paradoxical situation has not yet been found experimentally.

In 1997 Blackmond pointed out that the ML_2 system also can be discussed from the point of view of the reaction rates.[40-42] In the ML_2 model (Scheme 5) one can calculate the relative amounts x, y, and z of the three competing catalysts, then giving access to the total amount of product obtained for a given ee_{aux}. In other words, it is possible to get the relative rates of product formation as a



Scheme 7

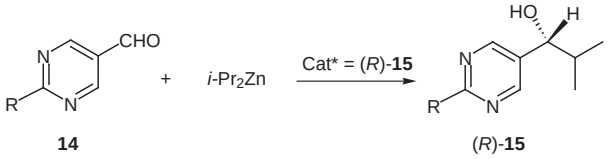
function of the initial enantiomeric excess of the ligands (ee_{aux}). Calculations showed for asymmetric amplification a decrease of rate when ee_{aux} decreases, and an increase of rate for (–)-NLE. In the absence of NLE the reaction rate is independent of the ee_{aux} values. The slow-down in reaction rate with asymmetric amplification is easy to understand and has been often experimentally observed. It occurs because of the storage of some amount of racemic ligand in the unreactive *meso* complex (or in a reservoir mechanism) which decreases the amount of acting catalyst (by respect to the enantiopure case). The bonus (highest ee_{prod} than expected) has to be paid by a malus (a decrease of reactivity).

4 Asymmetric amplification [(+)-NLE]

Asymmetric amplification attracted a lot of interest in asymmetric catalysis and has been described for a wide range of reactions. The size of the amplification has been usually approximated at a given ee_{aux} to the ratio ee_{prod} / ee_{linear}, where ee_{linear} is the theoretical value calculated from eq. 1. The method applies well if ee_{prod} and ee_{linear} are sufficiently different from each other, this often occurs when ee_{aux} is below 50%. In the case of large values of ee_{aux}, such as 90%, the above ratio is not a good indicator of the asymmetric amplification. For example let us assume that with ee_{max} (%) = 99 one recovers for 90% ee_{aux} a product of 98% instead of the expected $ee_{linear} = 99 \times 90\% = 89.10\%$. This means the modest asymmetric amplification of $ee_{prod}/ee_{linear} = 98.0/89.1 = 1.10$. The asymmetric amplification which occured has been clearly underestimated by the calculation method. It is why, instead, we proposed to compare the enantiomeric ratios (er), which often give a better description of the enantiomer distribution.[43] Ee's of 98.0% or 89.1% mean enantiomeric ratios of 99/1 = 99 and 94.5/5.5 = 17.3 respectively. In the above example one calculates the amplification as $er_{prod}/er_{linear} = 99/17.3 = 5.7$.

In a recent review on asymmetric amplification we compared the various cases by selecting in each reaction the maximum amplification index $I = er_{prod}/er_{linear}$, which usually occurs in the range of 20-30% ee_{aux}.[29] The highest amplification yet described (I = 30) seems to be given by DAIB, the Noyori catalyst.[31]

The asymmetric amplification is beneficial since one recovers a product of higher enantiopurity than expected for a given ee of the chiral auxiliary. It can be useful in asymmetric catalysis if the chiral auxiliary is difficult to get enantiomerically pure. Asymmetric amplification can also be helpful in autocatalytic reactions. Since the product is the catalyst of its own formation, its enantiomeric excess will be maintained close to the ee_{max} of the reaction because of a (+)-NLE, even if the chiral auxiliary is initially in a low enantiomeric excess. This has been beautifully established by Soai et al. in recent past, in the addition of diisopropylzinc on some pyrimidylcarboxaldehydes (Scheme 8).[44] For example 3.2 mg of β-aminoalcohol (*S*)-**15** (R = Me) (0.3% ee) produced in a one-pot operation 323.5 mg of (*S*)-**15** in 87.0% ee. It means that the combined use of asymmetric amplification and autocatalysis allowed to give an amplification of 14 on the enantiomeric ratios and of 107 of the initial amount of material. The reaction **14** → **15** is also catalysed by various families of chiral compounds. This transformation performed in the presence of a small amount of aminoacids of low ee's gave alcohol **15** (as zinc alcoholate) in low ee's (0.1%) which is reused as catalyst of the reaction **14** → **15**. In that way **15** with ee's in the range of 80% could be isolated.[45] The transformation **14** → **15** can be used as an "indicator" for the presence of some slight enantiomeric imbalance in a compound, also providing the absolute configuration of the predominant enantiomer. The presence of optically active inorganic solids such as quartz or sodium chlorate is also able to drive the reaction of Scheme 8 towards the formation of enantioenriched **15**.[45]



