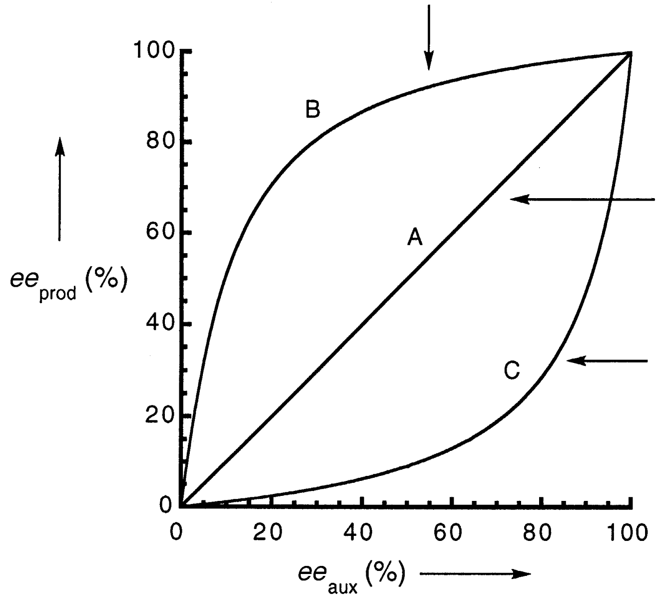
Enantioselective catalysis
with partially resolved chiral auxiliaries

(+)-nonlinear effect
(asymmetric amplification)



proportionality between ee_{prod} and ee_{aux}

(−)-nonlinear effect
(asymmetric depletion)

In many enantioselective reactions
ee_{prod} *is not always proportional* to ee_{aux}.

Nonlinear Effects in Asymmetric Synthesis and Stereoselective Reactions: Ten Years of Investigation

Christian Girard and Henri B. Kagan*

Dedicated to Professor Dieter Seebach on the occasion of his 60th birthday

The first preoccupation of organic chemists was to develop their ability to reproduce the organization of atoms in natural products. This incursion in nature's laboratory gave rise to numerous techniques to transform matter but led to the discovery of her subtle way of producing substances with chirality and the preference of one enantiomer over the other in the living matter gave a lesson in perfection. The development of asymmetric synthesis gave the opportunity to elaborate methods, reagents, and reactions in order to prepare enantiomerically pure compounds. But this journey is far from being over, and there is a lot of surprises left. No chemist would have thought that an enantiomerically impure chiral auxiliary or ligand could give a stereoselection higher than its own and even equivalent to the pure one. Molecules can behave in numerous ways in solution; aggregation or organization can occur depending on the nature of the molecule or its environment. These phenomena give rise to modification of the anticipated enantiomeric excess (*ee*) of the reaction product. The relation between the *ee* value of the auxiliary or ligand and the *ee* value of the product deviates from linearity to give what we now call nonlinear effects (NLEs). The nonlinear effects in asymmetric synthesis and stereoselective reactions reflect molecular interactions and complexity in reaction mechanisms. They can be used to generate products with high *ee*'s from an enantiomerically impure, and more economical to prepare, chiral auxiliary or ligand. Furthermore, the NLEs can also act as a probe to obtain information on the subtle mechanisms by which the enantioselectivity is generated.

Keywords: asymmetric amplification · asymmetric catalysis · asymmetric synthesis · autocatalysis · chiral auxiliaries

1. Introduction

In the early years of organic chemistry chemists became aware of the importance of chirality in nature. Differences between biological activities of two enantiomers were soon uncovered and the importance of producing mainly or exclusively one enantiomer was highlighted. From the study of enantiomeric mixtures, behavioral differences between racemic and enantiomerically pure compounds were discovered.

In 1848 Pasteur demonstrated that tartaric acid rotated the plane of polarized light, but in a different way depending on its origin.[1] This discovery triggered the use of polarimetry as the technique for gathering information on the enantiomeric purity of compounds, since enantiomers of opposite absolute configuration gave the same degree of deviation of the plane of light, but in opposite sign. Mixtures of enantiomers that differed from racemic composition were therefore analyzed in this fashion and the relative amounts of each constituents were deduced from the total rotation.[2]

However, exceptions to this method were found to be more than a few. Horeau's work on 1-ethyl-1-methylsuccinic acid showed that its specific rotation in chloroform was not strictly related to enantiomeric composition.[5] The phenomenon was explained on the basis of diastereomeric associations by hydrogen bonding that gave rise to a nonlinear relationship between the enantiomeric excess (*ee*) of the acid and its optical purity (*op*). When methanol was used as a solvent for recording this optical property a strictly linear interrelation ($ee = op$) was observed as a consequence of the solvent preventing the aggregation.

The general problem of diasteromeric interactions in a solution of a mixture of enantiomers was discussed in 1974 by Horeau and Guetté.[6] The physicochemical properties of such mixtures may be modified with a change of enantiomeric composition. For example the ^{1}H NMR spectrum (in solution)

---

[*] Prof. Dr. H. B. Kagan
Laboratoire des Réactions Organiques Sélectives
Institut de Chimie Moléculaire d'Orsay
Bâtiment 420, Université de Paris-Sud, F-91405 Orsay Cedex (France)
Fax: (+33) 169-15-46-80
E-mail: kagan@icmo.u-psud.fr
Dr. C. Girard
Laboratoire de Vectorisation Moléculaire et Cellulaire
Ecole Nationale Supérieure de Chimie de Paris
11, rue Pierre et Marie Curie, F-75231 Paris Cedex (France)
E-mail: cgirard@ext.jussieu.fr

1433-7851/98/3721-2923 $ 17.50+.50/0

of a racemic mixture or of an enantiopure compound may differ, as found for the first time by Uskokovic et al. in the case of dihydroquinine.[7] Recently the first example of fractionation by distillation of a non racemic mixture of enantiomers was discovered.[8] Isopropyl trifluorolacetate is highly associated by hydrogen bonding, it also shows variation in the infrared absorptions in the liquid (neat) phase. The enantiomeric composition of a non racemic mixture may also be modified significantly by chromatography with achiral stationary and mobile phases. There are several examples in the literature that were explained by diastereomeric associations in the mobile and (or) the stationary phases.[9–14] A mathematical simulation of this phenomenon has been performed.[15]

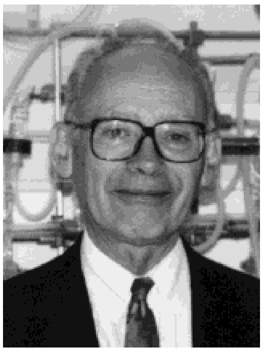
A nonideal behavior of a mixture of enantiomers may have some consequences on chemical reactions in solution. Wynberg and Feringa pointed out in 1976 that, based on symmetry considerations and free energy arguments, the surroundings of a given *R* enantiomer should be different if it is an enantiopure material or a racemic mixture.[16] In the latter *R/S* interactions may develop, which are absent in the enantiopure system. The authors proposed the following principle: *When a chiral substance undergoes a reaction, the reaction rate and the product ratio will depend—inter alia—upon the enantiomeric excess present in the starting material.* Wynberg and Feringa found some cases that are in agreement with the above principle. The diasteroselectivity of the $LiAlH_4$ reduction of camphor, the McMurry coupling of camphor, and the *ortho*-coupling of a phenol derivative were compared for the enantiopure and racemic systems. Significant differences could be observed. For example, the ratio of isoborneol to borneol was 90.2:9.8 or 88.7:11.3 for the reduction of (+)-camphor or racemic camphor, respectively. In the above publication there were no cases of reactions dealing with chiral substrates having an *ee* value different from 0 or 100%, nor discussion on the quantitative variation of the diastereoselectivity as a function of the *ee* of the substrate.

The chiral auxiliary that is needed in asymmetric synthesis is always of nonracemic composition, preferably of 100% *ee*. One may wonder if an enantiomeric excess lower than 100% will lower the enantiomeric excess of the product in a proportional manner, or if the *ee* of the product will have an unexpected value (as in the Wynberg and Feringa examples) because of a perturbation generated by the *ee* of the chiral auxiliary. This problem had almost never been questioned by the practitioners of asymmetric synthesis.[17] It was in 1986 that the quantitative aspects of the influence of the *ee* value of the chiral auxiliary on the corresponding *ee* value of the product were discussed and studied experimentally.[19] This review article will summarize the main results obtained in that area.[20] The cases of asymmetric catalysis, stoichiometric asymmetric synthesis, and diastereoselective reactions (with a chiral substrate) will be developed successively.

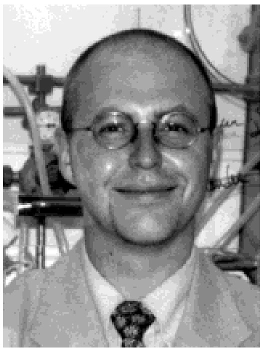
2. Asymmetric Catalysis

2.1. The First Examples—1986

In 1986 Kagan, Agami et al. considered the case of asymmetric synthesis with a chiral catalyst or auxiliary that was not enantiomerically pure.[19] The well accepted assump-



H. B. Kagan



C. Girard

Henri B. Kagan was born in Boulogne-Billancourt (France) in 1930. He graduated from the Sorbonne and Ecole Nationale Supérieure de Chimie de Paris in 1954. He did his doctorate with Prof. J. Jacques, as his first student, and obtained his diploma for work on modified steroids. He then joined Prof. A. Horeau at the Collège de France in Paris in 1962 as a research associate and became involved in studies on stereochemistry and asymmetric synthesis. In 1965 he worked with Prof. T. Mabry at the University of Texas, Austin (USA). He was appointed assistant professor in 1968 at the Université de Paris-Sud, Orsay (France); where he became full professor in 1973. Kagan has been the recipient of several French and international awards and distinctions over the years. He was elected a member of the Académie des Sciences of the Institut de France in 1991 and is a member of the Institut Universitaire de France.

Christian Girard was born in Grandes-Bergeronnes (Québec, Canada) in 1966. After graduating from the François-Xavier Garneau College with an Health Sciences diploma in 1985, he studied chemistry at the Université Laval (Québec, Canada) where he obtained his B.Sc. (1988) and M.Sc. (1990) with Prof. P. Brassard for work on quinonoid compounds. He then moved to Université de Montréal (Canada) where he completed his Ph.D. in 1994 with Prof. S. Hanessian on the use of samarium(II) iodide in carbohydrate chemistry. The same year, having been granted a Chateaubriand Postdoctoral Fellowship, he then joined Prof. H. B. Kagan at Université de Paris-Sud, Orsay (France) where he became involved in the study of nonlinear effects in asymmetric synthesis. Since 1996, he has been working as a post-doctoral fellow with Prof. J.-P. Genêt at Ecole Nationale Supérieure de Chimie de Paris, Paris (France), where he has been recently appointed as Maitre de Conférence.

tion that the *ee* value of the product (ee_{prod}) of an asymmetric synthesis is linearly correlated to the *ee* value of the chiral auxiliary (ee_{aux}) was questioned. The usual procedure to get an approximation of the experimental *ee* value (ee_{prod}) by correction, knowing the maximum *ee* value of the product (ee_{o}) is reached with the enantiopure chiral catalyst or auxiliary, was to use Equation (1). This linear relationship is

$$ee_{\text{prod}} = ee_{\text{o}} ee_{\text{aux}} \qquad (1)$$

represented for an $ee_{\text{o}} = 100\,\%$ as Curve A in Figure 1. Equation (1) takes into account only the highest enantioselectivity (ee_{o}) reached with the chiral auxiliary. This linearity was theoretically not to be encountered in systems subjected to other influences, such as interaction between the catalytic species. If the linear relationship is not followed one can expect a plain curve above (curve B, positive nonlinear effect, abbreviated as (+)-NLE) or below (curve C, negative nonlinear effect or (−)-NLE) the straight line, respectively (Figure 1). By convention, all graphs of NLE will be presented as in Figure 1, whatever the absolute configuration of the chiral auxiliary and the product. We will not consider negative coordinates unless there is a special need.

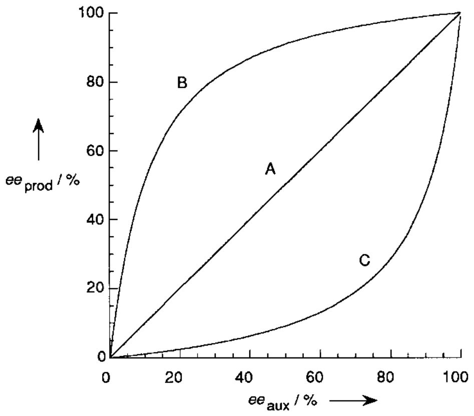


Figure 1. Typical curves for positive (B) and negative (C) nonlinear effects.

The nonlinearities shown in Figure 1 may in principle arise by auto association or association around a matrix of the initial chiral species, which give diastereomeric perturbations. Those perturbations should then be added to Equation (1) as a multiplication factor to divert the relation between ee_{prod} and ee_{aux} from linearity. Equation (1) must then to be used with caution.

Three systems were studied in 1986 to test this hypothesis.[19] The results that emerged from the data collected provided clear indications that in several cases such nonlinear effects were to be encountered.[20] The first reaction studied was the asymmetric Robinson annulation (Hajos-Parrish-Wiechert reaction[25]) of the triketone **1** using (*S*)-proline as a catalyst (Figure 2). When the *ee* value of (*S*)-proline (ee_{aux}) was plotted against the *ee* value of the *cis*-ketol **2** (ee_{prod}) a slight (−)-NLE was observed, as depicted in Figure 2. Mechanistic investigations by Agami et al. suggested that the reaction proceeds through the formation of a chiral enamine followed by a complexation with a molecule of catalyst. This was confirmed by a kinetic model based on a second-order reaction in respect to proline.[26] Furthermore, the (−)-NLE was explained by the fact that, by considering the complexes **3** as intermediates, the reaction involving heterochiral complexes proceed twice as fast as the one of homochiral complexes (Figure 3).

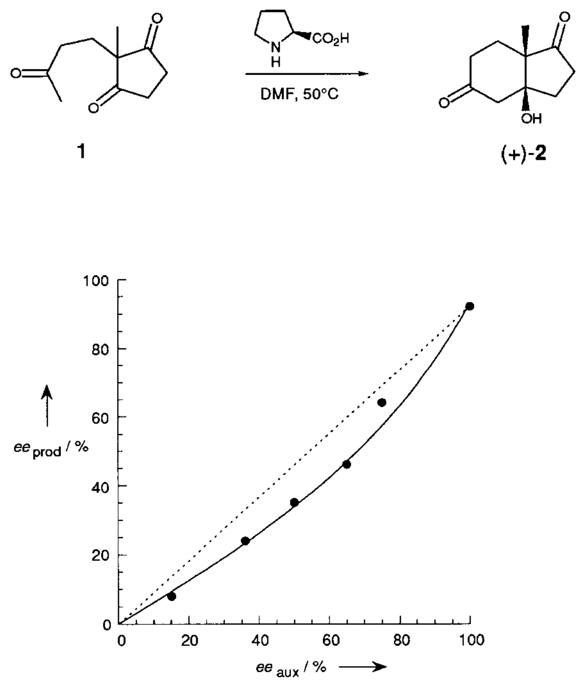


Figure 2. (−)-NLE in the Hajos-Parrish-Wiechert reaction of **1** to **2** catalyzed by (*S*)-proline (3 mol %).

A different effect was however observed in the Sharpless epoxidation[27] of geraniol (**4**) during this investigation.[19] A positive nonlinear effect takes place in this reaction with (*R*,*R*)-(+)-diethyl tartrate ((*R*,*R*)-(+)-DET) of various *ee*'s

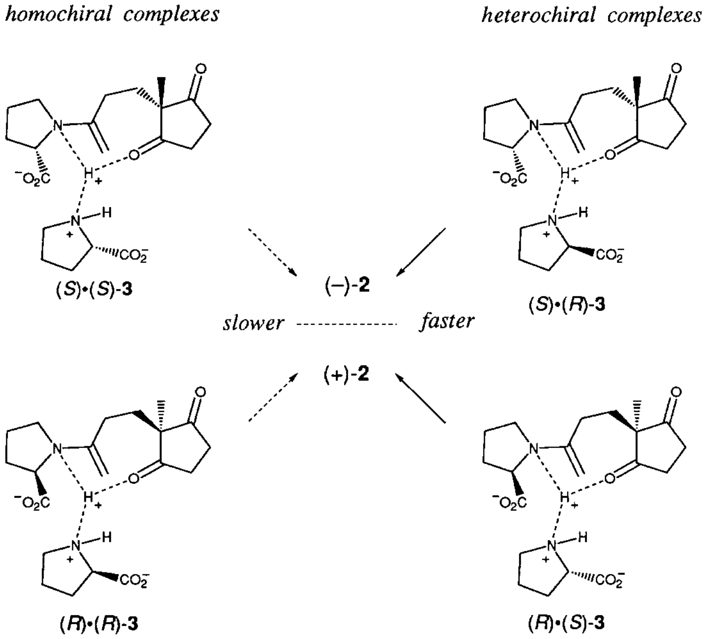


Figure 3. Intermediate complexes **3** in the asymmetric Robinson annulation of **1** to **2**.

(Figure 4). The enantiomeric excess of the produced epoxide **5** (ee_{prod}) when plotted as a function of the *ee* of (+)-DET (ee_{aux}) was indeed greater than expected. The use of a dimeric heterochiral species that is less reactive, and thus more stable, than its homochiral counterparts provides a way of understanding the (+)-NLE of the reaction, since some racemic DET will be retained in the inactive complex. This proposal is compatible with the Sharpless mechanism of asymmetric epoxidation, which indicates the intervention of a dimeric complex that introduces two tartrate units in the active species.[27b] The (+)-NLE discovered here for the first time has been found subsequently in many reactions and has been named "asymmetric amplification" by Oguni et al.[28]

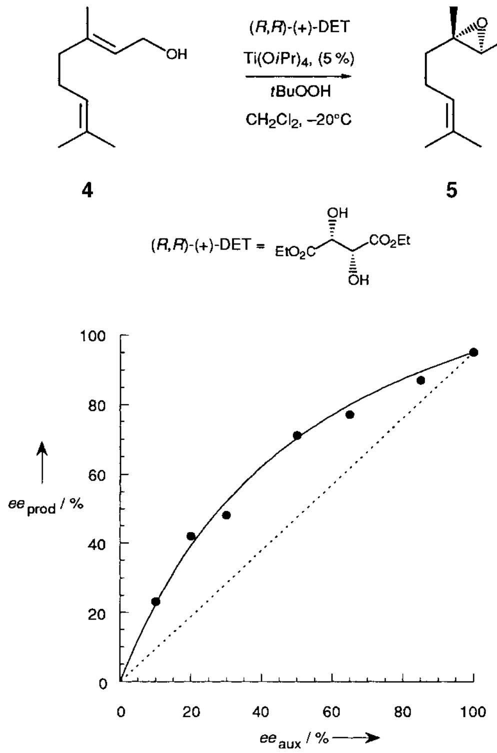


Figure 4. (+)-NLE in the Sharpless epoxidation of geraniol (**4**).

A water-modified Sharpless reagent has been developed by Kagan et al. for the asymmetric oxidation of sulfides by hydroperoxides.[29] The oxidation of methyl-*p*-tolyl sulfide **6** to sulfoxide **7** is quite unexpected by comparison with the results previously discussed (Figure 5). The relation between the *ee*'s is clearly a (−)-NLE, but this effect affects the enantioselectivity until the value of 70 % *ee* is reached for the diethyl tartrate. The linear relationship then prevails until enantiomerically pure DET is used. This perturbed behavior is indicative of a quite complicated structure for the water-modified reagent.[30]

These first experiments were a revelation in the behavior of mixtures of enantiomeric reagents or catalysts. They were an indication that some complex and subtle interactions were taking place in solutions with participation from a diastereomeric species. Furthermore, the analysis of the perturbations on the enantioselectivity of the reaction generated by mixing various amounts of enantiomers also gave information about the reaction itself. It became clear that the search for nonlinear effects in a given system also becomes a probe for analyzing the nature of the catalytic species or the nonreacting species involved in an asymmetric synthesis.

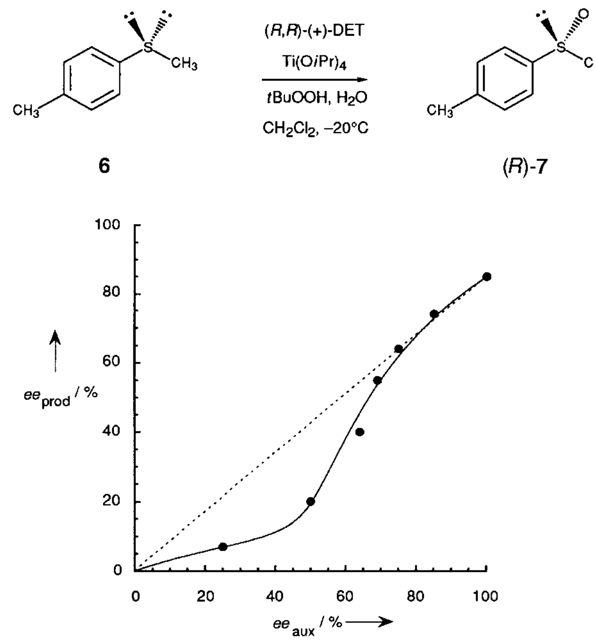


Figure 5. (−)-NLE in the asymmetric oxidation of sulfide **6** with a chiral titanium reagent.

2.2. Models and Principles

To get a better understanding and to have some insight into the behavior of catalysts during the course of a reaction that leads to a NLE, simplified mathematical models were developed by Kagan et al. in 1994.[31] These models were discussed in the cited article and will not be explained here in detail. The systems, equations, and the resulting curves will be presented in this section to demonstrate their usefulness.

2.2.1. The ML_2 System

The first model is based on a system in which a fast ligand exchange occurs at a metallic center (M) of a reactive species bearing two chiral ligands (L_R and L_S): the ML_2 system (Figure 6). The following discussion can easily be applied to $(ML)_2$ systems as well to reversible dimerization in the absence of the metal (e.g. association by hydrogen bonding). The model was based on the assumption of a steady state for the three expected complexes ML_RL_R, ML_SL_S, and ML_RL_S (in

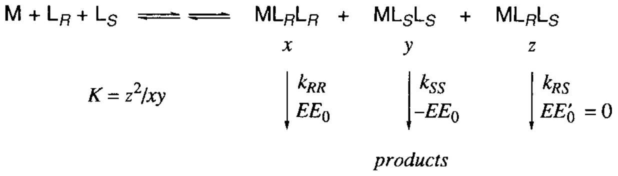


Figure 6. Illustration of the ML_2 system to explain NLEs.

the relative concentrations x, y, and z, respectively), a final irreversible step with pseudo-first order constants k_{RR}, k_{SS} ($=k_{RR}$), and k_{RS}, and a zero-order dependence with respect of the substrate. Furthermore, the *meso* catalyst (ML_RL_S) generated racemic product while the homochiral complexes gave enantiomeric products. It became easy to evaluate the *ee* of a product formed from this kind of system by obtaining the mathematical formula describing it. Equation (2) permits the

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

ee value of the product (EE_{prod}) to be calculated for each value of ee_{aux} by knowing the maximum value reached with enantiopure catalyst (EE_0) and the parameters for the studied system. The new parameters introduced in this equation are β, the relative amounts of the complexes ($\beta = z/(x+y)$), and g, the relative reactivities of the hetero- over the homochiral catalysts ($g = k_{RS}/k_{RR}$).

If $\beta = 0$ (no *meso* catalyst) or $g = 1$ (identical reactivities of hetero- and homochiral species), then Equation (2) is simplified to Equation (1) and a linear relationship is observed. In other situations the correction factor $(1+\beta)/(1+g\beta) \neq 1$ is needed and a nonlinear relation takes place. When this factor is greater than one the system displays a (+)-NLE; the amplitude of which will depend on the size of the value of this factor. This will be the case of systems where g is less than one, in which a less reactive heterochiral complex exists. However, if g is greater than one the system will present a (−)-NLE as a consequence of a greater reactivity of the *meso* catalyst. In order to calculate curves from this model it was necessary to transform Equation (2) in terms of ee_{aux} and the relative amounts of the complexes by using the variable $K = z^2/(xy)$ (which is the equilibrium constant if these complexes are in fast interconversion during their formation). The ratio β of the hetero- and homochiral species then becomes available from Equation (3).

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

It was then possible to evaluate the EE_{prod} by using Equations (2) and (3) and to plot curves derived from this model. In Figure 7 the results for two cases in which $K = 9$ and 2500 are presented. The curves are generated for different values of g. In the particular case where the ligands are statistically distributed between the complexes a simplification occurs and K becomes equal to four. Furthermore, the term β is also simplified and, from Equation (3), is given by $\beta = (1 - ee_{\text{aux}}^2)/(1 + ee_{\text{aux}}^2)$. By introducing these new values and formula into Equation (2), EE_{prod} can be calculated from the resulting Equation (4).

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

The maximum (+)-NLE that can be encountered in this system will be obtained at $g = 0$, when none of the heterochiral species reacts. Linearity could be observed here as well for $g = 1$. At greater g values the NLE will be negative. The computer-calculated curves for this model are presented in Figure 8.

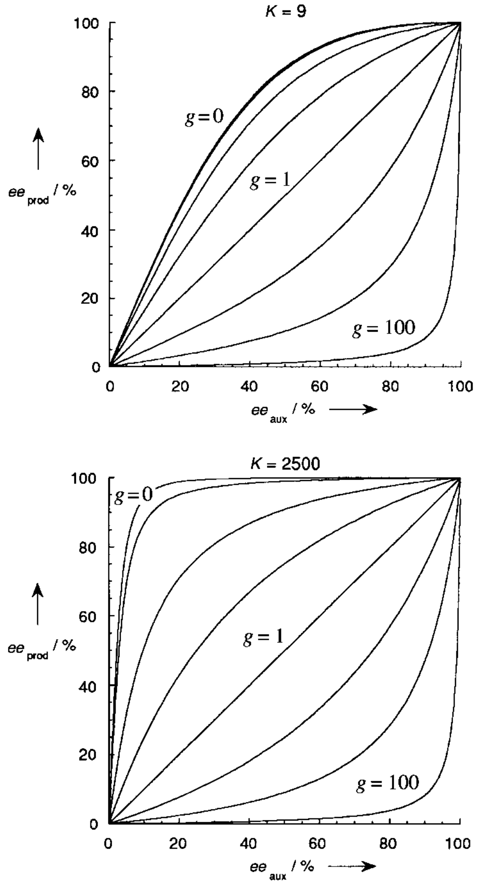


Figure 7. Computer-calculated curves for the ML_2 system for $K = 9$ and 2500.

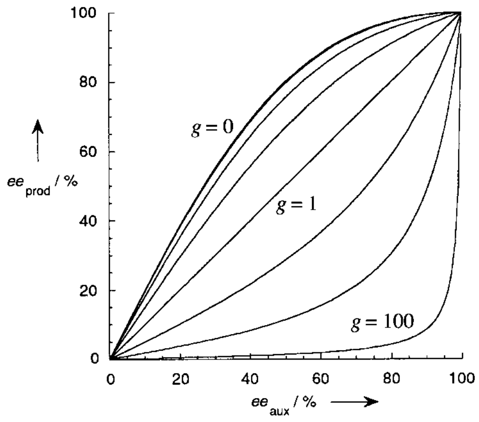


Figure 8. Computer-calculated curves for the ML_2 system with a statistical distribution of the ligands.

Good fits of experimental data can often be achieved from the nonstatistical distribution model, for example Equations (2) and (3).[30] For example, in the asymmetric epoxidation of geraniol (**4**) discussed in Section 2.1; the curve that corresponds well to the data is the one with $EE_0 = 95\,\%$, $K = 1000$, and $g = 0.35$ (Figure 4). These findings imply that the *meso* titanium complex is less reactive ($g = k_{RS}/k_{RR} \approx 1/3$) and much more abundant once the equilibrium is reached ($K = z^2/(xy) = 1000$). This example demonstrates that this model can be of some use in the study of NLEs and, furthermore, provides some parameters for the discussion of the possible catalysts involved in enantioselective reactions.

A useful development to the ML$_n$ model was reported recently by Blackmond.[20] The author showed that this model could be used to predict some relative reaction rates. These kinetic predictions may then be compared with the experimental data and provide an independent confirmation of the postulated model. For example, the calculations performed for the ML$_2$ model need to obtain the relative amounts (x, y, z) for the three complexes of Figure 6 as a function of ee_{aux} for a given K value. The overall rate may then be easily computed and compared to the rate for the homochiral complex ($ee_{\text{aux}} =$ 100%). The calculation has been carried out for the NLE of Figure 4 and showed a strong diminution of the reaction rate when ee_{aux} decreases. As often found in subsequent examples of this review a (+)-NLE usually comes at the cost of the rate of formation of the product.

2.2.2. M*L$_2$ System

A model, similar to the ML$_2$ system previously discussed, can be elaborated for the case in which the introduction of chiral ligands on M creates a center of chirality. In such a model, the *meso* complex ML$_R$L$_S$ encountered in the preceding section becomes M*L$_R$L$_S$. The stereochemistry on M is generated by the sequential introduction of the ligands, first producing the monoligated complexes M$_R$L$_R$, M$_R$L$_S$, M$_S$L$_R$, and M$_S$L$_S$. Subsequent reaction of those complexes with L$_R$ and L$_S$ finally gives the four pairs of enantiomers as illustrated in Figure 9. Here the heterochiral complexes such as M$_R$L$_R$L$_S$ and M$_S$L$_S$L$_R$ are enantiomers. Each stereoisomer in Figure 9 has its respective reactivity (k_i) and selectivity (EE_i) and will contribute to the final EE_{prod}. By using the same hypotheses as for the ML$_2$ system, the M*L$_2$ model can be treated with Equations (2) and (3), the only difference being in the definition of the parameters K, g, and EE_o.

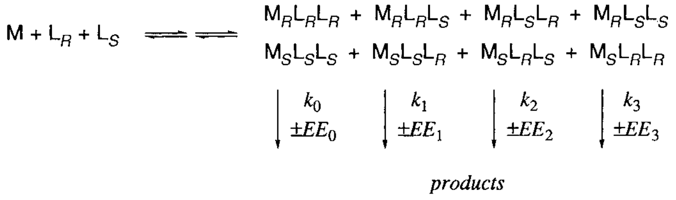


Figure 9. Another model for the NLEs: the M*L$_2$ system.

This model can be applied to reactions such as the asymmetric Robinson annulation (Section 2.1, Figure 2). The intermediates illustrated in Figure 3 are of the M*L$_2$-type and for example, in a complex such as M$_R$L$_R$L$_S$, M$_R$ symbolizes the creation of an asymmetric carbon atom with R configuration during the formation of the enamine with the first proline (L$_R$), and L$_S$ is the second proline molecule involved in the formation of the complex. In this particular situation, where only four stereoisomers are formed, the system can be treated with a statistical distribution as with the ML$_2$ model. Equation (4) gave, with $EE_0 = 93\%$ and $g(=k_{RS}/k_{RR}) = 2$, a curve fitting the experimental results. The same value was found by Agami et al. in their kinetic analysis of the reaction ($k_{homo}/k_{hetero} = 0.5$).[26]

The equations found for the ML$_2$ systems can be applied to cases where ML$_R$L$_R$, ML$_S$L$_S$, and ML$_R$L$_S$ complexes dissociate irreversibly to ML$_R$ and ML$_S$, with or without the influence of the substrate, that are implicated in the final irreversible catalytic step. This approximation gives fair results but will not be discussed here.[31]

2.2.3. ML$_3$ System

A model in which species of the type ML$_3$ or (ML)$_3$ are active catalytic species can be proposed. At least four entities may be responsible for the catalysis: ML$_R$L$_R$L$_R$, ML$_S$L$_S$L$_S$, ML$_R$L$_R$L$_S$, and ML$_S$L$_S$L$_R$. The heterochiral complexes encountered here are always chiral and an enantiomerically enriched product is generated simultaneously from homo- and heterochiral species (Figure 10). Calculation of EE_{prod} as a function of ee_{aux} is much more complex in this case. However, the assumption of a statistical distribution of the chiral ligands between the four complexes gives a simplified function (Equation (5)). In this formula, EE_0 and EE'_0 are the

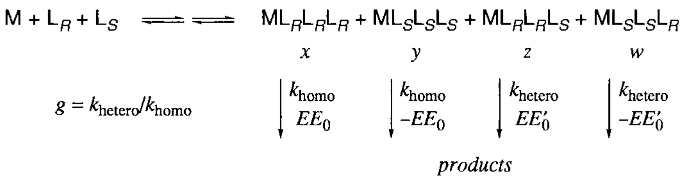


Figure 10. The more complex description of NLEs by the ML$_3$ system.

$$EE_{\text{prod}} = EE_0 ee_{\text{aux}} \frac{3 + 3g\,EE'_0/EE_0 + (1 - 3g\,EE'_0/EE_0)ee^2_{\text{aux}}}{1 + 3g + 3(1-g)ee^2_{\text{aux}}} \qquad (5)$$

enantiomeric excesses of the product from homochiral and heterochiral complexes (of 100% *ee*). The parameter $g = k_{hetero}/k_{homo}$ is defined as for the ML$_2$ system. Figure 11 shows some curves selected for a case where homochiral complexes are more selective ($EE_0 = 100\%$) than their heterochiral counterparts ($EE'_0 = 50\%$).

From these curves one can observe that if the homochiral complexes are more reactive ($0 \leq g < 1$) a (+)-NLE takes

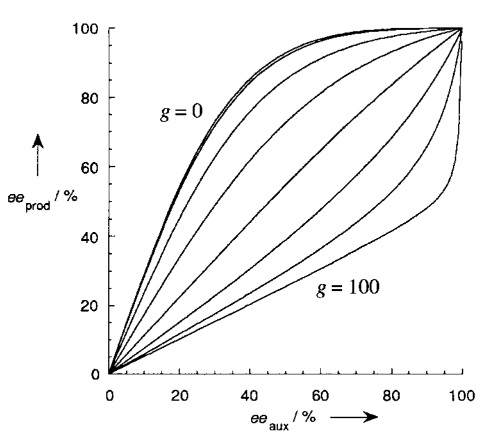


Figure 11. Computer-calculated curves for the ML$_3$ system with $EE_0 =$ 100% and $EE'_0 = 50\%$.

place. If the less selective heterochiral complexes react faster ($g > 1$), a (−)-NLE will then be observed. If the heterochiral complexes are more enantioselective than the homochiral ones, the situation will be quite different. By selecting $EE_0 = 50\,\%$ and $EE'_0 = 100\,\%$, the curves produced by the use of Equation (5) were plotted for various values of g (Figure 12).

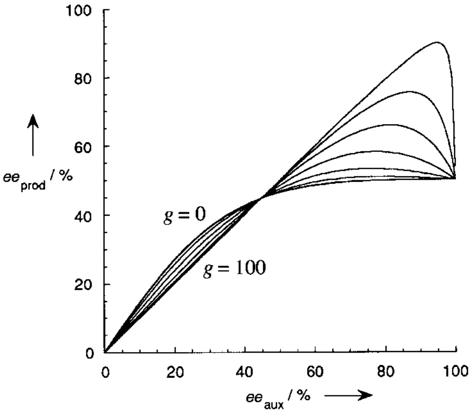


Figure 12. Computer-calculated curves for the ML_3 system for $EE_0 = 50\,\%$ and $EE'_0 = 100\,\%$.

For g values less than one, the curves display a similar behavior as in Figure 11. However, an interesting phenomenon occurs in this mathematical model for larger values of g. The EE_{prod} can be higher at lower ee_{aux} than at 100% ee_{aux}; at which it drops to the EE_0 (=50%) value. If a system can fit this model, the chiral auxiliary will be much more efficient when partially resolved than when enantiomerically pure!

2.2.4. ML_4 System

In an even more complicated scenario the complex can bear up to four chiral ligands to become a ML_4 or $(ML)_4$ system. This will generate the five following complexes: $M(L_R)_4$, $M(L_S)_4$, $M(L_R)_3L_S$, $M(L_S)_3L_R$, and $M(L_R)_2(L_S)_2$. If the $M(L_R)_2(L_S)_2$ complex is assumed to be a *meso* complex (which gives a racemic product), that no additional stereoisomers involving the M center are present, and that, finally, the ligands are distributed on the center in statistical mode, the system is greatly simplified. By introducing the relative reactivities of the two heterochiral complexes (g and f) and taking into account the enantioselectivities of enantiopure homo- (EE_0) and heterochiral (EE'_0) complexes, Equation (6)

$$EE_{prod} = 8\,EE_0\,ee_{aux}\frac{1 + ee_{aux}^2 + 2g\,(1 - ee_{aux}^2)EE'_0/EE_0}{(1+ee_{aux})^4 + (1-ee_{aux})^4 + 8g\,(1-ee_{aux}^4) + 6f\,(1-ee_{aux}^2)^2} \tag{6}$$

is obtained. When there is no statistical distribution between the four complexes, two additional parameters are needed to define the relative contribution of the complexes[31]

The ML_4 model can efficiently describe the behavior of catalysts such as the one used in the asymmetric oxidation of methyl-*p*-tolyl sulfide (**6**, Figure 5). A calculated curve that fits the experimental data can thus be obtained. The parameters used mean that an active, but poorly, selective heterochiral species and a large predominance of a weakly active *meso* complex are involved. Quite complicated curves can be generated by the use of the ML_4 model. As an example, two triple-shaped curves are presented in Figure 13.[31]

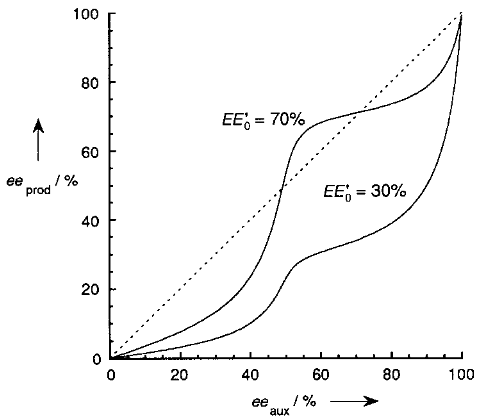


Figure 13. Computer-generated curves for the ML_4 system for $EE'_0 = 30\,\%$ or $EE'_0 = 70\,\%$, $K = 1000$, $K' = 1$, $g = 10$, and $f = 100$.

2.2.5. *The Reservoir Effect*

The use of a partially resolved chiral ligand in asymmetric catalysis can produce some perturbations generated by the formation of diasteromeric complexes, either within the catalytic cycle or at its periphery. Such perturbation in the cycle cannot be deduced from the sole behavior of the catalyst prepared from the enantiopure complexant. A more detailed analysis is needed and a model in which the active and inactive complexes are taken into account can better describe the system. The model presented here is based on the formation of those two types of catalysts (Figure 14).

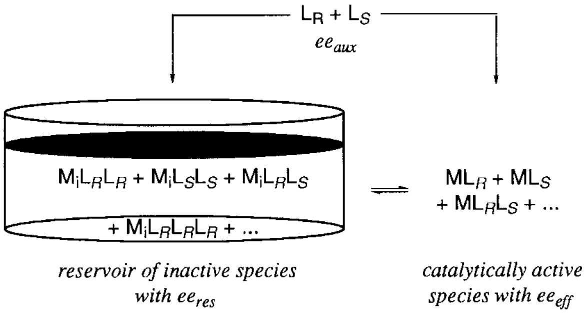


Figure 14. A large pool of unproductive complexes: the reservoir effect model. ee_{res} and ee_{eff} are for the ligands overall.

When a molar amount of ligand with a defined ee_{aux} reacts to form the different species, a part of this (α) can be diverted towards a reservoir; a pool of unproductive complexes with an ee_{res}. This storage will affect the resulting ee value of the active portion of the catalysts in such a way that a new value for the ee of the $1 - \alpha$ portion of the catalyst left will be attained and called the effective enantiomeric excess (ee_{eff}). This new value can be easily calculated from Equation (7). Such a reservoir

$$ee_{eff} = \frac{ee_{aux} - \alpha\, ee_{res}}{1 - \alpha} \tag{7}$$

can be created through several kind of processes. For example, aggregation can take place before, or in parallel with, the catalytic cycle reaching its steady state. The complexes can thus be stored in inactive oligomeric species, with the one with low aggregation numbers behaving as the catalyst or the catalyst precursor. A reservoir of racemic composition is more easily created by the formation of a heterodimer (*meso*), which is thermodynamically stable and catalytically inactive. Most of the reported (+)-NLEs presented in this review can be explained in such a way. In this simplified model ee_{eff} replaces ee_{aux} in Equation (1), and gives a fair approximation when used to draw curves that fit experimental data.[31]

The models presented in this section can be very useful in the understanding of the behaviors of catalysts. The mathematical expressions are in these cases utilized to extract quantitative parameters relative to the different oligomeric catalytic species that exist in solution. This approach is a mere mathematical interpretation of the experimental data recorded. The following Sections will present some of the results obtained by several groups in search of nonlinear effects in asymmetric synthesis.

2.3. Enantiomeric Catalysts

2.3.1. Addition of Organozincs to Aldehydes

One useful method of alkylating carbonyl compounds is the use of organozinc compounds coupled with a catalyst, which is needed for any reaction to be observed. During their work on the alkylation of benzaldehyde (**8**) by diethylzinc, Oguni et al. discovered in 1988 that a nonlinear effect was present when chiral *β*-amino alcohols were used as catalysts.[28] Figure 15 shows the results of alkylation in the presence of various chiral amino alcohols. All catalysts exhibited a (+)-NLE in this reaction (called asymmetric amplification by the authors). In Figure 15 (as in all the graphs of this article) positive values will be arbitrarily attributed to the ee_{prod}; such as here where (−)-PDB (or (−)-DDB) and (+)-P$_y$DB give alcohols of opposite absolute configuration. The (+)-NLE was explained by the authors by the formation of dimeric species in solution. This was confirmed by cryoscopic molecular weight measurements on catalysts generated by the treatment of diethylzinc on enantiomerically pure PDB and racemic PDB. Furthermore, kinetic experiments showed that the reaction with a catalyst prepared with 60% *ee* PDB was 5.5 times faster than the one from racemic PDB.

From these results one can assume that dimers, similar to those discussed in the preceding section, should participate in this amplification of the ee_{prod}. In this alkylation by diethylzinc, it is logical to conclude that if dimers are formed the heterochiral species that retains the minor enantiomer of the catalyst should be less implicated in the reaction; thus leaving the homochiral-enriched dimer free to operate as the active agent or its precursor. Oguni's system with PDB (Figure 15) may be described by the ML_2 model with $EE_0 = 94\%$, $K = 4000$ and $g = 0.015$ ($k_{RS}/k_{RR} \approx 1.5/100$), which shows again the lower reactivity and higher abundance of the heterochiral catalytic species. If the reservoir effect model is used instead the results are fitted by the use of similar parameters ($EE_0 = 94\%$, $ee_{res} = 0\%$ and $\alpha = 0.87$).

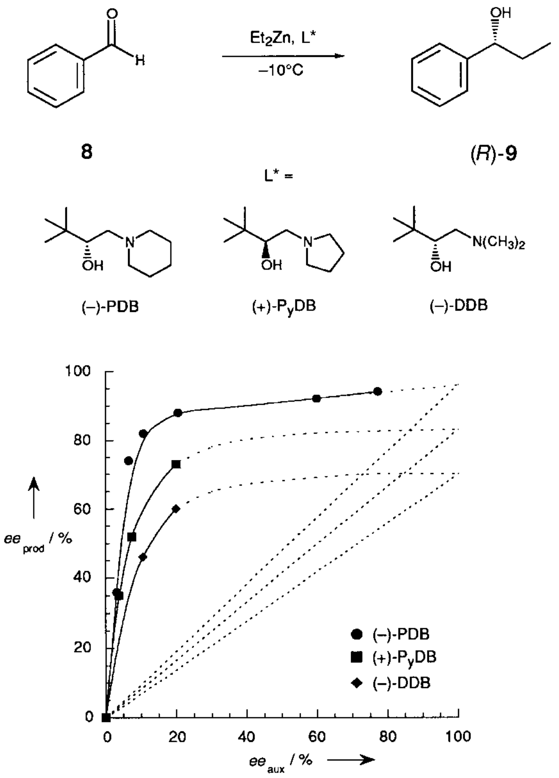


Figure 15. (+)-NLEs on addition of diethylzinc to benzaldehyde (**8**) in *n*-hexane catalyzed by aminoalcohol ligands L* (2 mol%).