Scheme 8

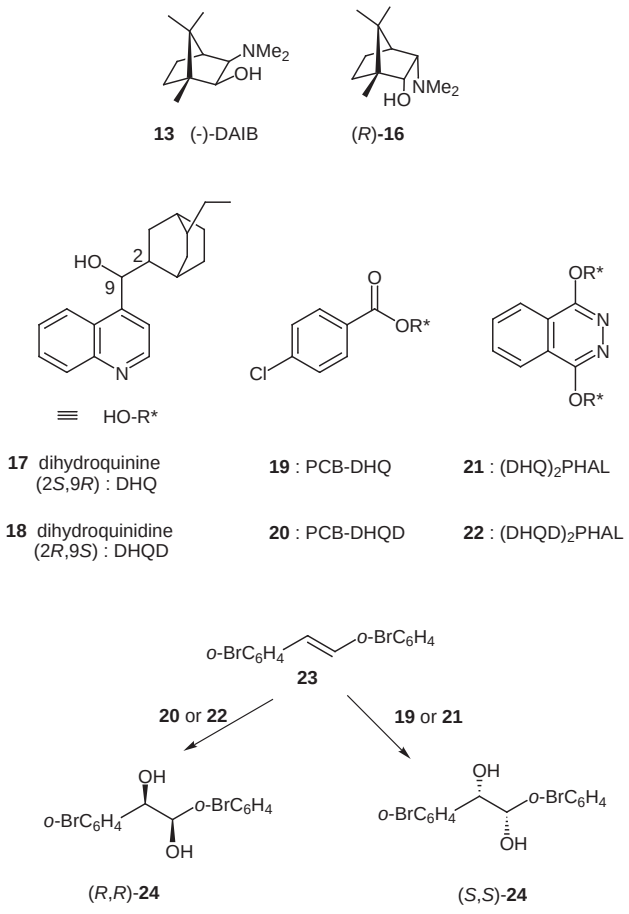
What is at the roots of the asymmetric amplification phenomena ? As said in the previous section the (+)-NLE is the result of the storage of some racemic auxiliary as inactive or slow-reacting species. A simple molecular mechanism which can operate is related to the "Horeau duplication method".[46] This method has been set up to increase the ee of a compound (A_R, A_S) without using a chiral auxiliary. It is based on the action of a difunctional achiral auxiliary which couple two A units, giving A_R-Z—Z-A_R+A_S-Z—Z-A_S+A_R-Z—Z-A_S. The coupling can be statistical and does not need a *meso* preference. The separation of the *meso* compound by any method will give enantioenriched mixture of the two homochiral compounds, which will be cleaved to regenerate the A_R, A_S

mixture of higher ee than the initial ee. The amplification of the enantiomeric excess has been paid by the loss of some amount of the initial material (as a racemic mixture). Horeau demonstrated the validity of this approach by increasing the enantiomeric excess of various alcohols through the transient formation of carbonates. Horeau did not notice that the same idea has been proposed earlier by Langenbeck, mainly as a possible mechanism to maintain the enantiopurities of some compounds in biological systems.[47] Langenbeck performed some experiments for the amplification of ee of menthol through oxalate ester formation.[48] What are the connections between the "Horeau-Langenbeck" duplications and the asymmetric amplification in catalysis? The similarities come from the amplification of ee's of the acting catalysts without help of external chirality. For example in the ML_2 model ($g < 1$) (Scheme 5) one recognise a "duplication" of ligands L, thanks to the coordination to the metal M. There is no physical separation of the *meso* complex from the heterochiral complexes, the removal of some racemic ligands is replaced by an in situ deactivation mechanism, which does not need an external chirality. In the "reservoir" mechanism of Scheme 7 the analogy with the "Horeau-Langenbeck duplication" is more evident, since some racemic part is stored in situ as an inactive *meso* dimer, while the catalysis is going on through the monomeric complexes. In all the cases of (+)-NLE the asymmetric amplifications result from some in situ "duplication", which removes from the catalysis a fraction of the chiral auxiliary as a racemic mixture.