In 1989 Noyori et al. published a mechanistic study on their system of catalyzed addition of organozinc complexes to aldehydes.[32] They also observed a strong (+)-NLE by using various *ee*'s of (−)-3-*exo*-(dimethylamino)isoborneol ((−)-DAIB) as a catalyst (Figure 16). This effect is even more important than the preceding one, with the maximum enantioselectivity of the reaction being reached at a very low *ee* of DAIB (curve ●). Thus, 1-phenylpropanol ((*S*)-**9**) can be prepared in high enantiomeric purity (95% *ee*) with a very impure catalyst (15% *ee*). A similar but less pronounced effect was also observed when dimethylzinc (curve ■) was used in the alkylation. Noyori et al. supposed that this strong (+)-NLE was a result of auto association of the chiral reagent generated by the reaction between (−)-DAIB and the organozinc compound. The organometallic DAIB–zinc complex formed undergoes dimerization as depicted in Figure 17. When a mixture of (−) and (+)-DAIB was used, two types of dimeric species were formed: homochiral ((−)·(−)-**10** and (+)·(+)-**10**) and heterochiral ((−)·(+)-**10**); the signs refer to the enantiomer of the chiral ligand included in the complex. The enantiomeric monomers DAIB–ZnR (R = Me or Et) are the active catalysts in this reaction and each one produces predominantly one enantiomer of alcohol **9**.

In a study on the influence of the amount of chiral catalyst on the outcome of the reaction, (−)-DAIB in 14% *ee* was used and the ee_{prod} of (*S*)-**9** was plotted as a function of the relative amount (mol%) of the catalyst (Figure 18). From

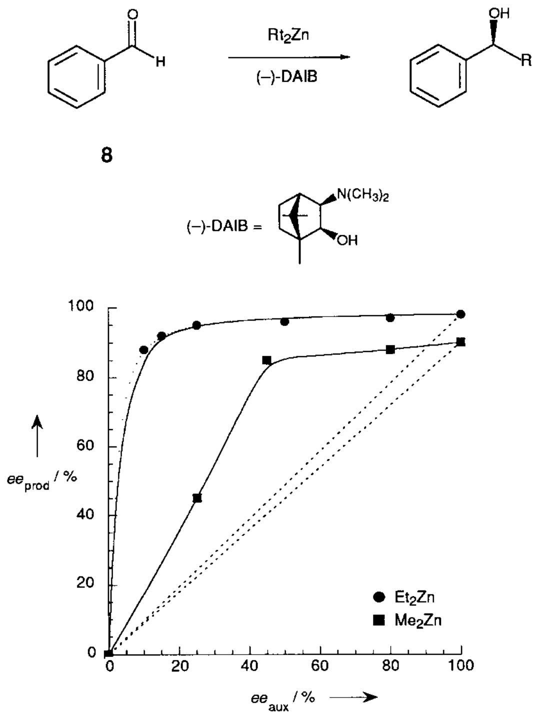


Figure 16. (+)-NLEs in the DAIB-catalyzed (8 mol%) addition of dialkylzinc compounds to benzaldehyde (**8**) in toluene.

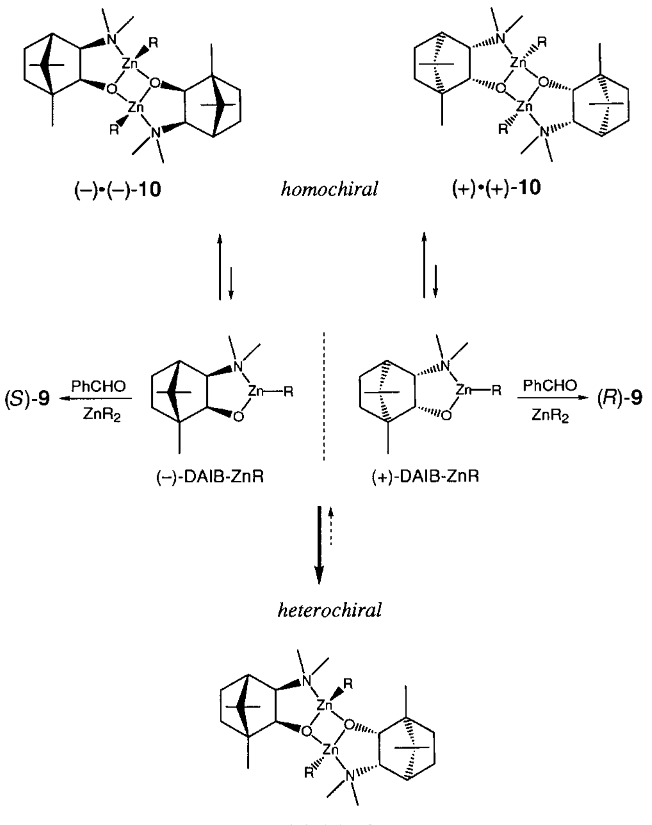


Figure 17. Homochiral and heterochiral dimers formed by the DAIB-alkylzinc reagent.

these results, the turnover efficiency of the homochiral precatalyst was estimated to be 1200 times greater than that of the heterochiral one.

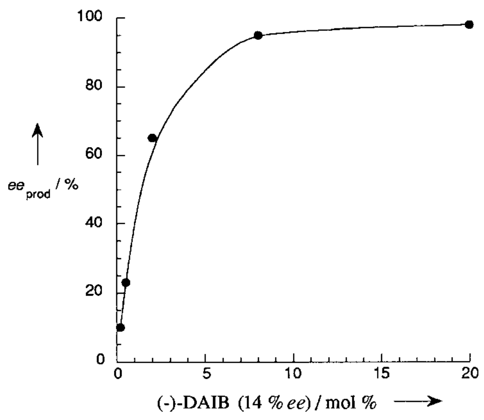


Figure 18. Variation in the ee_{prod} for (*S*)-**9** as a function of the amount of (−)-DAIB (14% *ee*) used in the addition of diethylzinc to benzaldehyde (**8**).

The existence and behavior of the dimeric species were well confirmed by numerous experiments. Cryoscopic molecular weight measurements demonstrated that DAIB – ZnR existed effectively as dimers in solution. NMR measurements of homochiral and heterochiral reagents gave insights as to the relative stability of the dimeric organozinc compounds. Noticeable changes were observed in the NMR spectrum of the homochiral dimer (−)·(−)-**10** upon addition of benzaldehyde, whereas the spectrum of the heterochiral complex (+)·(−)-**10** remained the same, thus revealing a greater stability.

The differences were understood by X-ray diffraction analysis of each of the dimers obtained by treatment of dimethylzinc with the chiral catalyst (Figure 19). The homo

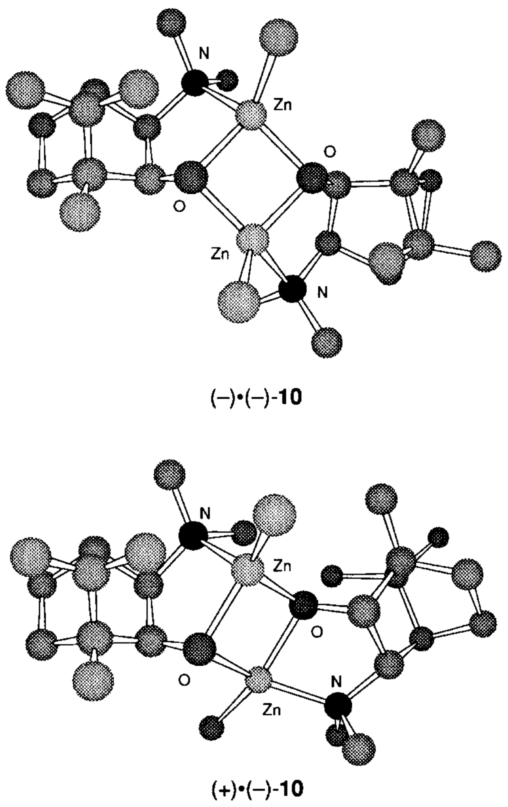


Figure 19. Three-dimensional models of the dimers of (−)-DAIB-methylzinc: (−)·(−)-**10** (homochiral) and (−)·(+)-**10** (heterochiral).

chiral species (−)·(−)-**10** ($R = CH_3$) possesses a C_2 symmetry with a Zn_2O_2 four-membered ring with a *syn* relationship between the methyl groups on the zinc atoms. This ring is “*endo* fused” relative to the DAIB–Zn system. The heterochiral dimer (+)·(−)-**10** ($R = CH_3$) also has a Zn_2O_2 cycle “*endo* fused” to the structure but the methyl groups on the metallic centers, as well as the DAIB fragments, are oriented in an *anti* fashion, which explains the greater thermodynamical stability of this dimer. This was later complemented by energetic calculations on simpler models by the same group.[32b]

If the ML_2 model is used for the reaction performed by Noyori et al. with their DAIB catalyst, the values of $EE_0 = 98\,\%$, $K = 5000$, and $g = 0.01$ ($k_{RS}/k_{RR} \approx 1/100$) give a curve that fits the experimental results. The results may also be analyzed using the reservoir effect model. Noyori’s system approximates better to $EE_0 = 98\,\%$, $ee_{res} = 0\,\%$, and $\alpha = 0.88$. The values extracted hereby confirm a greater stability ($k_{RS}/k_{RR} \approx 1/100$) of the heterochiral complex, and its preponderance ($K = 5000$), in regard to the homochiral one.

Bolm et al. worked on this alkylation reaction as well but used a substituted pyridine alcohol as the chiral catalyst (Figure 20).[33] The ethylation of benzaldehyde (**8**) was very efficient with 5 mol% of the catalyst and Et_2Zn and gave access to (*R*)-1-phenylpropanol ((*R*)-**9**). By varying the *ee* value of the pyridine catalyst, they discovered that a (+)-NLE was taking place, as seen in Figure 20.

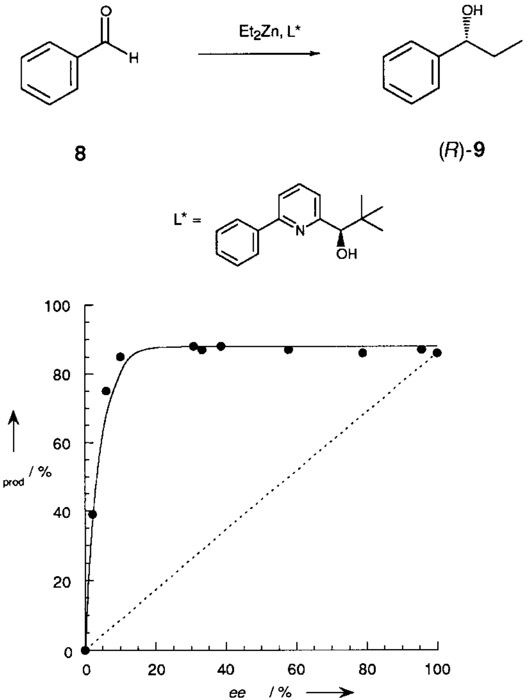


Figure 20. (+)-NLEs in the addition of diethylzinc to benzaldehyde (**8**) with a pyridine alcohol as the catalyst.

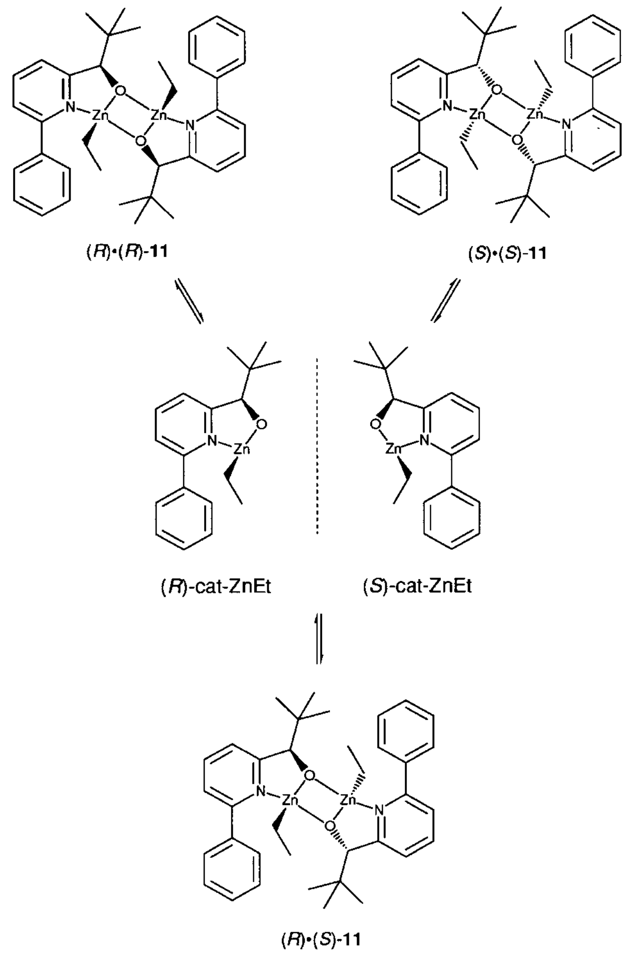
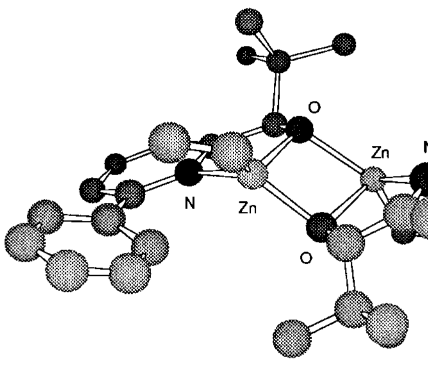


Figure 21. The different dimers formed in solution between the enantiomeric pyridine alcohol–ethylzinc reagents.

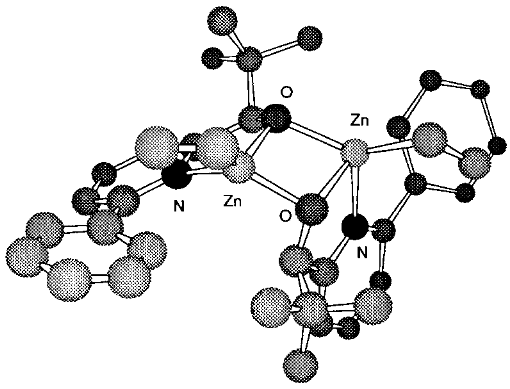
The (*R*)-cat-ZnEt and the (*S*)-cat-ZnEt can interact in solution to give the homochiral dimers (*R*)·(*R*)-**11** and (*S*)·(*S*)-**11** and the heterochiral species (*R*)·(*S*)-**11** (Figure 21). If the heterochiral complex is favored over the homochiral ones, the effect of diverting the minor enantiomer from the reaction mixture will be a net increase in the *ee* value of the active catalyst, thus generating this strong (+)-NLE.

Bolm et al. observed the formation of a white precipitate when the pyridine alcohol was treated with an excess of diethylzinc. Starting with a (*R*)-catalyst in 50 % *ee*, filtering off the resulting solid, and hydrolyzing both mother liquor and precipitate, two fractions of the ligand catalyst were obtained. The one from the crystalline material, and corresponding to 74 % of the starting materials, had a value of 44 % *ee*. However, the ligand recovered from the filtrate (26 % yield) was of 84 % *ee*. This was a clear indication of enrichment of the major enantiomer by predominant precipitation of the *meso* complex and suggested a possible greater stability of this species.

When the precipitation was conducted independently with the (*R*)-catalyst and its racemic form, the solid from the enantiopure pyridine alcohol was very unstable while the one from the racemic alcohol was stable enough to be isolated. The structure of the crystallized solid was determined by X-ray analysis and proved to be the one of a C_i-symmetric dinuclear zinc complex composed of each of the enantiomeric catalysts around a central Zn_2O_2 four-membered cycle; namely the heterochiral dimer (*R*)·(*S*)-**11** (Figure 22). The ethyl and *tert*-butyl substituents on each subunit are *syn* to



(*R*)•(*S*)-**11**



(*R*)•(*R*)-**11**

Figure 22. Structure of the dimeric species (*R*) · (*S*)-**11** in the crystal and proposed structure of (*R*) · (*R*)-**11**.

each other, but they end up *anti* to the substituents of the other unit in the global structure as a result of the overall symmetry. The speculated structure of the homochiral dimer is also presented in Figure 22. The (*R*) · (*R*)-**11** complex has C_2 symmetry with the usual Zn_2O_2 cycle. The alkyl chains on the subunits are still *syn* to each other but the complex system presents a molecular cavity. The steric congestion generated by this geometry, in conjunction with the fact that the zinc atoms are relatively exposed on the convex surface of the dimer, can be an explanation of its lower stability and high reactivity towards air and moisture.

The dimeric structure was easily detected by mass spectrometry. However, the solid isolated from the (*R*)-catalyst showed no evidence of such dimeric species with the molecular ion peak in the mass spectrum being very weak in intensity. This indicates that, if the homodimer is formed, it possess a low stability. The exact structure was not elucidated, but NMR spectroscopy of homo- and hetero-dimeric zinc compounds were reported to be different.

Another example of nonlinear effects in this area is the work of Kellogg et al. on derivatives and analogues of ephedrine as catalysts.[34] The reactions were performed with 5 mol% of *N*-methylephedrine (NME), *N*-methylephedrine disulfide (NMED), and *N*-methylephedrinethiol chlorhydrate (NMET · HCl) as shown in Figure 23. The ethylation of benzaldehyde (**8**) under those conditions leads to the alcohol (*R*)-**9** in all cases. The use of NME showed no particular irregularities in the linear relationship between its *ee* value and the *ee* value of (*R*)-**9** alcohol. However, when using NMED or NMET · HCl an evident (+)-NLE was observed, which was almost identical regardless of the catalyst used.

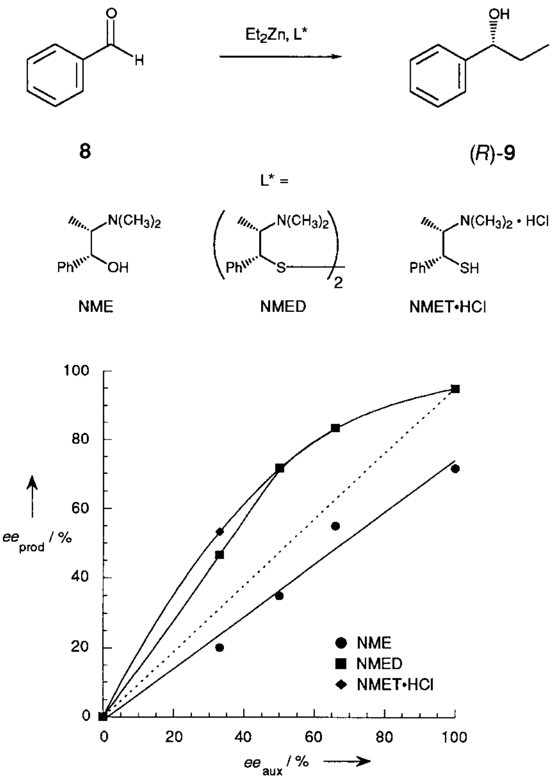


Figure 23. NLEs observed in the 1,2-addition of diethylzinc to benzaldehyde (**8**) catalyzed by derivatives and analogues of ephedrine (5 mol%, toluene, −20 °C).

In order to understand the differences between the catalysts cryoscopic molecular weight measurements were done with NME and NMET · HCl after reaction with various amounts of Et_2Zn. With one equivalent of diethylzinc, oligomeric structures seem to exist in solution in both cases. NME was expected to give rise to an equal mixture of dimer and tetramer based on the results, while NMET · HCl only gave the molecular weight of a tetrameric complex. Addition of an extra equivalent of the dialkylzinc compound only resulted in a total breakdown of the oligomeric structures, with only monomers being detected with the two chiral compounds. It was then proposed by the authors that, in order to observe any NLE, heterochiral (*meso*) aggregates have to be stable to extra diethylzinc and generate an aggregation-induced enrichment of the major enantiomer of the catalyst.

2.3.2. *1,4-Addition of Organozinc Compounds*

The use of alkylzinc compounds, far from being limited to the 1,2-addition reported in the preceding section, can also be extended to conjugated additions on α,β-unsaturated carbonyl compounds. This can be achieved by using nickel in catalytic amounts, the dialkylzinc compound, and a chiral catalyst in order to perform an asymmetric version of the reaction.

Bolm and his group studied this reaction with pyridine alcohol acting as the catalyst precursor (Figure 24).[35] The addition of diethylzinc to chalcone (**12**) in the presence of

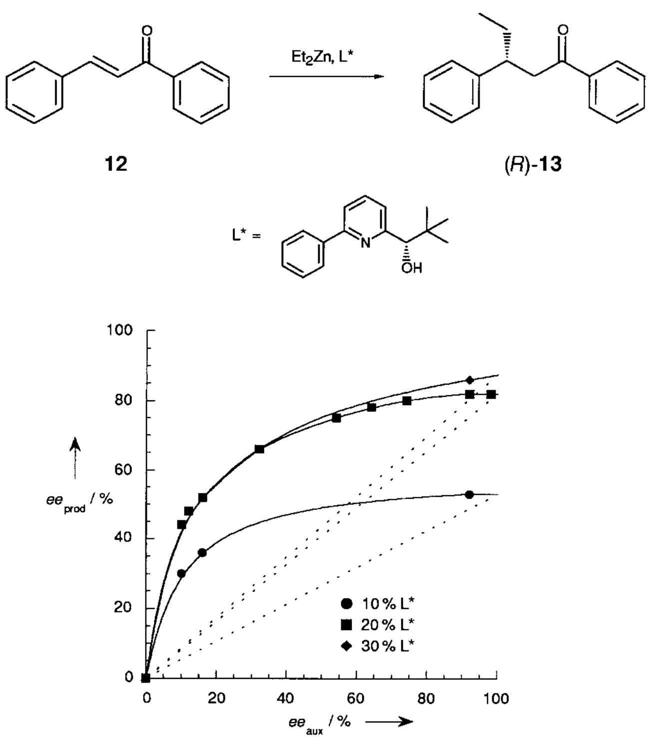


Figure 24. (+)-NLEs encountered in the pyridine alcohol (20 mol%) catalyzed asymmetric 1,4-addition of diethylzinc to chalcone (**12**) (1 mol% [Ni(acac)$_2$], acetonitrile, −30 °C).

20 mol% of the catalyst and 1 mol% of [Ni(acac)$_2$] gave efficient access to the ketone (*R*)-**13** (acac = acetylacetone acetate). When the catalyst was used in various enantiomeric excesses under these conditions, a strong (+)-NLE was observed. Moreover, the use of different quantities of the catalyst had an influence on the resulting curves. While 30 mol% gives essentially the same shape as with 20 mol% (curves ◆ and ■, respectively), a smaller amount of catalyst (10 mol%, curve ●) lowers the enantioselectivity and modifys the appearance of the curve.

The positive influence of the concentration of the catalyst was also confirmed by performing the reaction with the chiral pyridine ligand in 16% *ee* at various mol%. The results are shown in Figure 25a) and the plot against ee_{prod} clearly demonstrates the increased selectivity of larger amounts of the catalytic species, which reaches a maximum at 30–40 mol%. The asymmetric amplification was also tested against the time until the reaction was complete (Figure 25b). When a 19% *ee* catalyst was used in this reaction the ee_{prod} was shown to strongly decrease with the conversion. The use of the substituted pyridine with 89% *ee* also demonstrated a time dependence of the ee_{prod}, but in a less pronounced fashion.

The (+)-NLE was initially explained on the basis of the results and studies done by this group during the course of their research on the 1,2-addition of organozinc compounds.[33] Formation of dimeric zinc catalysts (Figure 21) is sufficient to understand the phenomenon taking place. The stable heterochiral dimer, which acts as a trap for the minor enantiomer, increases the *ee* value of the major one (reservoir effect). The more reactive homochiral dimers left should then react with nickel(II) to form the active catalyst with an *ee* value greater than the one of the chiral pyridine introduced to the mixture. The concentration effect can be explained by a shift in the equilibrium between monomers and dimers. The more concentrated the catalyst becomes, the more dimers should form and thus increase the (+)-NLE.

However, the use of coordinating solvents such as acetonitrile, needed for the nickel catalysis, has deleterious effects on enantioselectivities in carbonyl alkylation reactions. This is possibly the result of the solvent preventing the dimerization of the catalyst–zinc species. Another explanation was thus necessary and was offered by Bolm et al. (Figure 26). A similar type of homo and heterochiral relationship between the two molecules of catalyst implicated can be found here, but the metal complexation is quite different. In this case, it has been postulated that the chiral pyridine first reacted with [Ni(acac)$_2$] to form the two enantiomeric (*S*)- and (*R*)-**14**. These react further with another molecule of the pyridine with the same (homo) or the opposite (hetero) configuration. This leads to the formation of homochiral mononuclear complexes (*S*)·(*S*)-**15** and (*R*)·(*R*)-**15** and the heterochiral complexes (*S*)·(*R*)-**15**. The reaction of diethylzinc with these nickel complexes should proceed with the less stable ones and, from the (+)-NLE observed in this particular case, it has to be the homochiral (*S*)·(*S*)- and (*R*)·(*R*)-**15** dimers. A *meso*, or heterochiral species{(*S*)·(*R*)-**15**}, diverts the minor enantiomer from the catalytic pathway and generates this positive nonlinear effect.

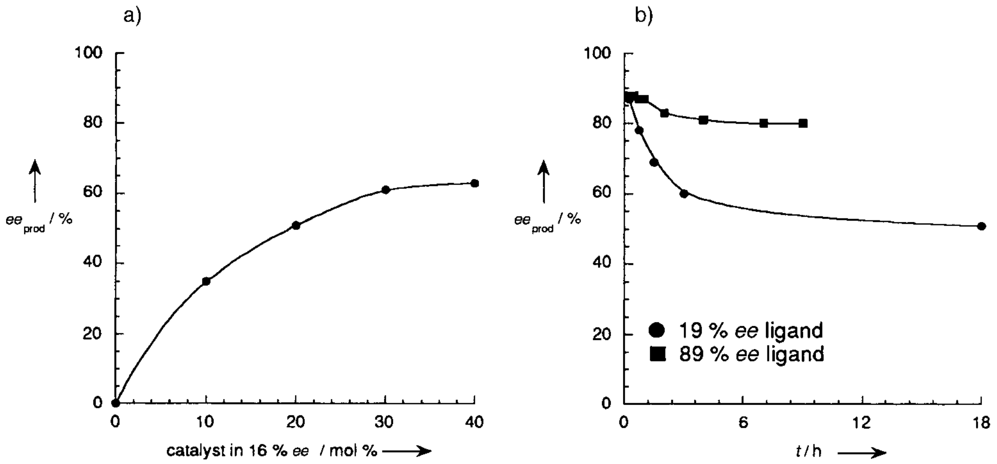


Figure 25. *ee* of product (*R*)-**13** as a function of a) the quantity of pyridine alcohol (16% *ee*) and b) the reaction time with the ligand in 19 and 89% *ee*.

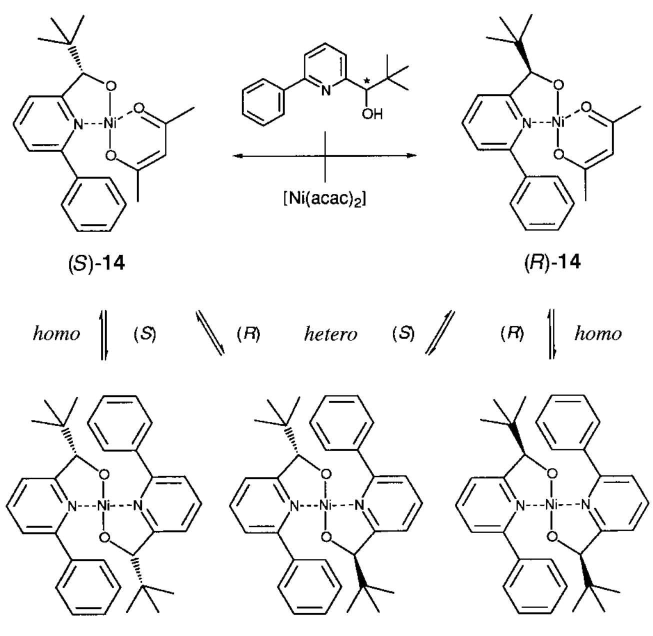


Figure 26. Proposed equilibrium between the monomers and dimers in the catalyzed addition of dialkylzinc compounds in the presence of nickel(II).

Since the formation of the heterochiral dimer reduces the total amount of active catalyst in solution, the decrease in the reaction rate on using a catalyst with a low *ee* value can be explained. One can see from the curves of Figure 25 that a reaction completed in 9 h with a 89% *ee* catalyst takes twice this time with a catalyst in 19% *ee*, because of the presence of a larger amount of the less reactive *meso* dimer. Even if the heterochiral complex is much more stable than the homochiral species longer reaction times seem to permit its dissociation, since ee_{prod} drops with conversion. The 89% *ee* catalyst, in which a lower amount of heterochiral dimeric structure is present, shows only a slight drop in the *ee* value while the one from 19% *ee* falls quite abruptly.

Bolm's 1,4-addition of diethylzinc to chalcone (Figure 24) displayed an $EE_0 = 82\%$, $K = 1000$, and $g = 0.1$ ($k_{RS}/k_{RR} \approx 1/10$) if one uses the ML_2 model to describe the system. These values and the experimental data are in accordance with the more stable *meso* complex hypothesis. The same reaction was studied by Feringa et al. but with (−)-DAIB as the chiral catalyst (Figure 27).[36] The 1,4-addition reaction to chalcone (**12**) was run with 16 mol% of DAIB. By varying its *ee* value and constructing a plot against the measured *ee* value of the resulting ethylated product (*R*)-**13** it was easy to visualize a (+)-NLE. This NLE was shown to be dependent on the concentration, as for Bolm's system, but in this case the influence of the amount of Ni^{II} salt was investigated. While the amount of DAIB was kept constant (16 mol%), the quantity of $[Ni(acac)_2]$ used for the reaction was of 1, 7, and 8 mol% (curves ●, ■, and ◆, respectively). The effect of increasing the nickel ratio was deleterious for both maximum enantioselectivity and the amplitude of the NLE.

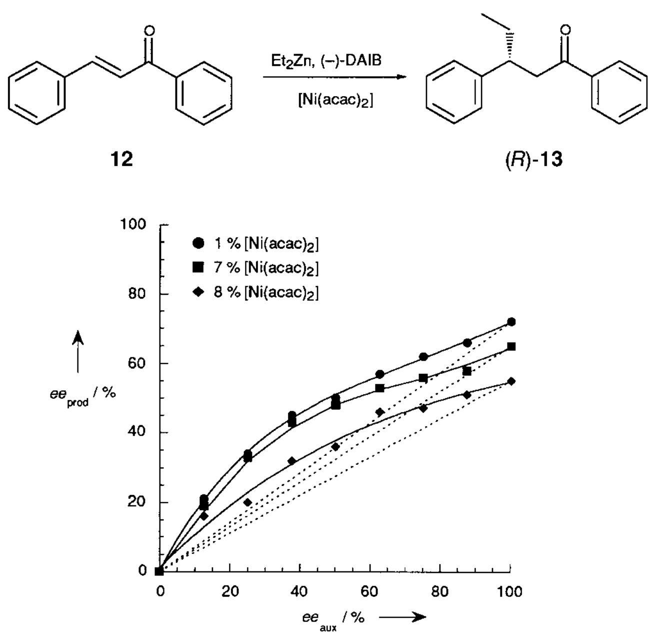


Figure 27. (+)-NLEs in DAIB-catalyzed (16 mol%) 1,4-addition of diethylzinc compounds to chalcone (**12**) (acetonitrile, −30 °C).

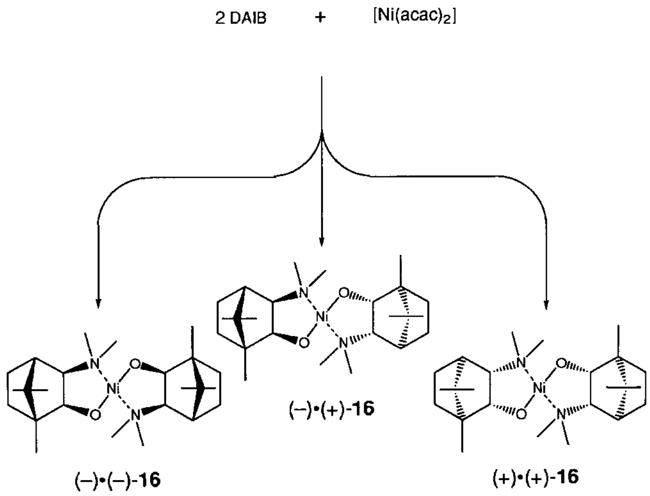


Figure 28. Intermediate dimeric species formed during the DAIB-catalyzed 1,4-addition.

It was suggested that two equivalents of DAIB reacted with $[Ni(acac)_2]$ as illustrated in Figure 28. Such an introduction of two molecules of the chiral auxiliary should give rise to three possible complexes: homochiral (−)·(−)-**16** and (+)·(+)-**16** entities and the heterochiral complex (−)·(+)-**16**. The (+)-NLE taking place here implies, as it was seen before, a greater stability of the *meso* (−)·(+)-**16** species. The structures shown in Figure 29 can help to understand structural differences

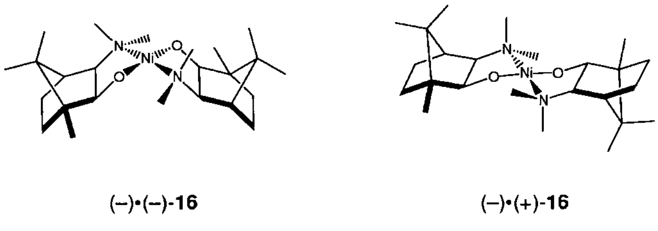


Figure 29. Perspective structural formulas of the DAIB – nickel complexes (−)·(−)-**16** and (−)·(+)-**16**.

between (−)·(−) and (−)·(+)-**16**. In the latter the two enantiomeric aminoisobornyloxy moieties are antiperiplanar, which assures lower steric interactions than its (−)·(−) analogue. The less stable homochiral structures should then be implicated more readily in the reaction than the heterochiral one, which keeps the minor enantiomer away in a thermodynamically-driven dimerization process.

2.3.3. *1,4-Addition of Cuprates*

Nonlinear effects in 1,4-addition reactions are not restricted to the reagents discussed previously, but can also be encountered when cuprates are used. In 1994 Pfaltz and Zhou reported a (−)-NLE in the addition of isopropylcuprate to cycloheptenone (**17**, Figure 30).[37] The use of a chiral copper oxazolinethiolate as the catalyst in this reaction gave access to the substituted suberone (*R*)-**18**. The *ee* value of this product was, for all ee_{aux}, lower than it should be, and thus generates the multishaped curve in Figure 30. This (−)-NLE is a clear indication of a different behavior of the copper catalyst when compared with the results of the 1,4-addition presented in the preceding section. Even if no explanation was given for this NLE, one can suggest that the aggregation of cuprates, which is usually more complex than with other organometallic reagents, is responsible for this effect. However, more information on the structure of the catalytic species involved is necessary to get a better understanding of this phenomenon.

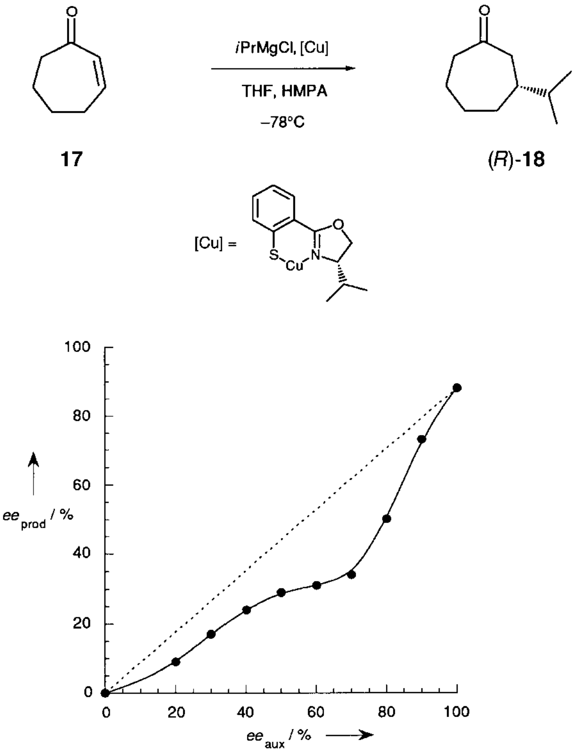


Figure 30. (−)-NLE observed in the copper catalyzed 1,4-addition of *i*PrMgCl to **17**.

This behavior seems to be a constant in cuprate addition reactions (at least with analogous catalysts); van Koten et al. discovered a multishaped NLE while working on the methylation of benzylideneacetone (**19**).[38] Thus, the chiral, aromatic copper aminothiolate (Figure 31) permits an effective alkylation and gives rise to the product (*S*)-**20**. A nonlinear effect that is just above the linear relation relationship between ee_{prod} and ee_{aux} was observed from 0 to 50% *ee*; at higher *ee* values, it becomes a moderate (−)-NLE. The intervention of multinuclear species as being responsible for this NLE has been invoked, but no exact explanation can be given here. The oligomeric structures should influence the *ee* value of the catalyst, and leave a mononuclear species with a modified enantiomeric excess. The curves of Figure 30 and 31 are reminiscent of those discussed for the ML_4 model.

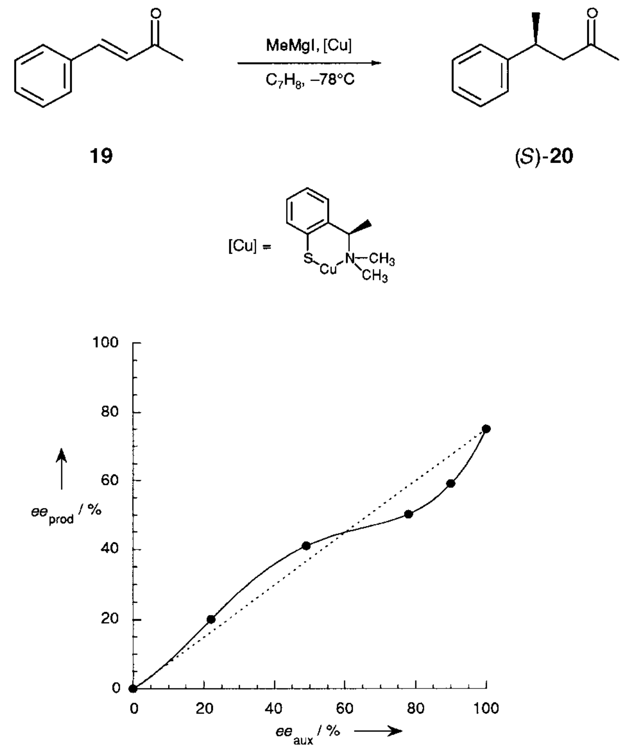


Figure 31. NLE in a copper-catalyzed 1,4-addition of MeMgI to benzylideneacetone (**19**).

2.3.4. *Glyoxylate–Ene Reaction*

One of the earliest and striking reports of nonlinear effects was published in 1990 by Mikami, Nakai et al.[39] In their study of the glyoxylate–ene reaction, mediated by chiral Lewis acid catalysts, they encountered a very strong (+)-NLE with the titanium catalyst derived from 1,1′-bi-2-naphthol (BINOL). Figure 32 depicts the reaction of α-methylstyrene (**21**) and methyl glyoxylate (**22**). The *ee* value of (*R*)-**23** was plotted against the one of (*R*)-BINOL (ee_{aux}). From the curves it can be observed that the effect is almost identical for catalysts prepared from (*R*)-BINOL and $(i\text{-PrO})_2TiBr_2$ (curve ●) or $[Ti(O\textit{i}Pr)_2Cl_2]$ (curve ○).

A series of studies were undertaken by this group and proved to be very helpful in understanding the exact nature of the catalyst in solution.[39c] The BINOL should react first with $[Ti(O\textit{i}Pr)_2X_2]$ (X = Cl, Br) to form, by alkoxy exchange, both

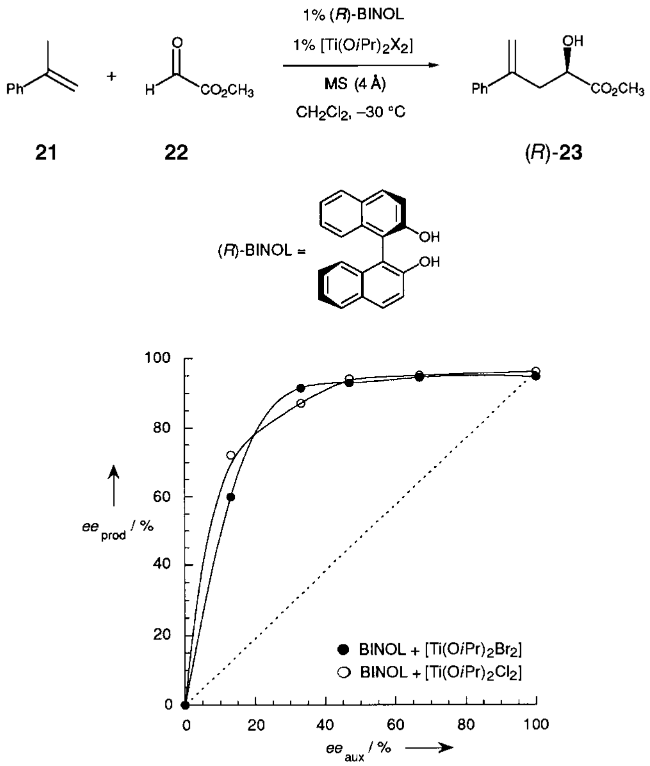


Figure 32. (+)-NLEs in the BINOL–titanium catalyzed ene reaction between **21** and **22**. MS = molecular sieve.