5 Extension of the concept of nonlinear effects

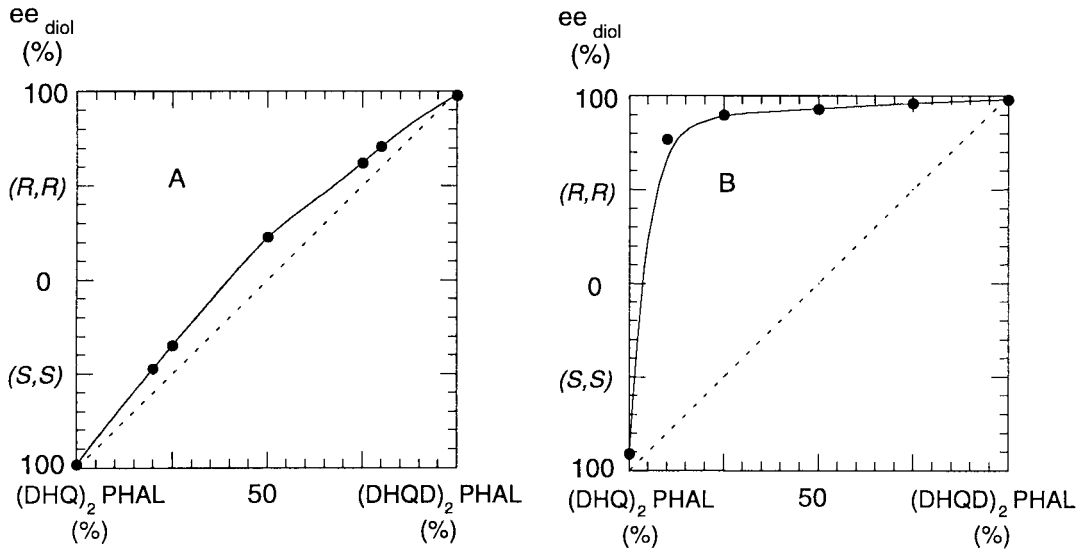
5.1 Pseudo-enantiomeric catalysts

Sometimes two catalysts of different structures can provide in a reaction products of similar ee's and of opposite absolute configuration. These catalysts will be named "pseudo-enantiomers" (referring to the products). This definition applies well to catalysts built with some diastereomeric ligands (quinine, quinidine etc).[50] The definition can be extended to couples of ligands such as dihydroquinine *p*-chlorobenzoate (PCB-DHQ) and dihydroquinidine phtalazine [$(DHQD)_2PHAL$] which give diols of opposite absolute configuration in osmium-catalysed dihydroxylation of alkenes.[51] Because of the non-enantiomorphic relationships between pseudo-enantiomeric catalysts one can envisage a different behaviour in the rates, in addition to the formation of products of opposite configurations. Consequently a mixture of pseudo-enantiomeric catalysts will provide a mixture of enantiomeric products which do not reflect the catalysts composition, as in nonlinear effects discussed previously. In 1995 the Noyori group and our group described such a complex behaviour for different systems. Noyori et al. studied the reaction of diethylzinc on benzaldehyde (Scheme 4) with mixture of (–)DAIB **13** and (*R*)-**16** (Scheme 9).[37] (–)-DAIB provided (*S*)-**11** with 98% ee while the pseudo-enantiomer **16** gave (*R*)-**11** with 94% ee. The authors studied the curve ee_{prod} as a function of the catalyst composition (expressed as the mole equivalent (%) of the two catalysts) and their relative reactivities. The experimental curve showed some significant deviation from the calculated curve, because of the preferential formation of a heterodimer of low reactivity. A nonlinear effect is apparent here, while the mixture of (–)-**13** and (*S*)-**16** gave (*S*)-alcohol with almost perfect linearity. The rates of reaction were also shown to be very sensitive to the composition **13**/**16**, with a strong departure to predictions, with an important slow-down close to the 1:1 composition of the two catalysts.



Scheme 9

We investigated the asymmetric dihydroxylation of dibromostilbene **23** by the Sharpless catalysts OsO_4 / alkaloids. Sharpless et al. established that dihydroquinine and dihydroquinidine derivatives gave diols of opposite absolute configuration.[51] Moreover they found that the phtalazine catalysts **21** or **22** afforded faster reactions and higher enantioselectivities. We studied the enantiomeric excess of diol **24** as a function of the composition of a mixture of alkaloids affording products of opposite configuration.[52] The curve $ee_{aux} = f(\text{catalyst composition})$ has been studied first for the mixtures of two diastereomeric ligands, $(DHQ)_2PHAL$ and $(DHQ)_2PHAL$, which give (*S*,*S*)-diol



Scheme 10

24 and (*R*,*R*)-diol **24** respectively in 98-99% ee. The experimental curve (Scheme 10) is very close to a straight line, as expected if two independent catalysts are acting in a simple kinetic scheme at similar rates and similar enantioselectivities, but giving products of opposite configuration. By contrast, the mixture of $(DHQD)_2PHAL$ and PCB-DHQ provided a curve very similar to a nonlinear effect. It means that even minor amounts of $(DHQD)_2PHAL$ are able to dominate the reaction. Presumably, the larger affinity of this ligand (with respect to PCB-DHQ) towards OsO_4 and the rate acceleration observed with phtalazine ligands are responsible of this unusual curve, which could not be predicted from the behaviour of the independent ligands.