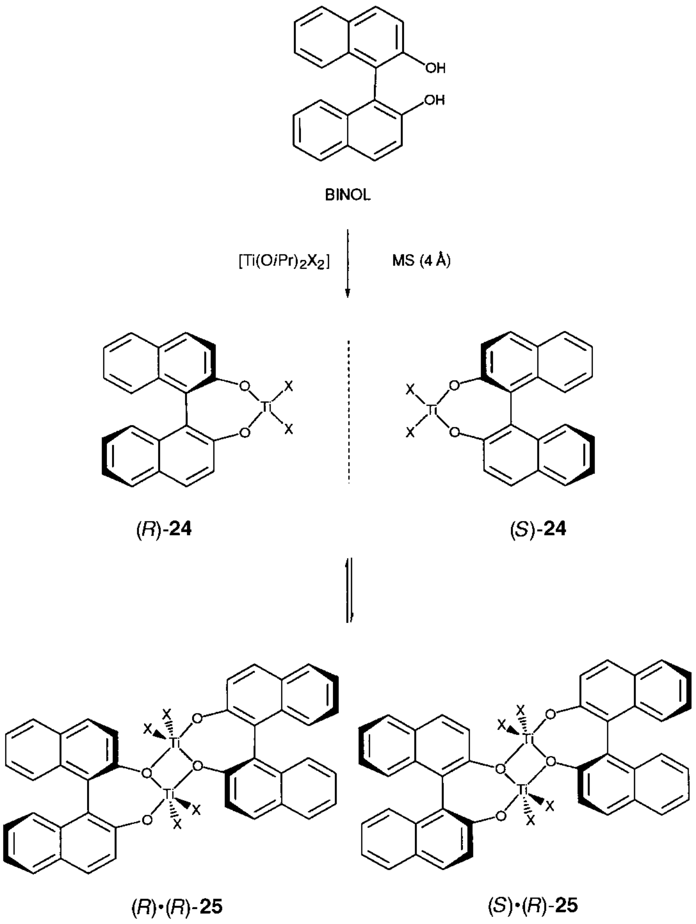
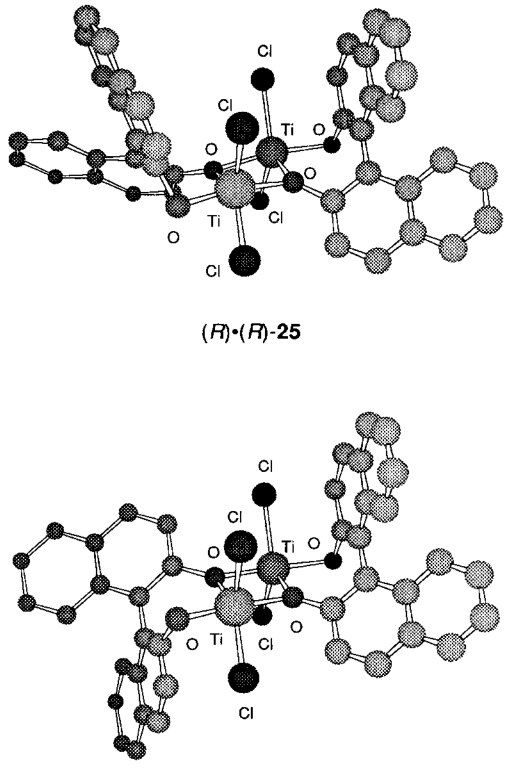


Figure 33. Homochiral ((*R*) · (*R*)-**25**) and heterochiral ((*S*) · (*R*)-**25**) dimers formed between the enantiomeric BINOL–titanium catalysts.

enantiomers of BINOL-TiX_2, (*R*)- and (*S*)-**24** (Figure 33). Those monomers then become implicated in an equilibrium with their dimers (*R*) · (*R*)-**25**, (*S*) · (*S*)-**25** (not shown here), and (*S*) · (*R*)-**25**. The same behavior discussed previously must be encountered to generate the (+)-NLE. Vapor pressure osmometry measurements showed that dimers are formed. Furthermore, the molecular weight of the complex prepared from enantiomerically pure (*R*)-BINOL (homochiral) was concentration dependent, whereas the one from *rac*-BINOL (heterochiral) does not change at all with dilution. This observation is an indication of a greater stability of the *meso* dimer. Kinetic measurements showed (*R*) · (*R*)-**25** to be 35 fold more active than (*S*) · (*R*)-**25**. Since the monomeric species are held responsible for the catalysis, these experiments clearly show that the homochiral dimeric structures dissociate more readily than the corresponding heterochiral ones.

Stability differences can be understood by simply looking at three-dimensional representations of the dimers proposed by the authors (Figure 34). Both structures possess a central four-membered Ti_2O_2 ring around which are organized the chiral units. Steric interactions are much more important in the C_2 symmetrical dimer (*R*) · (*R*)-**25**, since the binaphthyl moieties are *syn*-periplanar and close together. However, in the heterochiral complex (*S*) · (*R*)-**25**, which has a C_i symmetry and a coplanar instead of distorted Ti_2O_2 ring, the spatial orientation of the ligands (*anti*-periplanar) seems in fact to offer a greater stability.



(R)•(R)-25

(S)•(R)-25

Figure 34. Structures of the dimeric species (*R*) · (*R*)-**25** and (*S*) · (*R*)-**25**.

The effect of the amount of catalyst on the NLE was also investigated. Various quantities of (*R*)-BINOL (31% *ee*) ranging from 1 mol% to 100 mol% were introduced in the mixture and the ee_{prod} measured. Figure 35 shows that an increase in the amount of catalytic species, and thus its concentration, lowers the NLE. This observation is in total disagreement with the monomer/dimer equilibrium. This divergent behavior was, however, explained from molecular weight determinations on the catalyst prepared from 31% *ee* BINOL by the appearance of a trimeric species at higher concentrations.[39c, d] The Mikami and Nakai ene-reaction with a BINOL-derived catalyst can however be described with the following parameters for the ML_2 system; $EE_0 = 98\%$, $K = 2300$ and $g = 0.005$ ($k_{RS}/k_{RR} \approx 1/200$), which give the best fit with the experimentally derived curve.

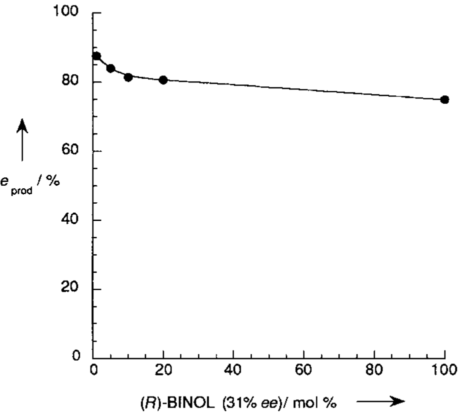
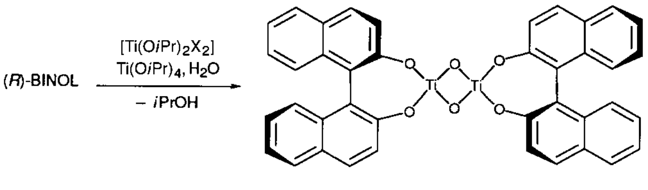


Figure 35. ee_{prod} of (*R*)-**23** as a function of the amount of (R)-BINOL (31% *ee*).

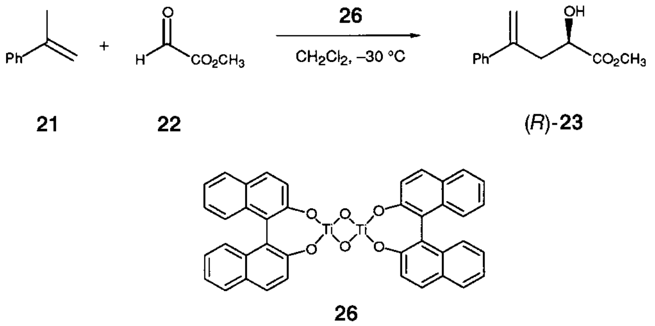
The glyoxylate–ene reaction can also be driven by another type of catalyst developed more recently. Mikami and Terada,[40] and later Nakai et al.,[41] reported the preparation of this new titanium catalyst **26** (Figure 36). Reaction of (*R*)-BINOL with either [Ti(O*i*Pr)$_2$X$_2$] (where X = Cl, Br) or [Ti(O*i*Pr)$_4$] and water, followed by heating and the azeotropic removal of isopropyl alcohol in refluxing toluene led to the formation of the μ-oxo titanium complex (*R*)·(*R*)-**26**. The existence of such a μ-oxo dimeric species in solution was confirmed by molecular mass measurements by vapor pressure osmometry and infrared spectroscopy,[40] as well as by mass spectrometry and NMR spectrocopy.[41] Moreover, the μ-oxo complex mass has a different behavior depending on the *ee* value of the BINOL used to prepare it.[40] When enantiomerically pure (*R*)-BINOL was utilized the apparent molecular weight was shown to be concentration-dependent; while with the racemic BINOL it remained unchanged upon dilution. This indicates a greater stability of the μ-oxo dimer prepared from *rac*-BINOL in solution over the homochiral complex (see above). This was an indication of a possible nonlinear behavior with this new catalyst.



(*R*)•(*R*)-26

Figure 36. Synthesis of **26**.

When the ee_{prod} was tested in the glyoxylate–ene reaction against the *ee* value of the BINOL used to prepare the catalyst **26** a strong (+)-NLE was observed (Figure 37). The amount of the catalytic species had little effect on the amplifying phenomenon. The *meso* μ-oxo catalyst accounted for the increase of the *ee* value of the catalytic substance. In fact, the homochiral catalyst possessed a catalytic activity nine times superior to that of the heterochiral one. Furthermore, molecular modeling on the three-dimensional representations of the μ-oxo (*R*)·(*R*)- and (*S*)·(*R*)-**26** (Figure 38) showed the heterochiral (*S*)·(*R*)-**26** to be 1.08 kcal mol^{-1} lower in energy.[40]



26

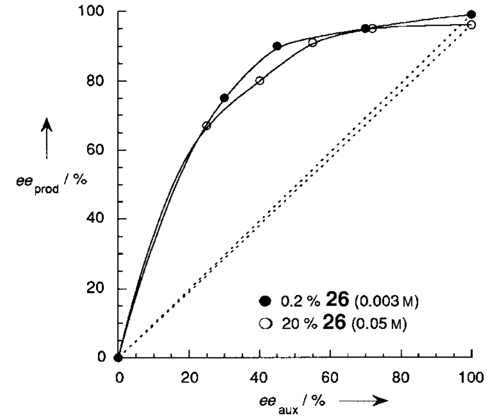


Figure 37. (+)-NLE observed in the ene reaction catalyzed by **26**.

2.3.5. Trimethylsilylcyanation of Carbonyl Compounds

Oguni et al. investigated the asymmetric cyanation of carbonyl compounds with trimethylsilylcyanide (TMSCN), as illustrated in Figure 39.[42]. The catalyst is prepared by freeze-drying a solution of an equimolar mixture of (+)-diisopropyl tartrate {(+)-DIPT} and [Ti(O*i*Pr)$_4$]. It is then used in the reaction in the presence of isopropyl alcohol. This reaction gives trimethylsilylated cyanohydrines in both good chemical yields and enantioselectivity. For example, benzaldehyde (**8**) gives the corresponding compound (*R*)-**27**. This

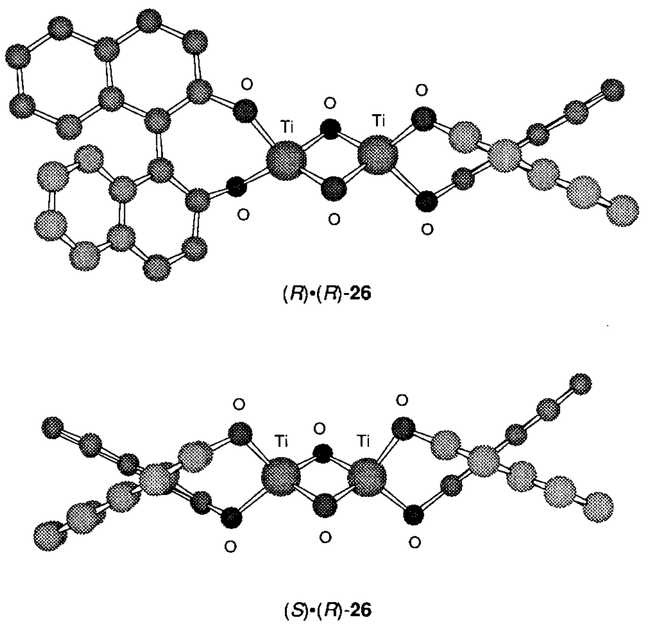


Figure 38. Three-dimensional representations of homo- and heterochiral μ-oxo-titanium complexes $(R)\cdot(R)$- and $(S)\cdot(R)$-**26**.

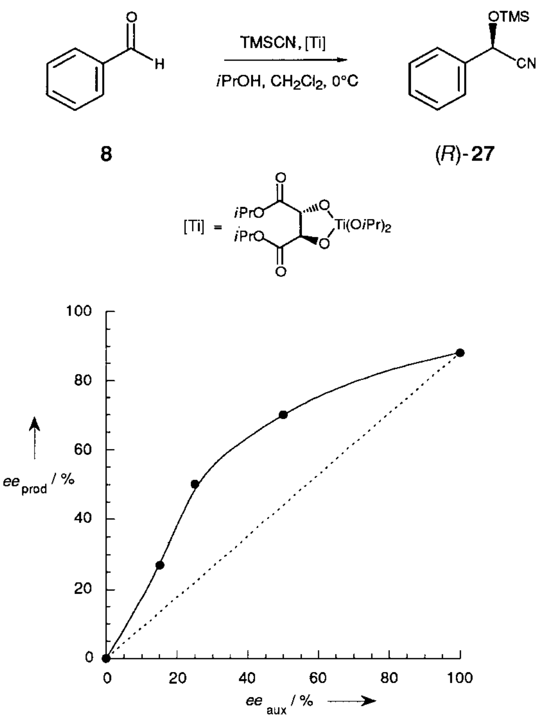
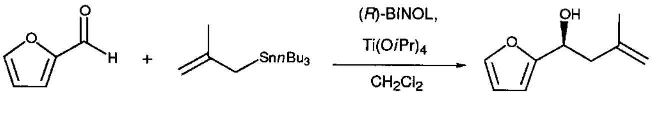


Figure 39. (+)-NLE in the trimethylsilylcyanation of benzaldehyde (**8**) with a chiral titanium catalyst (20–100 mol%).

asymmetric synthesis works well with 20 mol% of the catalyst, but selectivities are better with stoichiometric amounts. The authors tested the effect of the incorporation of partially resolved (+)-DIPT in the preparation of the catalyst. By using one equivalent of this species, the enantiomeric excesses of the product **27** were measured and a nonlinear effect observed (Figure 39). This effect was not explained because of the lack of information on the structure of the catalyst. However, the spectral analysis of the freeze-dried compound suggested an oligomeric structure of the type $[\{Ti(OiPr)_2(DIPT)\}_n]$, which breaks down to a simpler structure upon addition of the alcohol to the mixture.[42b] This NLE is reminiscent of the one encountered in the Sharpless epoxidation discussed in the Section 2.1.

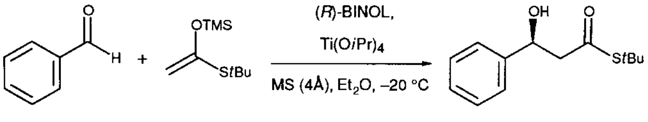
2.3.6. Allylation and Aldol Condensation on Aldehydes

Keck et al. studied the asymmetric allylation and aldolization of aldehydes with a BINOL-derived titanium catalyst.[43] In their work they investigated the effect of using a chiral ligand that was not enantiomerically pure. In the allylation reaction furfural (**28**) was treated with tri-*n*-butylmethallylstannane (**29**) to give the product (*S*)-**30** (Scheme 1).[43a] When the catalyst was prepared by the reaction of an equimolar mixture of BINOL and $Ti(OiPr)_4$, in the presence of molecular sieves (4 Å), a positive nonlinear effect could be detected when the reaction was performed at −20 °C. The use of 50% *ee* or 100% *ee* BINOL gave **30** with an *ee* of 88 or 99%, respectively. By comparison, simple mixing of BINOL and $Ti(OiPr)_4$ (in a 2:1 ratio) at room temperature without molecular sieves led to a strictly linear relationship between ee_{aux} and ee_{prod}. The departure from linearity can be explained as a result of the formation of the usual, more stable heterochiral dimer. The molecular sieves play an important role in the formation and interaction of the complexes, since in its absence no NLE is observed. The nature of the catalyst in the latter case is however unknown and maybe quite different from the one discussed previously.



Scheme 1. The asymmetric BINOL–titanium catalyzed allylation of furfural (**28**) with a dependence of a NLE on the presence of molecular sieves.

The same catalyst was then used in the aldol condensation of aldehydes.[43b] Reaction of benzaldehyde (**8**) with the ketene acetal **31** gives access to the thioester (*S*)-**32** when 20 mol% of the BINOL-titanium catalyst, prepared in the presence of molecular sieves, is employed (Scheme 2). In this reaction the ee_{prod} varies nonlinearly with respect to different *ee*'s of the BINOL. A (+)-NLE takes place as expected for this type of catalyst, which is almost identical to the one presented in Scheme 1. The use of BINOL with 50% *ee* gave a product with an enantiomeric excess of 91% while the enantiopure diol gave the adduct with 97% *ee*.



Scheme 2. Asymmetric aldol condensation of benzaldehyde (**8**) with **31**.

Faller et al. and Tagliavini et al. were also interested in the allylation of aldehydes and reported a similar study of nonlinear effects in this reaction. A comparison was done between two types of BINOL-metal catalysts in the reaction of allyltributyltin (**34**) and aldehydes, as illustrated in Figure 40. Faller et al. prepared their catalyst by mixing (*R*)-BINOL with various *ee*'s with $Ti(O\textit{i}\text{-}Pr)_4$ in the presence of 4-Å molecular sieves.[44] The use 30 mol% of this catalyst in the allylation of benzaldehyde (**8**) gave rise to the usual (+)-NLE seen for BINOL catalysts (curve ○). Tagliavini et al. studied the reaction of octanal (**33**) catalyzed by 20 mol% of the complex that was prepared by reaction between (*S*)-BINOL and $[Ti(O\textit{i}Pr)_2Cl_2]$ in the presence of molecular sieves, and observed a pronounced (+)-NLE (curve ●).[45] A strong resemblance with the effect reported with the same catalyst in the ene reaction (Section 2.3.4.) is seen. In the allylation reaction the homochiral dimeric species was calculated to be 100 times more active than its heterochiral equivalent and, therefore, explains the NLE observed here.

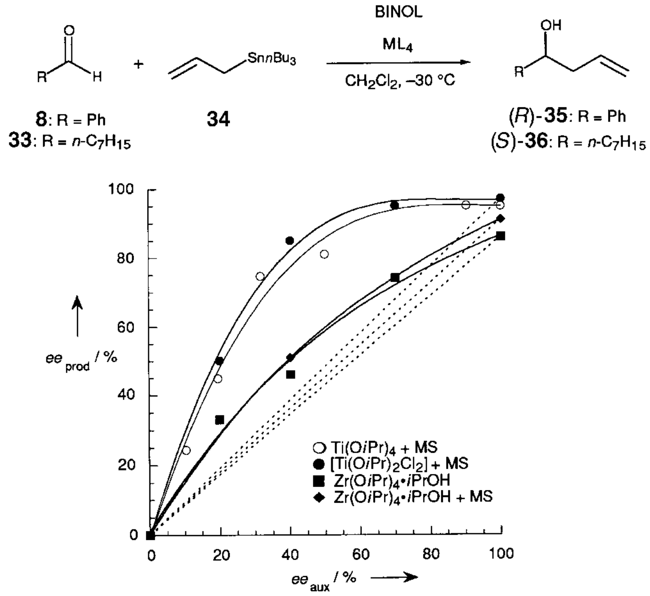


Figure 40. NLEs observed in the asymmetric allylation of aldehydes with various BINOL–metal catalysts (20–30 mol%).

When the chiral catalyst was prepared from $Zr(O\textit{i}Pr)_4 \cdot \textit{i}PrOH$, with (curve ■) or without (curve ◆) the addition of molecular sieves, a moderate (+)-NLE could be recorded. The similarity of the results, for both methods of preparation, has been explained from the NMR analysis. While solutions of BINOL and $[Ti(\textit{i}PrO)_2Cl_2]$ remained unchanged if no molecular sieves are added, those of BINOL and $Zr(O\textit{i}Pr)_4 \cdot \textit{i}PrOH$ showed the formation of the catalyst $[Zr(O\textit{i}Pr)_2BINOL]$ with and without molecular sieves. Only a slight modification in the level of enantioselectivity takes place.

Kinetic experiments with the zirconium catalyst showed that the one prepared from pure (*S*)-BINOL needed four hours to complete the reaction, while the other catalyst derived from *rac*-BINOL was a little less active (10 h). The moderate deviation from the linear relationship was further explained by the activity of the homochiral zirconium complex being only two times greater. This value is quite small when compared to the activity difference in the case of the titanium catalysis. Tagliavini et al. found out, from the ML_2 model, that the BINOL–titanium catalyst possesses a $g = 0.01$ ($k_{RS}/k_{RR} = 1/100$), while the BINOL–zirconium one displays a $g = 0.6$ ($k_{RS}/k_{RR} \approx 1/1.7$).

Carreira et al. reported similar results from the allylation of pivalaldehyde with allyltrimethylsilane with a BINOL–Ti catalyst prepared from BINOL and TiF_4. In their case, the use of 50% *ee* BINOL gave an allylic alcohol with 82% *ee* while the enantiopure BINOL gave 95% *ee* for the same alcohol.[46]

2.3.7. Asymmetric Epoxidation

In 1994 Kagan et al. reported an additional example of nonlinear effects during a Sharpless epoxidation (for geraniol epoxidation, see Section 2.1.) that involved the formation of the epoxide **38** from the allylic alcohol **37** (Figure 41).[31] A moderated amplification of the expected enantiomeric excess was noted. Based on a model in which two chiral ligands are bound to the metallic center, this NLE was explained by the formation of the usual diasteroisomeric species. The heterochiral species was shown to possess half the catalytic activity of one of the homochiral complexes. On the basis of the ML_2 model, this asymmetric epoxidation of an allyl alcohol is described well by the parameters $EE_0 = 99\%$, $K = 1000$ and $g = 0.5$. The heterochiral species is slightly more stable ($k_{RS}/k_{RR} \approx 1/2$) and abundant ($K = 1000$).

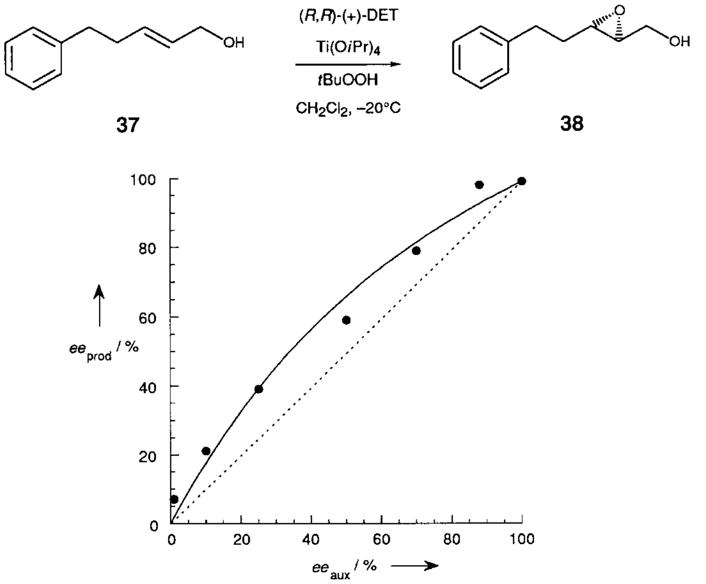


Figure 41. (+)-NLE in the Sharpless epoxidation of **37**.

2.3.8. Asymmetric Sulfoxidation

One of the first nonlinear effects was discovered by Kagan et al. during sulfide oxidation mediated by a chiral titanium complex.[19] The negative nonlinear effect resulting from this reaction was discussed in Section 2.1. Uemura et al. reported interesting results in their study of asymmetric oxidation of sulfides promoted by a chiral BINOL–titanium catalyst.[47a] The method employs a reagent similar to Kagan's, but with BINOL as the chiral unit. This complex can be used at the catalytic level and sulfides such as **6** are efficiently transformed into sulfoxide (*R*)-**7** (Figure 42).

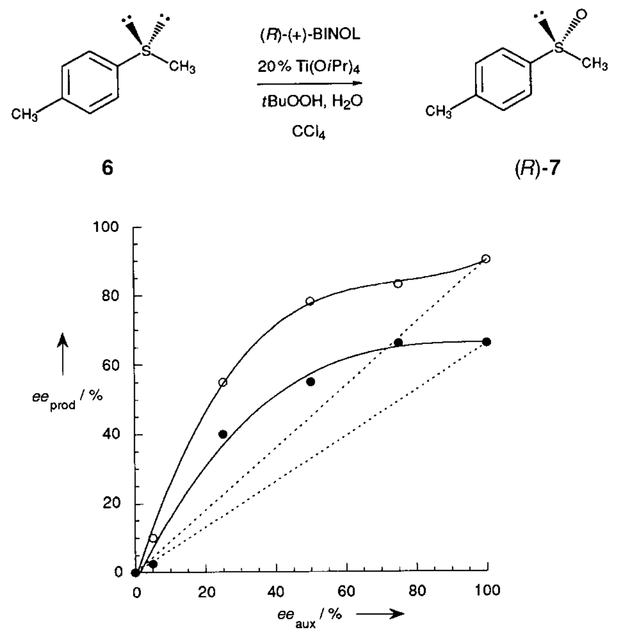


Figure 42. (+)-NLE in a BINOL–titanium catalyzed oxidation of sulfide **6** under various reaction conditions. Curve ●: Argon, −20 °C; curve ○: air, 0 °C.

The variation of the *ee* value of (*R*)-BINOL generated a (+)-NLE in the case of the two sets of experimental conditions, namely under argon at −20 °C (curve ●) and in air at 0 °C. When the reaction was performed under argon with a solution of *t*-BuOOH in toluene a moderate (+)-NLE was observed as well as a low selectivity at 100% *ee* of BINOL. The enantioselectivity of the transformation was however much better when the second method was employed; the use of 70% aqueous *t*-BuOOH at 0 °C with the reaction being carried out open to the atmosphere, generated higher levels of asymmetric induction as well as a stronger (+)-NLE (curve ○). The authors concluded that the existence of a (+)-NLE with this catalyst, in comparison with the negative effect observed with Kagan's reagent, was a result of a strong difference between the two catalysts. However, neither the NLE nor the structure of the catalyst itself was analyzed.

The presence of a NLE in this system can easily be understood if one takes into account the results already discussed with BINOL-metal catalysts (Sections 2.3.4 and 2.3.6). However, Uemura et al. discovered, by studying the evolution of the ee_{prod} over time, that a second reaction was also involved in the stereochemical outcome of the reaction.[47b] With the enantiopure BINOL, the *ee* value of the sulfoxide **7** was shown to increase considerably with the advancement of the reaction. This augmentation of the enantiomeric excess was accompanied by increased amounts of the overoxidation product, namely the corresponding sulfone. As the formation of the sulfone proceeds a process of kinetic resolution[48] takes place, which assures a better *ee* value of (*R*)-**7** over time. A study showed that racemic **7** indeed gave rise to a kinetic resolution in which there is some asymmetric amplification. The curves of Figure 42 are thus a complicated function of (+)-NLE for both the sulfoxidation and the subsequent kinetic resolution.[47b]

2.3.9. Allylic Oxidation

Feringa et al. reported that NLEs can be observed in the asymmetric allylic oxidation with copper salts and (*S*)-proline.[49] This NLE is however modified by the presence or absence of a catalytic amount of anthraquinone as seen in Figure 43. When proline of different enantiomeric excesses was introduced alone into the reaction mixture a small (−)-NLE took place (curve ●) in this reaction of low enantioselectivity. When 4 mol% of anthraquinone was added to the mixture, an increase in the reaction selectivity as well as a moderate (+)-NLE were encountered. Both procedures transform cyclohexene (**39**) into (*S*)-2-cyclohexenyl propionate ((*S*)-**40**).

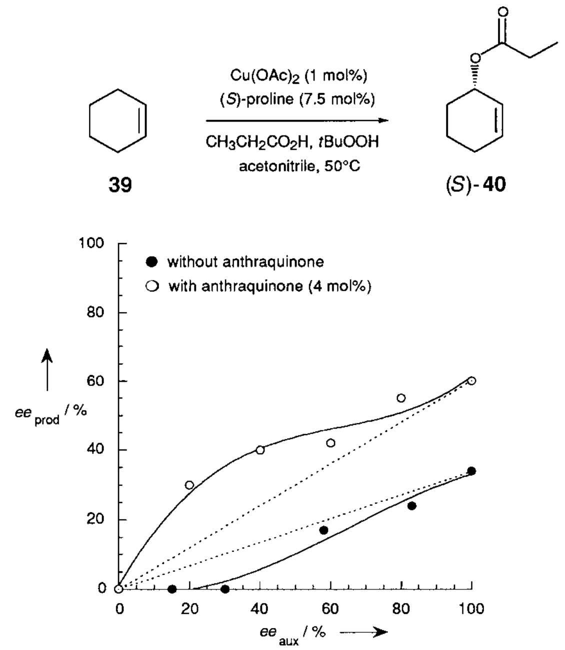


Figure 43. Modification of the NLE in an asymmetric allylic oxidation of **39** catalyzed by (**S**)-proline with the addition of anthraquinone.

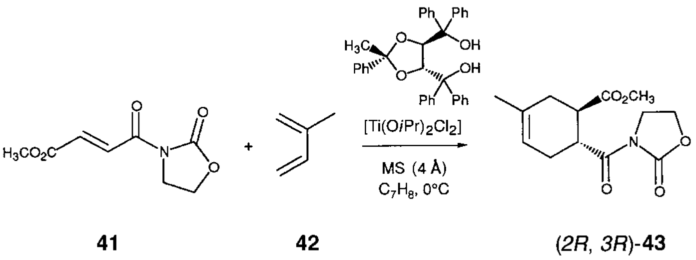
The authors stipulated that the generation of the (−)-NLE by the use of proline with copper(II) acetate was the result of more than one proline molecule being involved in the stereodiscriminating step, as was the case in the example from Agami (Section 2.1). It is also possible that dinuclear or oligonuclear catalytic complexes are implicated. The blue solution formed with the copper salt becomes more turbid when the *ee* value of proline is lowered. It was suggested that the precipitate was composed of the *meso-* or heterochiral complex (*R*)-prolinato-(*S*)-prolinato-copper(II). Moreover, the (*R*)·(*S*)-complex remaining in solution must be more reactive than the homochiral ones, $(R)\cdot(R)$ and $(S)\cdot(S)$, in order to observe the negative effect.

Feringa et al. proposed that in the presence of anthraquinone a mechanistic or structural change occurred, which involved the interaction of the catalyst and quinone. The effect of anthraquinone cannot be ascertained, but since the reaction passes through a Cu^{III} intermediate, one can propose that it should play a role in the redox pathways of the reaction.

2.3.10. Diels–Alder Reaction

The Diels–Alder reaction, one of the most powerful methods for the synthesis of 6-membered rings, was studied in great detail and its asymmetric version developed with a certain success. Since chiral catalysts are utilized in the reaction, several groups tested the existence of nonlinear effects during its course.

As early as 1989 Narasaka et al. observed a peculiar behavior of a TADDOL-type diol when used with titanium as a catalyst in the Diels–Alder reaction illustrated in Scheme 3 (TADDOL = tetraaryldioxolanedimethanol.[50] When the 3-acyl-1,3-oxazolidin-2-one **41** was allowed to react with 2-methyl-1,3-butadiene (**42**), in the presence of the catalyst generated by using the diol and $[Ti(OiPr)_2Cl_2]$, the product *(2R,3R)*-**43** derived from the *endo* transition state was isolated. When the authors took a diol with 25 % *ee* for preparing the catalyst, the product **43** was isolated with an *ee* of 83 %. Furthermore, a precipitate was observed during the preparation of the catalytic species. This observation was an indication of interactions in solution that lead to a NLE-type of behavior for the catalyst. This was further proved by admixing the diol (25 % *ee*) and $[Ti(OiPr)_2Cl_2]$, removal of the precipitate, and performing the reaction with the supernatant solution. Once again the product **43** was isolated with 83 % *ee*. The filtrated solid was hydrolyzed to retrieve the diol, which was in this case racemic. This result suggested that the species formed was at least dimeric, and the 1:1 ratio of enantiomers was an indication that the precipitated compound was the heterochiral complex.



Scheme 3. Asymmetric Diels–Alder reaction between **41** and **42** with a TADDOL–titanium catalyst.

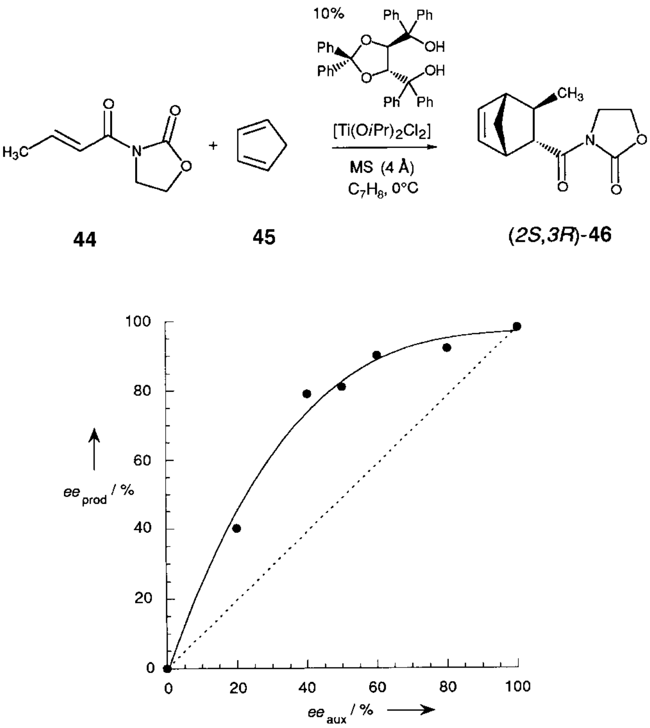


Figure 44. (+)-NLE in an asymmetric Diels–Alder reaction of **44** and **45** with a TADDOL–titanium catalyst.

Irrure et al. reported some years later a more complete study of NLE in the Diels–Alder reaction by using a similar diol as the chiral unit of the titanium catalyst.[51] With 10 mol% of the catalytic species, the cycloaddition of the oxazolidinone **44** and the diene **45** gave the expected product **46** (Figure 44). By varying the *ee* value of the diol, a (+)-NLE was observed for the *ee* of the product. The greater stability of the *meso*-dimeric species can be appreciated qualitatively by the formation of a precipitate when starting from the *rac*-diol, while enantiopure diol produced only a clear and limpid solution of the catalyst.

By keeping a constant amount of catalyst, and using the same reaction conditions, the influence of the enantiomeric purity of the diol on the chemical yield as well as the formation of the *endo* product **46** was evaluated (Figure 45). The racemic diol generates a poor catalytic system and, after 21 h at 0 °C, only 6 % of **46** was obtained with a diastereoselectivity of 58 % in favor of the *endo* isomer. This suggested that the very insoluble heterochiral dimer was very stable and thus, less easily implicated in a catalytic cycle. The enantiopure diol-derived catalyst is however much more efficient. Since it is constituted only of totally soluble homochiral dimeric species, it gave under the exact same conditions 68 % of **46** at 87 % *de* (diastereomeric excess). Figure 45 allows visualization of the effect of the variation of the *ee* value of the diol between 0 and 100 % *ee* on the yield (a) and diastereoselectivity (b) in this reaction.

Mikami's group also studied an asymmetric Diels–Alder reaction but with their BINOL-titanium catalyst, and again obtained excellent results.[52] Condensation of the diene **47** with methacrolein (**48**) gave efficient access to the carbocycle **49**, as depicted in Figure 46. In this reaction, the (*R*)-BINOL/$TiCl_2$ catalyst ((*R*)-**24**) was prepared in the usual way (see Section 2.3.4.) and the molecular sieve filtered-off before using it for catalysis. To study NLEs in this reaction the authors decided to vary the *ee* value of the catalyst **24** using two methods: In the first, molecular sieve-free (*R*)-**24** and *rac*-**24**, prepared independently from enantiopure or racemic BINOL respectively, were admixed to reach the desired *ee*

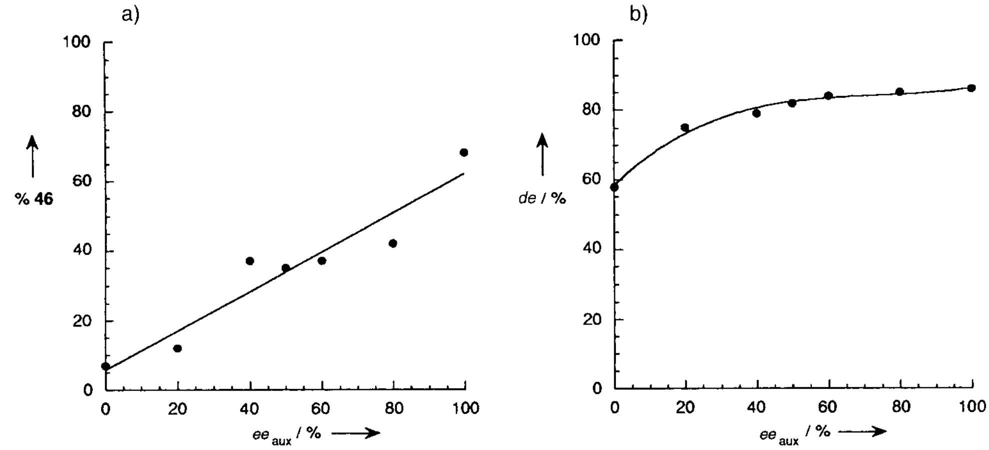
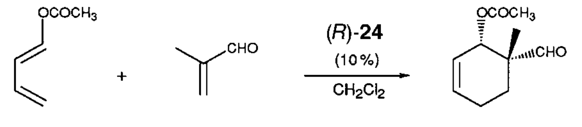
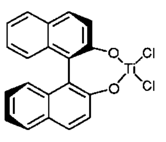


Figure 45. Yield and diasteromeric excess (*de*) of the product **46** with variation in the *ee* value of the diols.



47 + **48** $\rightarrow$ **49**



(*R*)-**24**

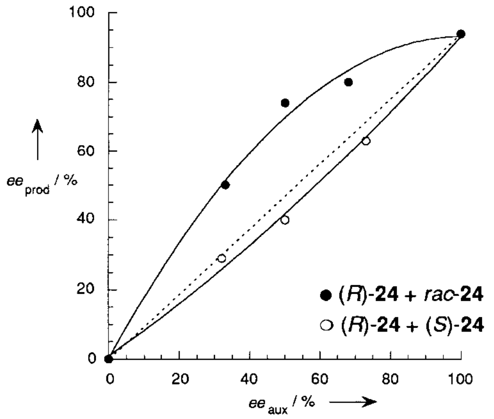


Figure 46. Variation of the NLE observed in a BINOL–titanium catalyzed Diels–Alder reaction with variation in the preparation of the catalyst.

value. The results of the asymmetric induction using this approach generated the curve ● of Figure 46, with a moderate (+)-NLE being observed.

In the second method, molecular sieve-free (*R*)-**24** and (*S*)-**24** were synthesized separately before using them to prepare the catalyst of various enantiomeric purities (curve ○). In this case, the relation was almost linear, which shows a strong difference with the preceding method of preparation and the results from Section 2.3.4. This result suggests that the presence of molecular sieves is important for establishing the equilibrium between the dimers. The fact that a mix of (*R*)-**24** and *rac*-**24** leads to a NLE, while (*R*)-**24** and (*S*)-**24** admixing gives a linear relationship, confirms that little exchange between the dimeric species takes place in the absence of molecular sieves. Thus in the first method catalyst *rac*-**24**, which exists as the more stable and less catalytically active heterochiral dimeric species, is mixed with the homochiral dimer generated from (*R*)-**24**. Since the exchange is almost nonexistent, the reaction will mainly be catalyzed by (*R*)-**24** that is readily liberated from the homochiral complex, with the *meso* complex acting mainly as a spectator. For the other technique homochiral dimers act independently in the reaction to give a product with an *ee* value reflecting the enantiomeric composition of the catalyst. It is intriguing that in this case the liberated monomeric (*R*)- and (*S*)-**24** seem to be implicated only in the catalysis and not in a heterochiral dimerization process. If the catalyst prepared from BINOL with 50% *ee*, followed by the filtration of molecular sieves, is used in this reaction, product **49** is isolated with an *ee* of 76%. This is the result of the formation of homo- and heterochiral species prior to removal of the molecular sieves.

The greater stability of the *meso* dimer was evaluated by kinetic experiments. The molecular sieve-free catalyst prepared from (*R*)-BINOL (curve ●) was shown to be five times catalytically more active than the one obtained from *rac*-BINOL (curve ○, Figure 47). The same group also observed a (+)-NLE of the same amplitude when using the catalyst prepared from (*R*)- and *rac*-**24** in an hetero-Diels–Alder reaction. The effect was examined in the reaction between the diene **50** and methyl glyoxylate (**22**) to afford the dihydropyrane **51** (Figure 48).

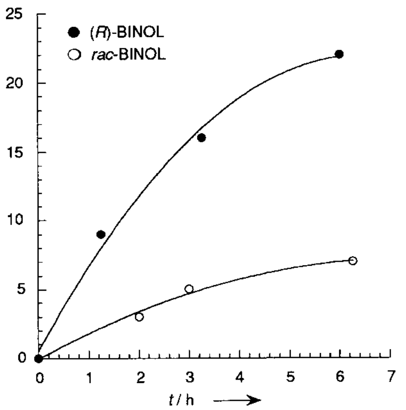


Figure 47. Yield of the product **49** as a function of reaction time for enantiomerically pure (*R*) and racemic BINOL.

In their study of the asymmetric version of the Diels–Alder reaction Kobayashi et al. discovered various kinds of non-

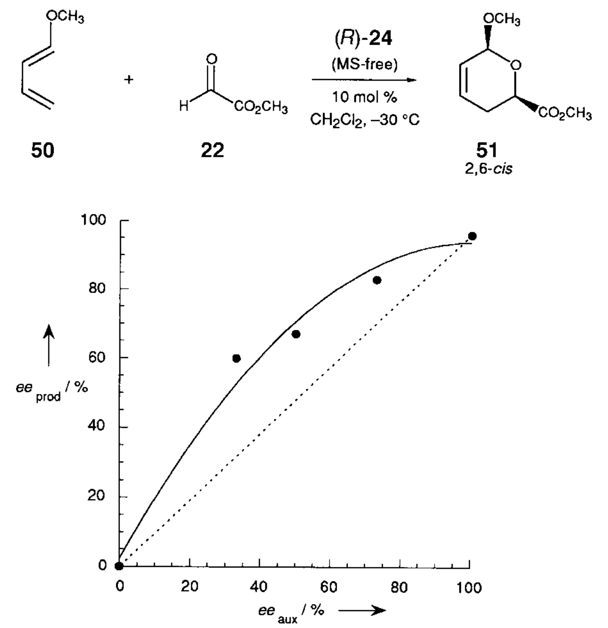


Figure 48. (+)-NLE in an asymmetric hetero-Diels–Alder reaction between **50** and **22** with a BINOL–titanium catalyst.

linear effects with some BINOL–lanthanide catalysts.[53] When (*R*)-BINOL was treated with scandium(III) triflate (Sc(OTf)$_3$) in the presence of *cis*-1,2,6-trimethylpiperidine (TMP) and molecular sieves, an efficient catalyst was prepared. The structure is the one of a simple chelate of the three constituents, namely [Sc(tmp)$_2$((*R*)-BINOL)]·(OTf)$_3$. When this catalyst was prepared from BINOL of various *ee* values, a (+)-NLE was observed for the *ee* value of the *endo* product **53** formed from the reaction between the acylated oxazolidinone **44** and cyclopentadiene (**52**), as seen in Figure 49 (curve ●).

The aging of the catalyst was proven to have deleterious effects on the selectivities of the reaction. While the scandium catalyst can be used as such in quick reactions, its ytterbium analogue needed stabilization in order to work properly. Furthermore, the additives used to stabilize the catalyst can even have a direct effect on the enantiofacial selectivity in this Diels–Alder reaction. When the Yb^{III} catalyst was prepared in the usual way, but with some 3-acetyl-1,3-oxazolidin-2-one (AOD) added as a stabilizer, the resulting nonlinear effect was much different from the preceding one. A (−)-NLE takes place with BINOL of to 60 % *ee*, the value at which the linear relationship is observed for the enantiopure BINOL (curve ■). By changing the reaction temperature as well as the additive, in this case 3-phenylacetylacetone (PAA), a strong change was observed in the stereochemical outcome of this cycloaddition. Not only was the facial selectivity completely inverted, leading to (2*R*,3*S*)-**53** , but the NLE became strongly negative (curve □).