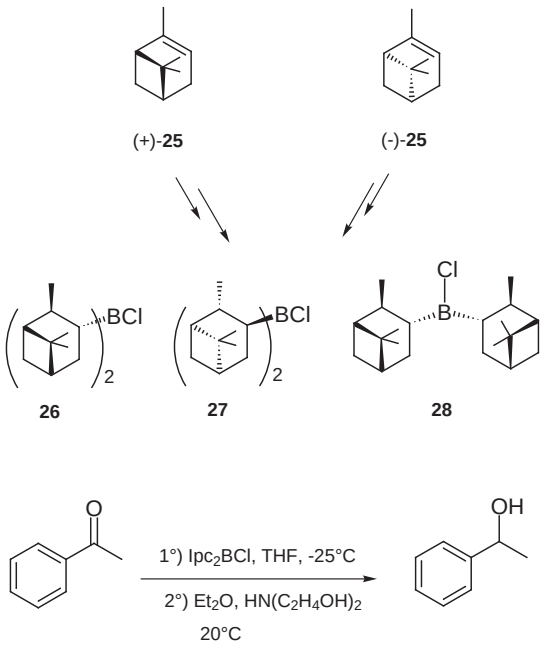
The rough evaluation of the relative rates of two chiral catalysts is often done by using a 1:1 mixture of catalysts giving products of opposite configuration.[53-55] It means that in the case of mixtures of **21**/**22** or **19**/**22** this type of evaluation would be carried out by considering ee_{prod} for 50% of each ligand. This procedure shows (curve **A**) ee_{prod} 5% (*R*,*R*), expressing a slightly higher reactivity of $(DHQD)_2PHAL$ with respect to $(DHQ)_2PHAL$. Curve **B** gives ee_{prod} = 90% (*R*,*R*), very far away from the expected 1% ee expected for equivalent reactivities.This is indicative of the higher reactivity of the phtalazine ligands with respect to the PCB ligand. The case of mixture of diastereomeric catalysts has been quantitatively analysed in the asymmetric hydrogenation of dimethyl itaconate by some diphosphite-rhodium catalysts.[56] An increasing number of examples of pseudo-enantiomeric or diastereomeric catalysts are described in literature.[50] One interesting aspect is the possibility to run a reaction with a mixture of chiral but non-enantiomeric catalysts, if one is much more reactive and enantioselective than the other. This is a situation quite similar to asymmetric amplification [(+)-NLE] previously discussed. Asymmetric poisoning[57,58] or asymmetric activation[39] of racemic catalysts involve the formation of complexes of different reactivities and will not be discussed here.

5.2 Chiral reagents

A chiral reagent is usually prepared by attachment of a chiral auxiliary to an achiral reagent. If the chiral auxiliary is enantioimpure it will generate a mixture of enantiomeric reagents. A chiral reagent can also involve in its structure two chiral units or it can give rise to oligomers (as often observed with organometallics). In both cases new diastereomeric species have the opportunity to be created under certain circumstances, introducing a complex behaviour in the asymmetric synthesis. The stoichiometric asymmetric synthesis differs from the catalytic mode by the fact that the enantiomeric excess (ee_{prod}) will become dependent of the conversion. This will occur if there are different reactivities for the diastereomeric reagents produced from non-enantiopure chiral auxiliaries. Obviously, the most reactive one will react in the early stages of the reaction, and then the slow-reacting reagents will be progressively be involved. Consequently the enantiomeric excess of the product cannot be predicted by the ML_2 model, which is based on a fix concentration of the three stereoisomeric complexes (Scheme 5). A way to connect catalytic and stoichiometric asymmetric reactions is to use an excess of the chiral reagent (with respect to substrate). The relative amounts of the competing reagents will remain constant, the reaction becoming pseudo first-order with respect to the reagent.

Ipc_2BCl is a very useful reagent discovered by Brown, and prepared from α-pinene.[59] In 1995 we investigated the behaviour of Ipc_2BCl of various enantiomeric purities in the reduction of acetophenone.[60] The reagent was prepared from non-enantiopure (–)-α-pinene by the Brown proce-

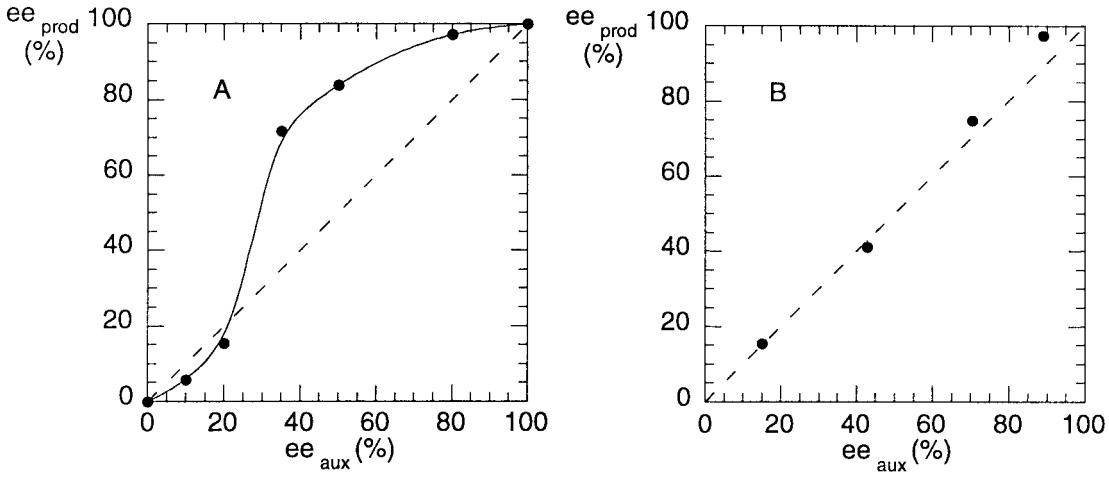
dure, which involves the initial formation of Ipc_2BH and its transformation by HCl into Ipc_2BCl. (*R*)-1-Phenyl-ethanol was predominently obtained (Scheme 11). By using one equivalent of the reagent we observed a significant deviation from linearity (Curve **A**, Scheme 12). The reagent was also prepared by mixing in various amounts of (+)-Ipc_2BCl and (–)-Ipc_2BCl prepared from enantiopure pinenes. In that case there is a perfect linearity between ee_{prod} and ee_{pinene} (Curve **B**, Scheme 12). These experiments were interpreted in the following way. The *meso* reagent **28** was produced only by starting from a mixture of the two enantiomers of α-pinene **25**. The linearity given by the alternate procedure proved that, in the conditions of the acetophenone reduction, there is no formation of *meso* **28** by a reversible process. The asymmetric amplification is indicative of the presence of *meso* **25** (presumably not far from the statistical distribution, and of very low reactivity). Moreover the reaction became extremely slow when α-pinene was below 20% ee, which may give no reliable data in that range of enantiomeric excesses.We observed that the asymmetric amplification increased with the excess of Ipc_2BCl (till 4 equivalents) with respect to acetophenone, in agreement with the low reactivity of the *meso* reagent.[61]



Scheme 11

In the 1994-1997 period interesting publications from Merck described the asymmetric sythesis of an alcohol which is a key intermediate in the synthesis of a LTD_4 antagonist.[62-64] The authors reduced an aromatic ketone by Ipc_2BCl prepared from BH_2Cl and (–)-(α)-pinene of 98% ee or 70% ee. They obtained the desired alcohol in 97% ee or 95% ee respectively. A detailed study of the relationships between the ee values of the alcohol and the ee values of α-pinene provided a curve displaying a strong asymmetric amplification. The data were collected at low or high conversion, the (+)-NLE was more pronounced at low conversion.[64] A good fit with the experimental curve was obtained for a statistical distribution of the three reagents (**26**, **27** and **28**), assuming no reactivity for the *meso* Ipc_2BCl.

Recently the asymmetric reduction of ketones by enantioimpure Ipc_2BCl has been reinvestigated by Blackmond.[65] She established a kinetic model and used the data at initial conversion to predict the NLE curve at total conversion. In order to get a good fit with the experimental data of the Merck group (vide supra) it was necessary to slightly modify the assumptions which were previously done concerning Ipc_2BCl.[60-64] Indeed, from the initial enantioselectivity it was calculated that the *meso* reagent **28** was formed in higher amount than expected (K = 49 instead of K = 4 for statistical distribution), and it had some reactivity (g = 0.1). This analysis was later confirmed by Sowa et al., who set up an in situ method to analyse the *meso* **28** content as function of the enantiomeric excess of initial α-pinene.[66]