The differences between the scandium and ytterbium catalyst are the result of different levels of aggregation, especially when chelating additives are used. The perturbation created by the use of such compounds was shown to have a strong influence on the importance of the NLE.[53]

Seebach et al. studied the same reaction as Kobayashi's group, with the only difference being in the catalyst utilized.[54]

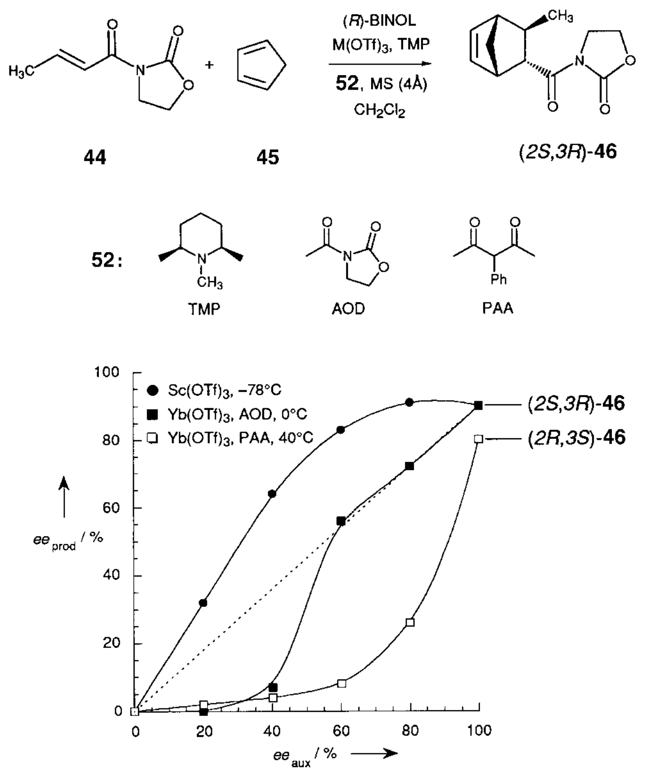


Figure 49. NLEs in a Diels–Alder reaction catalyzed by different BINOL–metal catalysts (20 mol %) in the presence of additives **52**.

The authors chose to use a highly hindered TADDOL-type diol to prepare the titanium catalyst needed to perform the Diels–Alder (Figure 50). When the diol of various *ee* values was allowed to react with [Ti(O*i*Pr)$_2$Cl$_2$] in order to form the

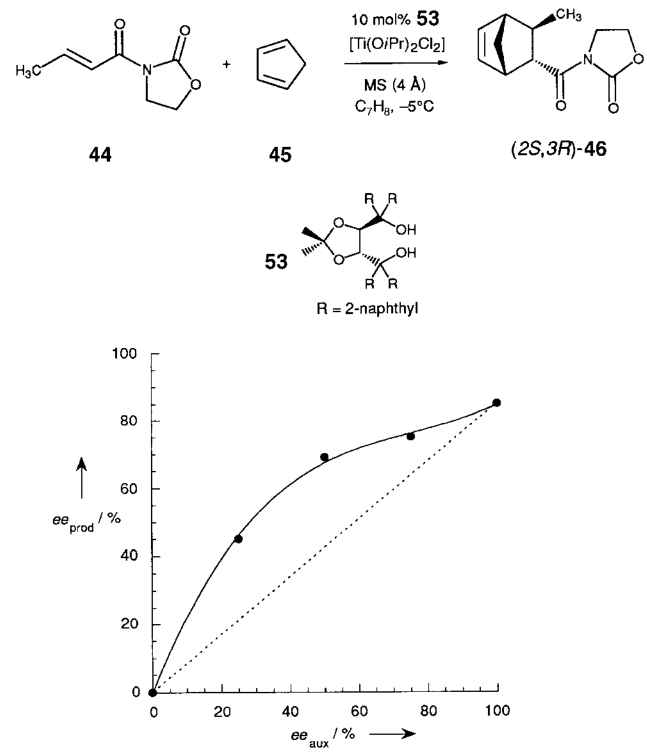
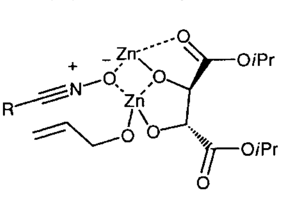


Figure 50. (+)-NLE in a titanium-catalyzed Diels–Alder reaction between **44** and **45**.

catalyst, which was then used in the reaction, a (+)-NLE was easy to observe. The same homo- and heterochiral species should be implicated here in the building of the amplification. However, unlike Narasaka's use of another TADDOL, there was no formation of a precipitate. The reaction mixture stayed homogeneous during the course of the transformation (except for the molecular sieves present in it) for all *ee*'s of the diol.

2.3.11. 1,3-Dipolar Cycloadditions

It has been found recently that Et_2Zn promotes the 1,3-dipolar cycloaddition of nitrile oxides to allyl alcohol in the presence of catalytic amounts of diisopropyl tartrate (DIPT).[55] From this method, 2-isoxazolines are obtained in good yields and up to 90 % ee. A positive nonlinear effect has been observed during the reaction between allyl alcohol (**54**) and the nitrile oxide generated in situ from the hydroxymoyl chloride **55** to give the isoxazoline **56** (Figure 51). Presumably the (+)-NLE originates from soluble inactive zinc aggregates with DIPT. In this procedure, 1,4-dioxane is needed in order to avoid precipitation of highly aggregated complexes containing DIPT and zinc salts. The authors postulated that the key step of the cycloaddition involves the complex **57**.



57

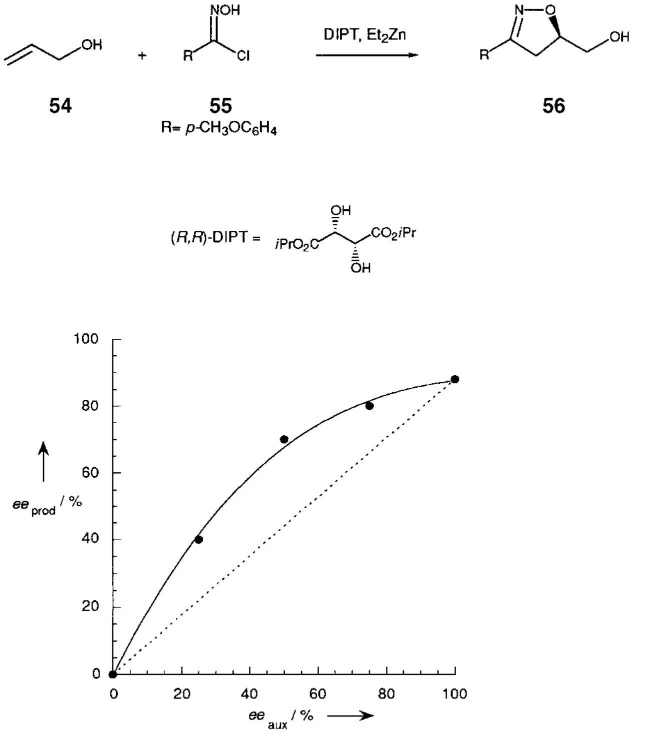
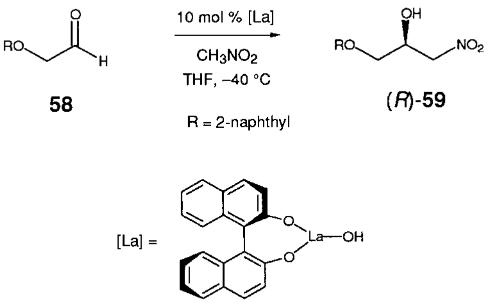


Figure 51. (+)-NLE in a 1,3-dipolar cycloaddition in the presence of DIPT (20 mol %) and Et_2Zn (dioxane, $CHCl_3$, 0 °C).

2.3.12. Nitroaldol Reaction

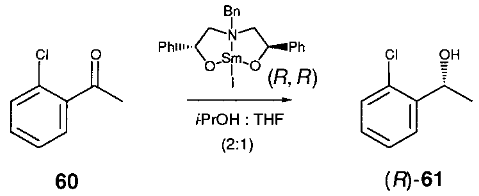
Shibasaki et al. reported that a BINOL–lanthanum complex is active in an asymmetric version of the Henry reaction (Scheme 4).[56] The nitroaldolization of α-naphthoxyacetaldehyde (**58**) in the presence of this enantiopure catalyst gave the nitroalcohol (*R*)-**59** in 87 % *ee*. If the BINOL used to prepare the catalytic species was not enantiopure, in this case 56 % *ee*, the enantiomeric excess of the product **59** was higher than expected (68 % *ee*). This observation was an indication of an additional example of (+)-NLE for a BINOL-derived catalyst. The authors explained the NLE encountered with this lanthanum catalyst by its existence as an oligomer.



Scheme 4. Nitroaldolization of **58** with a BINOL–lanthanum catalyst.

2.3.13. Meerwein-Ponndorf-Verley Reduction

During the course of the elaboration of an asymmetric version of the MPV reaction, Evans et al. tested a chiral aminodiol-samarium(III) catalyst for NLEs (Scheme 5).[57]



Scheme 5. Meerwein-Ponndorf-Verley reaction with a chiral samarium catalyst (5 mol %) at room temperature.

They discovered that the use of an aminodiol of 80 % *ee* in the preparation of the catalyst, and its subsequent use in the reduction of *o*-chloroacetophenone (**60**), gave the product (*R*)-**61** in a higher *ee* value than expected (95 % *ee*). The use of an enantiopure catalyst gave the product with 97 % *ee*. A more stable heterochiral dimer (*R*,*R*) · (*S*,*S*) was suggested as a trap for the minor enantiomer, which thus increased the *ee* value of the major one that is implicated both in the homodimer formation and catalysis.

2.3.14. Ring-Opening of meso-Epoxides

Jacobsen et al. described a catalytic system for the asymmetric nucleophilic ring-opening of *meso* epoxides (Figure 52).[58] In their investigation in to the nature of the catalytic system, the authors discovered that the chiral (salen)chromium(III) complex used in this reaction showed a nonlinear behavior when its *ee* value was modified. The reaction of cyclohexene oxide (**62**) with the trimethylsilylated azidoalcohol **63** showed a (+)-NLE. On the basis of kinetic considerations and measurements, the authors postulated the formation of a bimetallic species to account for the observed

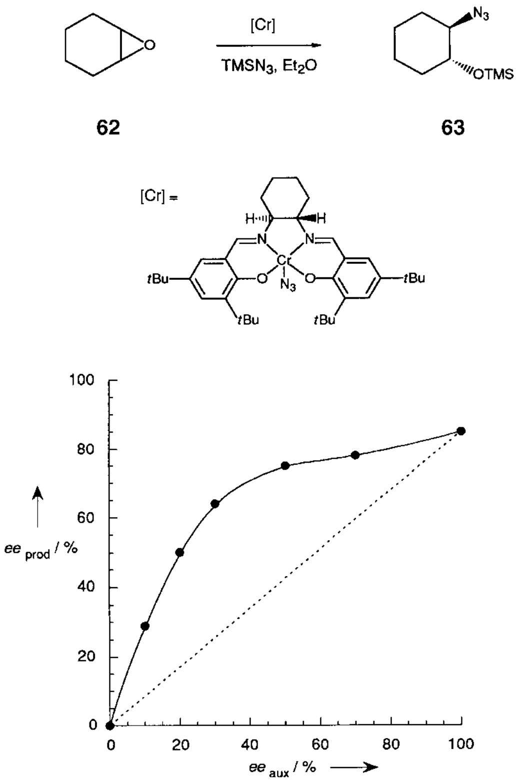


Figure 52. Ring-opening of *meso*-epoxide **62** catalyzed by a Salen–chromium catalyst (2 mol%).

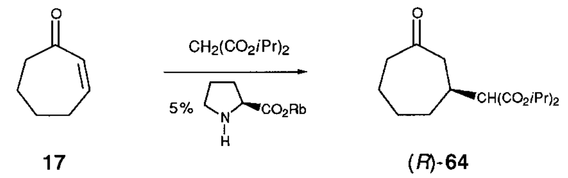
NLE. The epoxide is activated by one chiral salen–chromium unit, while the nucleophilic attack involves a second azido salen–chromium entity. The rate-determining step involves the prefered homochiral combination. Thus the evaluation of the nonlinear effects gave confirmation of the suggested mechanism that the catalyst is a bimetallic species that can act as both a nucleophile and an electrophile.

2.3.15. Nonlinear Effects as a Probe

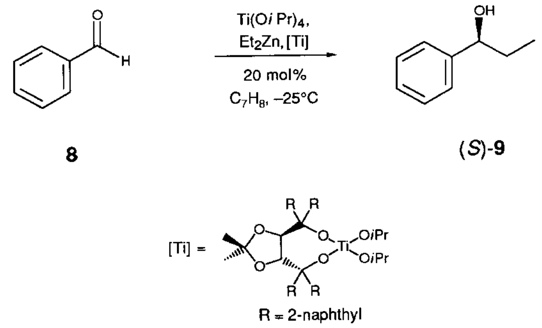
The preceding Sections clearly demonstrated that the study of nonlinear effects in asymmetric catalysis could be more than useful in understanding and getting quantitative information about the species involved in the catalytic cycle and their behavior in solution. This Section will now describe the qualitative use of NLEs by a number of groups to ascertain the nature of the catalytic entity responsible for the enantioselective reaction.

Yamaguchi et al. used NLE as a probe for the determination of the mechanism in asymmetric Michael additions with proline salts.[59] The 1,4-addition of diisopropyl malonate to cycloheptenone (**17**) by using a proline–rubidium salt gave them the opportunity to prepare the alkylated ketone (*R*)-**64** (Scheme 6). In contrast to the Hajos-Parrish-Wiechert reaction with proline presented in Section 2.1, the variation of the *ee* value of the proline salt resulted in a linear relationship with ee_{prod}. The authors concluded that the transition state of their reaction contained only one molecule of prolinate.

Seebach and Schmidt[60] used the NLE test to determine the nature of their catalytic species in diethylzinc addition on aldehydes. Their experiments regarding benzaldehyde (**8**) are included in Scheme 7. By variation of the enantiomeric purity of the TADDOL-type diol used to prepare the spirotitanate catalyst, and by determination of the resulting *ee* value of the product, they discovered that no NLE was present. A strict linear relationship was obtained, which suggested that only one chiral unit was involved in the stereochemical rate-determining step of the stereoselective reaction. These results are in sharp contrast to those they obtained with the same catalyst in the Diels–Alder reaction (Section 2.3.10, Figure 50), where a moderate (+)-NLE was observed.

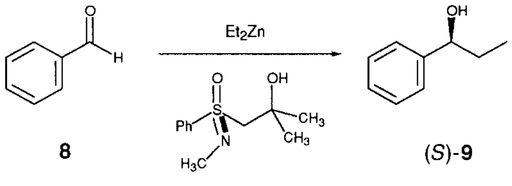


Scheme 6. 1,4-Addition of a malonate to the enone **17** catalyzed by a proline–rubidium salt ($CHCl_3$, room temperature).



Scheme 7. TADDOL-titanium catalyzed addition of diethylzinc to benzaldehyde (**8**).

Bolm et al.,[61] were interested in getting a better understanding of the catalyst used in the enantioselective addition of diethylzinc to aldehydes catalyzed by β-hydroxysulfoximines. The use of the enantiomerically pure sulfoximine illustrated in Scheme 8 for the addition to benzaldehyde (**8**), gave the corresponding alcohol **9** with an *ee* of 85%. The nonmonomeric nature of the catalyst was proven by the authors by performing the same reaction with a sulfoximine of 23% *ee*, which gave rise to an alkylation product with an amplified *ee* of 70%.



Scheme 8. Chiral sulfoximine (10 mol%) catalyzed 1,2-addition of diethylzinc to benzaldehyde (**8**).

The structure of the zinc species was later suggested to be dimeric in nature from NMR experiments.[61b] Furthermore, homochiral aggregates were estimated to react five times faster than *meso* species, which explained the (+)-NLE observed in this case. The origin of the stability difference between the oligomers can be visualized by spatial representations of both *meso* and homochiral species (Figure 53). The ethyl chains on the zinc atoms in the Zn–O four-membered cycle of the *meso* complex are *anti* to each other, whereas in the homochiral complex they end up *syn*, which has a destabilizing effect on the structure.

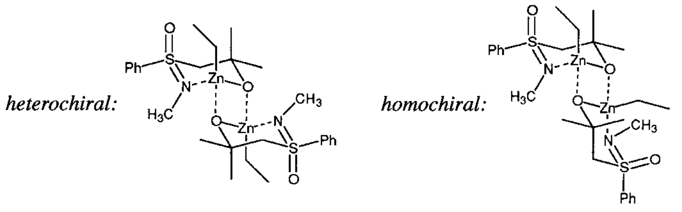
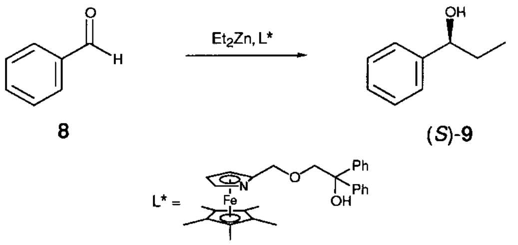


Figure 53. Dimers formed from the reaction shown in Scheme 8..

Another example of the addition of diethylzinc was performed by Fu and his group with a ferrocenyl chiral ligand (Scheme 9).[62] Despite several encounters with NLE in the use of amino alcohols (Section 2.3.1.) the authors obtained a linear relationship in this case when their ligands with various *ee*'s were used.



Scheme 9. Addition of diethylzinc to benzaldehyde (**8**) catalyzed by a chiral ligand (3 mol%, toluene, room temperature).

During the course of the elaboration of a catalytic asymmetric epoxidation with a BINOL-derived catalyst, Shibasaki et al. tried to determine the exact structure of their catalyst.[63] Unfortunately, the spectroscopic analyses were unsatisfactory and the only conclusion was that the species were of oligomeric nature. In order to obtain more insights on the structure, the authors performed the NLE analysis. The chiral catalyst prepared from (*R*)-BINOL and Yb(O*i*Pr)$_3$ in the presence of molecular sieves was used in different *ee*'s in the epoxidation of benzylideneacetone (**19**) by *tert*-butylhydroperoxide (Figure 54). A (+)-NLE was observed in this case and the authors concluded that the oligomeric structure of the lanthanoid–BINOL complex should play a key role in their asymmetric epoxidation of enones. This type of NLE was not observed when chiral SALEN-type catalysts as reported by Schwenkreis and Berkessel were used, where perfect linearity is obtained.[64]

Bolm and Bienewald reported that in the asymmetric oxidation of sulfides the use of an imino alcohol chiral ligand with a vanadium salt and hydrogen peroxide oxidized methylphenyl sulfide (**66**) to sulfoxide **67** with a good enantioselection (Scheme 10).[65] No NLEs were found in this system. The authors concluded that the catalyst contained only one molecule of chiral ligand.

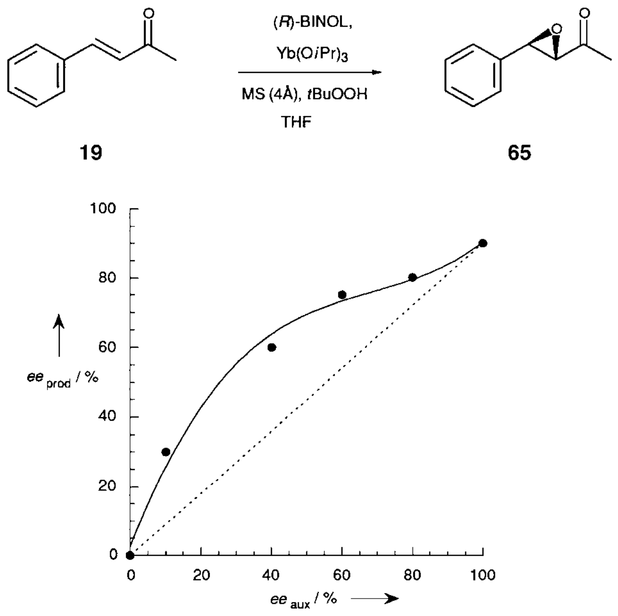
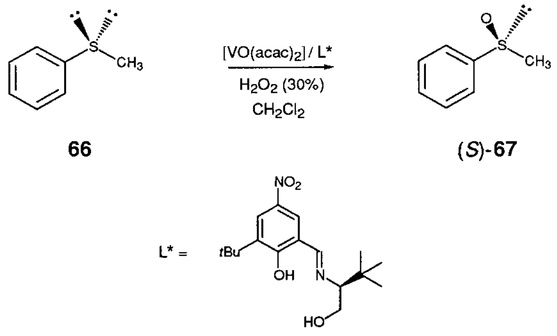


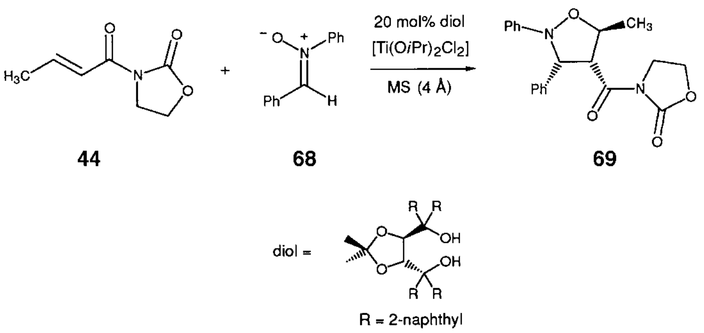
Figure 54. (+)-NLE in the asymmetric epoxidation of benzylideneacetone (**19**) catalyzed by a BINOL–ytterbium catalyst (5 mol%).