Scheme 12

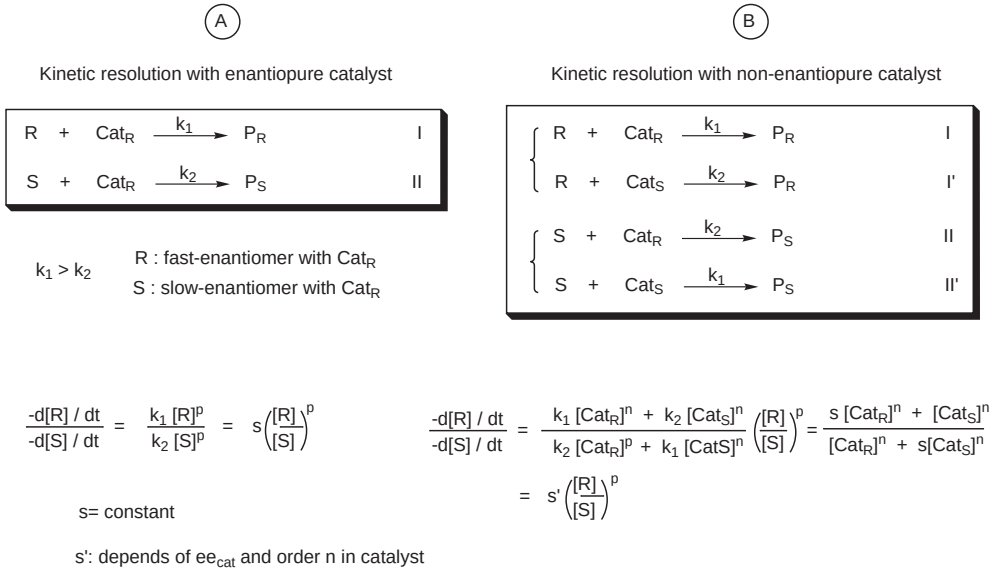
5.3 Kinetic resolution

Non-enantiopure catalysts can give rise to kinetic resolution by the selective transformation of one enantiomer of a racemic mixture. For a given conversion extent one expects a lower ee for the recovered starting material (ee_{sm}) than when using the enantiopure catalyst. If the catalyst does not display NLE in enantioselective reactions, because the absence of aggregation or of ML_2 species, one can calculate the relationships between ee_{aux} and ee_{sm} at various conversions. This is the "normal" situation, which is complicated since the ee of the recovered starting material is conversion-dependent.[67] The classical parameter (enantiopure catalyst) to define the efficiency of a kinetic resolution is the stereoselectivity factor *s*, which is equal to the relative rate k_{rel} between the two enantiomers: $s = k_{rel} = k_1/k_2$ ($s > 1$) (if the *R*-enantiomer is the fast-reacting substrate) (Scheme 13). The use of *s* avoids to consider the conversion C together with ee_{sm}, since it is constant as shown by kinetic treatment on simple models. If the kinetic resolution is first-order in substrate and any order in catalyst, one ends with eq. 3 (C and $ee_{sm} \leq 1$) where ee_{sm} concerns enrichment into *S*-enantiomer.

$$s = \ln[(1-C)(1-ee_{sm})] \,/\, \ln[(1-C)(1+ee_{sm})]$$

Equation 3

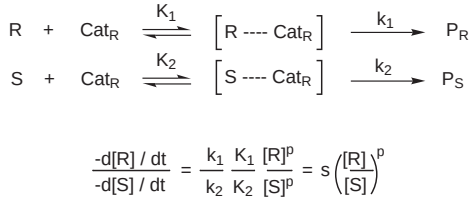
The knowledge of *s* allows to calculate ee_{sm} for a given C value. What happens if the catalyst is no more enantiomerically pure (ee_{cat}) and behaves as a "normal" catalyst (no aggregation)? One can apply formal kinetics in order to calculate the perturbation introduced by ee_{cat}. For first-order reactions in substrate, eq. 3 is no more valid. The intrinsic selectivity k_1/k_2 remains unchanged but the overall selectivity is "spoiled" by the use of a non-enantiopure chiral auxiliary. We considered various combinations of kinetic schemes, with first- or second-order in substrate and first- or second-order in catalyst. The beginning of the calculations is indicated in Scheme 13, the calculations show that the catalyst order is necessary to consider when a non-enantiopure catalyst is used.[68] Independently, Ismagilov published a similar mathematical treatment, limited to first-order reactions in substrate and non-enantiopure catalyst.[69] To simplify the discussion we introduced an additional parameter, the apparent stereoselectivity factor *s'*, which is the rate ratio in kinetic resolution occuring with non-enantiopure catalysts (Scheme 13). Even at initial conversion *s'* will be not equal to *s*, since it involves ee_{cat} as variable. In case of reactions first-order in substrate and catalyst it is interesting to point out that ee_{sm} can be calculated by an equation similar to 3, where *s* is replaced by *s'*. We proposed to qualify *s* as the intrinsic stereoselectivity factor, since it is the key factor which is at the roots of the enantio-differentiation process, while *s'* is a factor depending of ee_{cat}. The formal kinetics based on simple sets of competitive reactions depicted in Scheme 13 clearly showed that it is possible to predict the influence of ee_{cat} on ee_{sm}.[68] What happens if the catalyst is of the type of the one giving nonlinear effects in enantioselective reactions? Deviations from the above calculations should be possible. If ee_{sm} or *s'* are larger than expected by calculations there is an asymmetric amplification phenomenon surimposed to the kinetic resolution, while lower values indicate an asymmetric depletion. In our 1999 paper we did not qualify these deviations of nonlinear effects, since we did not find linear plots for $ee_{sm} = f(ee_{cat})$ in the regular situation.[68] Simultaneously in 1999 Johnson and Singleton published a study of kinetic resolution by a non-enantiopure catalyst for reactions first-order both in substrate and catalyst.[70]



Scheme 13

They set-up the basic equations of the process and were also interested by some possible deviations, that they qualified of nonlinear effects, by introducing a parameter called the "differential kinetic enantiomeric enhancement" (DKEE). DKKE is equal to $(k_{rel} - 1)/(k_{rel}+1)$. For enantiopure catalyst $k_{rel} = s$, while otherwise $k_{rel} = s'$. The authors calculated DKKE in the ML_2 model, they end with the equation: $DKEE = DKEE_0\ ee_{cat}\ (1+\beta)(1+g\beta)$, which is very similar to the equation 2 that we have developed for ML_2 systems. Johnson and Singleton concluded, as we did, that the experimental data given by Uemura et al. concerning the kinetic resolution of racemic *p*-tolyl methyl sulfoxide by asymmetric oxidation may be interpreted as a case of asymmetric amplification.[71] They also studied the kinetic resolution of racemic epoxides and concluded to an asymmetric amplification.

Very recently Blackmond analyzed the classical treatment in kinetic resolution based on sets of competitive reactions. She pointed out that the stereoselectivity factor $s = k_{rel}$ will be not necessarily constant over the whole course of the reaction.[72] Similar situations are known in some enzymatic reactions.[67b,73] She introduced the concept of "kinetic partitioning", which occurs when the actual catalytic cycles involve prequilibriums. Calculations were runned on the simplest form of Michaelis-Menten kinetics, as described in Scheme 14. The *s* factor includes the ratio of equilibrium constants, as already described for enzymatic reactions (E factor[67b]). Then the conclusions in **A**, Scheme 13, are unchanged. However when the catalyst is not enantiopure, the description **B** in Scheme 13 has to be modified by the introduction of four pre-equilibriums. Consequently, the equations obtained from the calculations are more complex, the apparent stereoselectivity factor *s'* as described in Scheme 13 will include terms related to conversion and is no more constant. The expression "kinetic partitioning" of the enantiomeric catalysts $(cat_R)_{total}$ and $(cat_S)_{total}$ has been proposed when the various intermediates in the competing catalytic cycles change over the course of the reaction. This effect may perturb the predictions, giving the equivalent of asymmetric amplification or asymmetric depletion, which in some cases can superimpose to the classical nonlinear effects. The kinetic partitioning will not operate if the binding constants are identical, or if they are both very low in combination with a very low substrate concentration.



Scheme 14

In conclusion, the concept of nonlinear effect applies to kinetic resolution, although with some cautions. Even if the stereoselectivity factor is invariant with conversion (no kinetic partitioning) it is not possible to get a linear plot relating ee_{prod} and ee_{cat}. One solution has been proposed by Johnson and Singleton, it is to retain DKEE as a parameter, which is linearly correlated to ee_{cat} (vide supra).[70] We suggest here to consider the reaction rate k_{rel} and the enantiomeric excess of the product (ee_p) specifically close to zero conversion. The enantiomeric excess of the remaining starting material (ee_{sm}) obviously remains close to zero, but the enantiomeric ratio (P_R/P_S) of the tiny amount of product is close to $s = k_1/k_2$ (Scheme 13) or to $s = (k_1/k_2)(K_1/K_2)$ (Scheme 14). This is well known, and is due to the fact that at very low conversion the substrate composition is almost unchanged.[67] The initial enantiomeric excess of the product is then $(ee_p)_0 = (s\text{-}1)(s+1)$. This expression is exactly the above term DKKE. There is a close analogy between the enantioselective reactions, where the 1:1 ratio of *Re* and *Si* faces remains constant, since the two faces are parts of the same molecule, and the kinetic resolution at initial conversion, where the two enantiomeric products are formed from a 1:1 mixture of *R* and *S* enantiomers. Then the concepts of nonlinear effects apply in the same way in the both processes.[74]

6 Conclusion

There are many practical aspects which are connected with the nonlinear effects in asymmetric catalysis.[75] An obvious application is linked to (+)-NLE (asymmetric amplification). In asymmetric synthesis the chiral auxiliary does not need to be enantiomerically pure in order to control the formation of a product of very high enantiomeric excess, either in catalytic or stoichiometric reactions. This was well highlighted by the Noyori catalyst DAIB **13** (Scheme 4).[31] Reduction of ketones with Ipc_2BCl may be carried out with a reagent prepared from cheap commercial α-pinene of low enantiomeric purity, as examplified at Merck during the synthesis of a LTD_4 antagonist.[63-65] The presence of an important (-)-NLE in asymmetric catalysis can be a handicap in the screening of a ligand of 95-98% ee, since the results could be so poor that they will obscure the actual excellent enantioselectivity with enantiopure ligand.

Asymmetric autocatalysis combined to asymmetric amplification allowed to get spectacular results in the addition of organozincs on aromatic aldehydes.[44] One may expect more developments coming in that area.

The most useful application of nonlinear effects is presently its use as a mechanistic tool. It gives a simple way, by a plot ee_{prod} versus ee_{aux}, to check some hypotheses about the structure of a reagent or a catalyst. An aggregation state or the formation of species including several chiral auxiliaries units can be supported by an abnormal curve. However, it should be noticed that if there is linearity it does not fully disprove association between chiral auxiliaries, because of special conditions such as g = 1 in eq. 2 of the ML_2 model (Scheme 5).

We entered in the area of nonlinear effects because of our interest to get some insight into catalytic asymmetric reaction.[25] When a catalytic reaction is second-order with the chiral catalyst, some informations may be gained by the study of $ee_{prod} = f(ee_{aux})$. this have been discussed (vide supra) in the proline catalysed cyclisation of **3** into ketol **4** (Scheme 1), where the key step **5** involving two proline molecules has been proposed.[20,25] Jacobsen et al. discovered that a chiral salen-Cr complex catalysed the nucleophilic opening of *meso* epoxides by N_3TMS, the reaction is second-order with respect to the salen-Cr catalyst.[76] The involvement of two molecules of the Cr-N_3 complex was nicely confirmed by a strong (+)-NLE. Clearly one Cr complex activates the epoxide, while simultaneously another salen Cr-N_3 species acts as a nucleophilic reagent.

The NLE may be used as an "observer" or a "finger-print" when the formation of a catalyst is highly sensitive to experimental conditions. Thus we found that asymmetric oxidation of a sulfide to the corresponding sulfoxide by an hydroperoxide strongly depends on the titanium/diethyl tartrate catalyst preparation.[77] Nonlinear effect could be shifted from (+)-NLE to (–)-NLE just by changing the catalyst loading. Similarly, NLE in Diels-Alder reactions catalysed by some chiral lanthanide complexes are very dependent of the experimental conditions.[78] If a chiral catalyst is prepared by various experimental conditions, NLE can give some light on processes occuring in situ. For example, Mikami et al. studied a chiral Lewis acid catalyst for Diels-Alder reaction.[79] The catalyst was prepared from $Ti(OiPr)_2Cl_2$ and binol. One procedure used enantiomerically impure binol to get the catalyst, the alternate procedure involved the separate preparation of the two enantiopure catalysts, which are subsequently mixed in various amounts. This last method gave linearity, while the first procedure was associated with a strong (+)-NLE. These experimental observations are in agreement with an easy dimerisation of the $TiCl_2$binolate complex catalysed by molecular sieves. In absence of molecular sieves the various dimeric complexes are not redistributed in the experimental conditions of the ene-reaction. The absence of interconversion between stereoisomeric reagents during the reduction of acetophenone by Ipc_2BCl has been proposed.[60] It is based on the strong (+)-NLE given by the reagent directly prepared from the enantiopure α-pinene and the absence of NLE when the reagent was prepared from the two enantiopure reagents. The use of the experimental data collected at low conversion, combined with a suitable kinetic law, allowed to predict ee_{prod} at various conversions and to estimate the relative rates as a function of ee_{pinene}.[65]

The growing number of reports on NLEs for a wide range of reactions shows how useful the concept is, providing some insights to a given process and some practical consequences.[75] One may anticipate new developments in the near future.

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(74) We made a distinction between the stereoselectivity factors for enantiomerically pure catalysts ($k_{rel} = s$) and for non-enantiopure catalysts ($k_{rel} = s'$).[68] If one retains the sigle *s* for the both cases (as in refs 70,72) then on can differentiate them by writing s_{max} if $ee_{aux} = 100\%$.
Consequently *s* becomes a function of s_{max} and ee_{aux}, increasing from 1 ($ee_{aux} = 0$) to s_{max} ($ee_{aux} = 100\%$). If the term $(s\text{-}1)(s\text{+}1) = (ee_p)_0$ (ee of the product at initial conversion) is considered instead of *s*, one calculates (in absence of kinetic partitioning) for any order with respect to substrate and first-order in catalyst that $(ee_p)_0 = (ee_p)_{max}\, ee_{aux}$ (eq. 4), where ee_{max} is the ee of the catalyst. There is a close analogy between eq. 1 and eq. 4. The first one gives the ee of the product of an enantioselective reaction, while the last one gives the ee of the initial product of a kinetic resolution. Nonlinear effects will be observed if eq. 1 (enantioselective synthesis) or eq. 4 (kinetic resolution) are not obeyed.
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