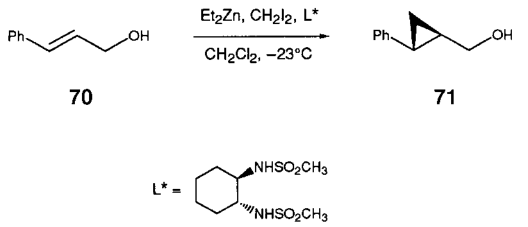
Scheme 10. Asymmetric oxidation of sulfide **66** with catalytic amounts (1 mol%) of a vanadium salt and a chiral iminoalcohol ligand.

Seebach et al., as part of their studies on the use of TADDOL-type ligands with titanium salts, were interested in probing the nature of the catalytic species that was involved in the [3+2] cycloaddition between **44** and the nitrone **68** to give **69** (Scheme 11).[66] The relationship between the *ee* value of the product and that of the chiral diol used to prepared the catalyst was strictly linear. This result was in sharp contrast with the (+)-NLE encountered with the same catalyst during a Diels–Alder reaction (Section 2.3.10, Figure 50).

Denmark and co-workers studied the cyclopropanation with a catalyst prepared from zinc salt and C_2-symmetrical disulfonamide (Scheme 12).[67] The use of this ligand in conjunction with bis(iodometyl)zinc permitted an enantioselective cyclopropanation of cinnamyl alcohol (**70**) to the corresponding carbocycle **71**. The relation between the *ee*'s of the ligand and the product was found to be perfectly linear. The authors interpreted these results as a consequence of only



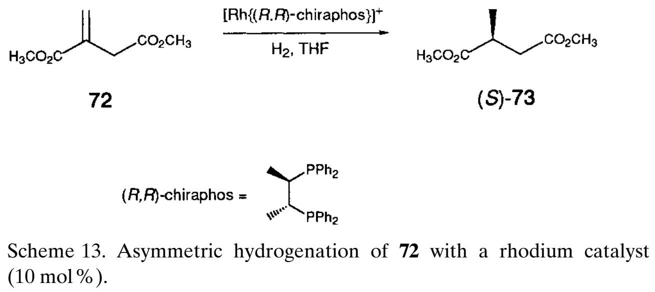
Scheme 11. [3+2] cycloaddition of **44** and **68** with a TADDOL–titanium catalyst (toluene, room temperature).



Scheme 12. Cyclopropanation of cinnamyl alcohol (**70**).

one molecule of ligand being present in the transition state responsible for the enantioselectivity, and that the stable species of all the ligand–zinc complexes is monomeric or dissociates with low activation energy.

Finally, Faller et al. reported the use of the NLE test to obtain information about the nature of the complexes implicated in some asymmetric hydrogenation reaction.[68a, 68b] The use of a cationic rhodium complex [Rh(norbornadiene)(chiraphos)]BF_4 in the hydrogenation of dimethyl itaconate (**72**) led to the corresponding methylsuccinate (*S*)-**73** in 98% *ee* (Scheme 13). When the chiraphos–rhodium complex used had a 33% *ee*, the product **73** was obtained in 60% *ee*, which was indicative of a (+)-NLE. This effect was explained by the formation of dimeric species generated by the hydrogenation of [Rh(norbornadiene)(chiraphos)]BF_4 into $[\{Rh(chiraphos)\}_2]^{2+}$.[68c–e] Accordingly to this scenario, the use of enantiomerically impure chiraphos should generate homo and heterochiral dimeric species. The authors reported that ^{31}P NMR studies in nonpolar solvents showed that the heterochiral dimer was the more stable. The dissociation of the dimers to give the monomeric, catalytically active species in this case explained the positive nonlinear effect observed. Burgess and van der Donk found that the use of a chiral rhodium catalyst incorporating DIOP in hydroboration reactions led however to linearity (DIOP = 2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphanyl)butane).[69]



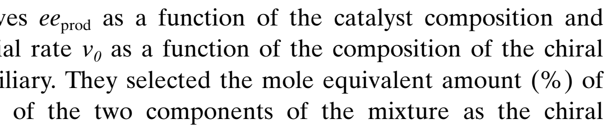
Scheme 13. Asymmetric hydrogenation of **72** with a rhodium catalyst (10 mol%).

The results presented in this Section demonstrate that the study of the presence or absence of NLE in a catalytic system can complete the usual analyses, and can even be used as the sole analysis when all the others fail to give some insights into the nature of the involved species. However, this was limited to catalysis on mixtures of enantiomers. The Sections to come will present the study of NLEs in different systems and the information that can be extracted by this method of analysis.

2.4. Diastereomeric Catalysts

One may assume that the phenomena that are at the origin of nonlinear effects when using a mixture of *enantiomers* of chiral auxiliary, will remain if the chiral auxiliary is now a mixture of *diastereomers*. This assumption means that some deviations are expected from the predictions of the *ee*'s of the product as a result of the diastereomeric composition.

Noyori et al. have studied the mechanism of asymmetric amplification with DAIB as the promoter of the chiral catalyst (Section 2.3.1).[32] They concluded that a quite stable *meso* dimer of DAIB–zinc alcoholate was at the origin of the strong (+)-NLE, because of the storage of some racemic DAIB (reservoir effect). Recently these authors studied the effect of various mixtures of (−)- or (+)-DAIB and the *endo* diastereomer (*R*)-**74** or (*S*)-**74**.[70] These two catalysts gave (*R*)- or (*S*)-alcohols **9** with 94% *ee* while (−)-DAIB provided (*S*)-alcohol with 98% *ee*. Noyori et al. also compared the catalytic efficiency of these catalysts when enantiopure. Aminoalcohol **74** is 2.6 times more reactive as a promoter of the reaction than DAIB.



From the above data the authors computed the expected curves ee_{prod} as a function of the catalyst composition and initial rate v_0 as a function of the composition of the chiral auxiliary. They selected the mole equivalent amount (%) of one of the two components of the mixture as the chiral auxiliary composition. A curve and not a straight line was calculated for the relationship between ee_{prod} and the composition of the chiral auxiliary, but experimental data shows some significant departure to the calculated curve (Figure 55a).[71] The nonlinear effect is apparent for the mixture of (−)-DAIB with (*R*)-**74**, where the two individual catalysts generate alcohols of opposite absolute configuration. The catalysts prepared from (−)-DAIB or (*S*)-**74** gave alcohol (*S*)-**9** (see above) with similar rates of reaction. The mixture of these two catalysts showed almost perfect linearity for ee_{prod}. The formation of aggregates **10**, **76**, and **77**, with higher stability for the mixed dimer **76**, explains the above data (Figure 56). This was confirmed by measurements of the rates

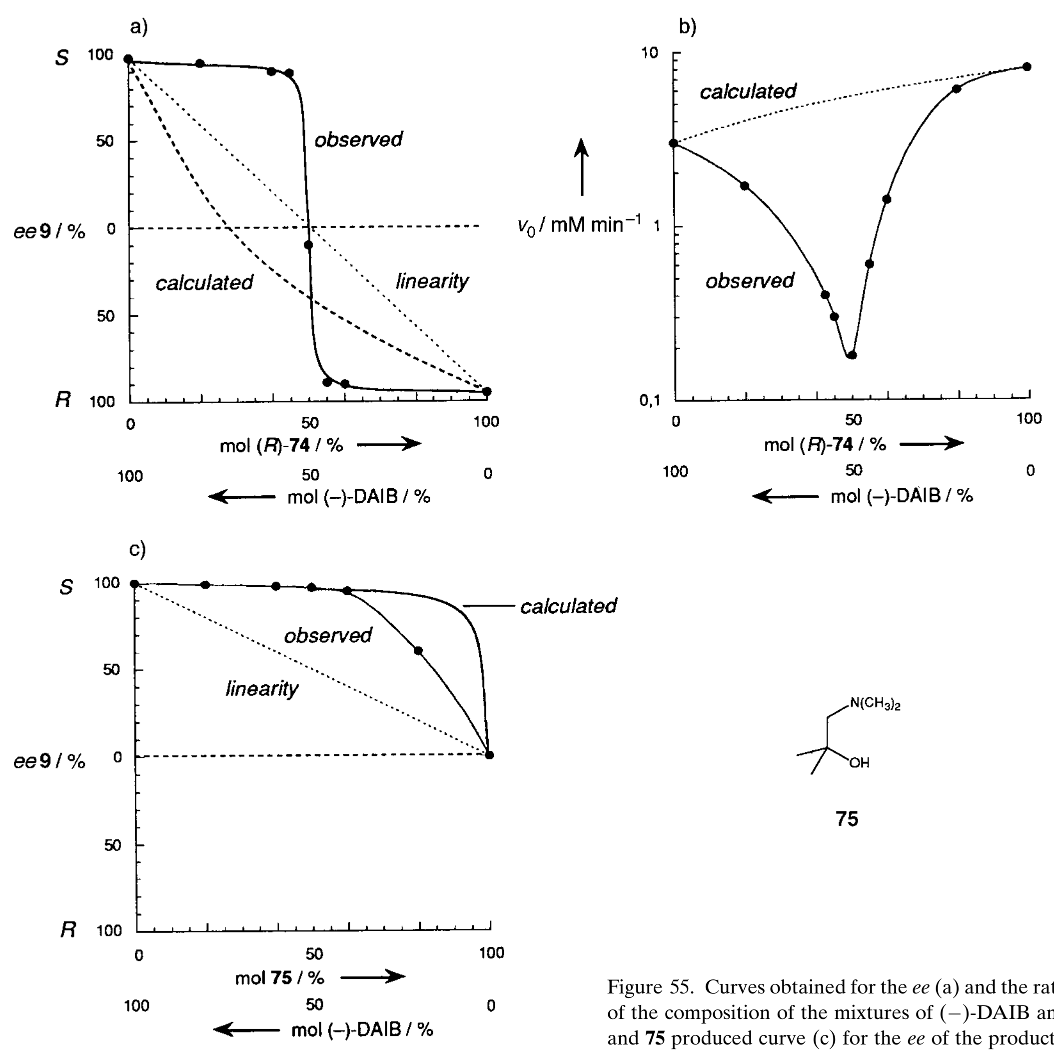


Figure 55. Curves obtained for the *ee* (a) and the rate of the reaction (b) as a function of the composition of the mixtures of (−)-DAIB and (*R*)-**74**. Mixtures of (−)-DAIB and **75** produced curve (c) for the *ee* of the product.

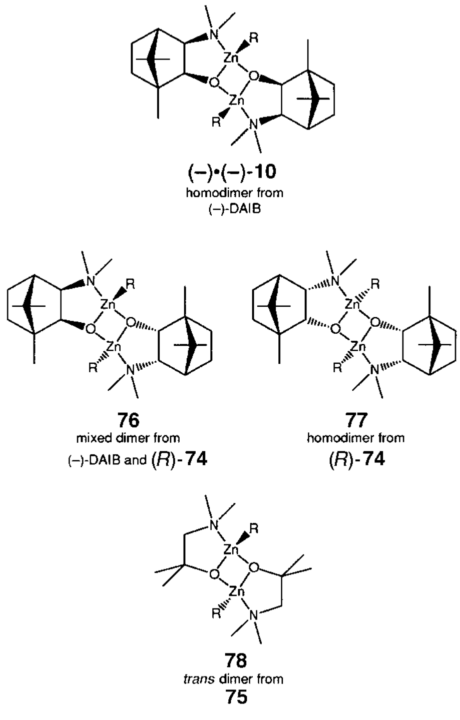
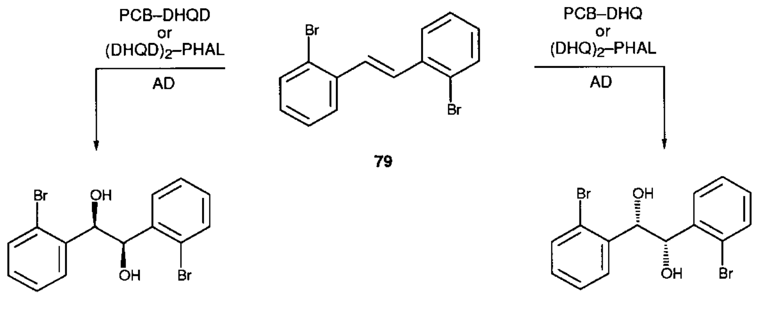


Figure 56. Some of the various dimers formed in the mixtures of DAIB and other aminoalcohols.

as a function of the catalyst composition. For example a mixture of (−)-DAIB and its diastereomer (*R*)-**74** showed a sharp minimum around a 1:1 composition, indicative of the preferred formation of heterodimer **76** of low reactivity (Figure 55b). In an additional experiment the enantioselectivity of (−)-DAIB in the presence of various amounts of the *achiral* β-aminoalcohol **75** was investigated (Figure 55c). The curve has been interpreted by the occurrence of *trans* dimer **78**, which is more stable than the *cis* dimer (not represented); which is itself more stable than homodimer **10**.

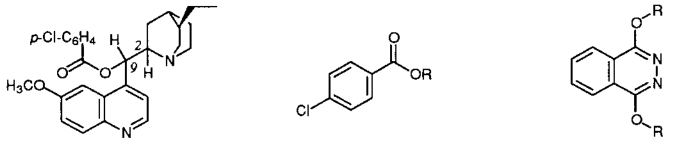
Kagan et al.[72] studied the Sharpless asymmetric dihydroxylation (AD)[73] of dibromostilbene (**79**) since several classes of diastereomeric ligands based on alkaloids are easily available. The *p*-chlorobenzoate of dihydroquinine (PCB–DHQ) gave (*S,S*)-diol **80** in 97% *ee*. The ligands of the second generation, namely phthalazine bisdihydroquinine (PHAL(DHQ)$_2$) and quinidine (PHAL(DHQD)$_2$) led to (*S,S*) and (*R,R*)-diols **80** in 98–99% *ee* in a faster reaction. Mixtures of PHAL(DHQ)$_2$ and PHAL(DHQD)$_2$ gave a curve very close to a straight line (Figure 57a), as expected from two pseudoenantiomeric ligands (similar reaction rates and similar enantioselectivities, but of opposite chirality). This experiment is in agreement with the reaction proceding through independent catalysts, and not through or involving a mixed



79

(*R*, *R*)-80

(*S*, *S*)-80



dihydroquinine : (2*S*, 9*R*)
dihydroquinidine : (2*R*, 9*S*)

PCB–DHQ : R = DHQ
PCB–DHQD : R = DHQD

(DHQ)2–PHAL : R = DHQ
(DHQD)2–PHAL : R = DHQD

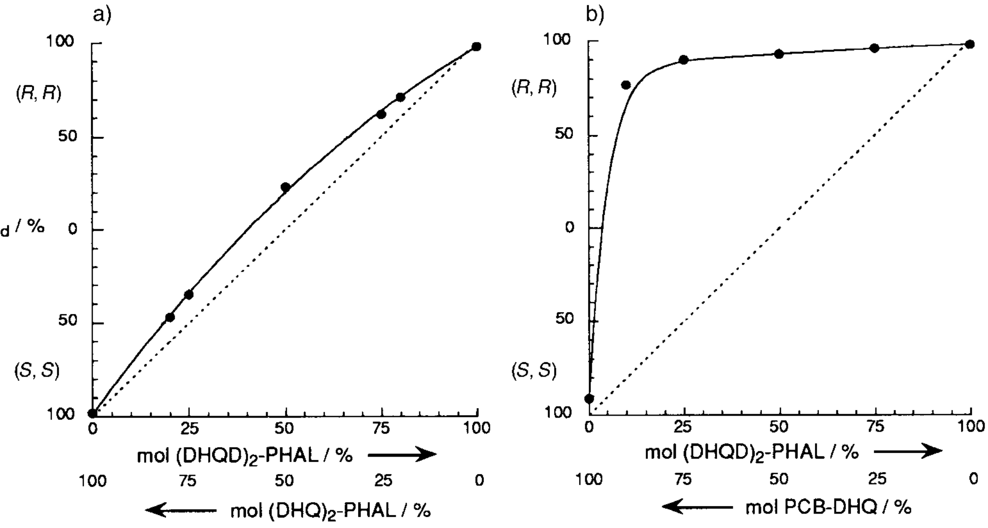
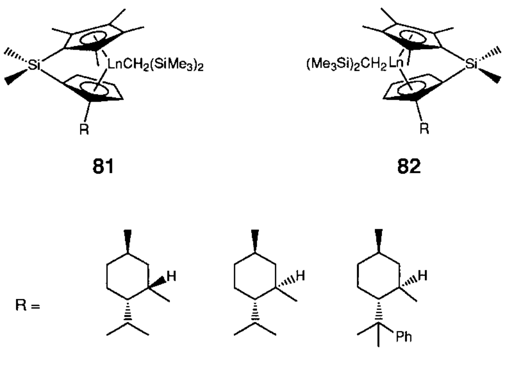


Figure 57. Curves of the *ee* of **80** obtained in the asymmetric dihydroxylation of **79** by mixing (DHQD)$_2$PHAL with (a) (DHQ)$_2$PHAL and (b) PCB–DHQ.

species. The mixture of PCB–DHQ and PHAL(DHQD)$_2$ gave a very strong nonlinear behavior (Figure 57b). This observation reflects the higher reactivity of the catalyst based on PHAL(DHQD)$_2$, presumably because of the larger affinity of this ligand (with respect to PCB–DHQ) towards OsO$_4$, as well as by the rate-acceleration given by the "chiral pocket mechanism" which has been established with the phthalazine ligands.[73]

Corey et al. evaluated the relative reactivities of some osmium catalysts, prepared from two different ligands derived from alkaloids, for AD.[74] They also used ligands (1:1 mixture) of opposite enantioselectivities in AD of styrene derivatives as a way to study these systems.

Marks et al. prepared diastereomeric chiral lanthanide complexes **81** and **82** as catalysts for the enantioselective hydrogenation of alkenes or hydroamination/cyclization of amino olefins.[75] Surprisingly the enantioselectivity in hydroamination reactions is insensitive to the metallocene chirality, since a 1:1 mixture of the two complexes gave the same *ee*$_{\text{prod}}$ as diastereomerically pure **81**. This behavior has been explained by epimerization around the lanthanide center (equilibrium of decomplexation and complexation during the reaction). In the hydrogenation of 2-phenyl-1-butene there is a significant difference between of **81** and **82**, in both rates and enantioselectivities. The 1:1 mixture of the two complexes gives rates and *ee*$_{\text{prod}}$ that are very close to the calculated values. Obviously there are no NLE effects with these catalysts that act independently from each other.



81 82

2.5. Autocatalytic Systems

The reactions where a compound catalyzes its own formation were considered for a long time as important in prebiotic chemistry. They are of special interest in the generation and propagation of optical activity on earth.[76, 77] In the ideal case where a chiral compound (100% *ee*) replicates with 100% *ee* one may consider that the problem is solved. Actually the most efficient chiral catalysts presently known seldom reach enantioselectivities higher than 99.9% *ee* (enantiomer ratio: $er = 1999$). These spectacular levels of efficiency are however unsatisfactory for the large scale production of chiral compounds by asymmetric autocatalysis. This is easily demonstrated by considering a simplified description of an asymmetric catalysis (Figure 58) where the two enantiomeric products *R* and *S* are derived from a chiral catalyst *R* (100% *ee*). A rough computation may be done by an iterative process.

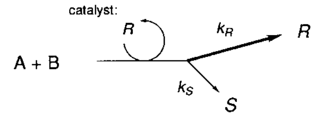


Figure 58. The asymmetric autocatalysis process.

If the rate ratio k_R/k_S is high (1999) 1 mol equivalent of the product (by respect to catalyst) will be considered to be formed after one catalytic cycle with $ee = 99.9\%$ ($er = 1999$). After mixing this product with 1 mole equivalent of the initial *R* catalyst ($ee = 100\%$, $er = \infty$) one ends up with 2 mole equivalent ($ee = 99.95\%$, $er = 3999$). The next catalytic cycle will provide 4 mole equivalents of catalyst ($ee = 99.85\%$, $er = 1337$). There is an endless erosion of the enantiomeric excess of the product which ineluctably will accumulate in a large amount, but in racemic composition.

Kinetics models have been proposed to overcome the above inherent tendency of *ee* degradation in asymmetric autocatalysis. Frank[76] first described a simple model where each enantiomer catalyzes its own formation but is competitively deactivated by interaction with the enantiomer of opposite configuration (Figure 59). In this model complete enantioselectivity is assumed during the catalysis by the *R* or *S* enantiomer. The initial *R/S* enantiomeric ratio of the catalyst (close to 1) is amplified because of the autocatalysis (which ensures the growth of the amount of catalyst), which is combined to a continuous removal of a racemic material. In conclusion asymmetric autocatalysis from a small amount of enantiopure catalyst has no chance of propagating molecular chirality on a large scale unless it is sustained by additional reactions (such as the mutual inhibition of enantiomers in the Frank model). The situation is even worse if the initial catalyst is of low enantiomeric excess.

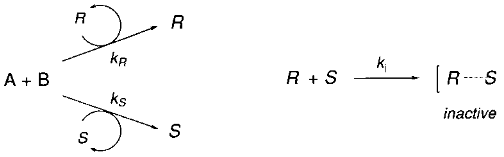
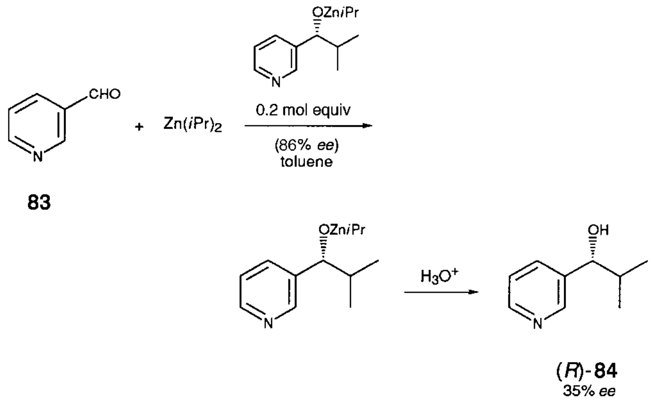


Figure 59. Frank's model with deactivation by dimerization.

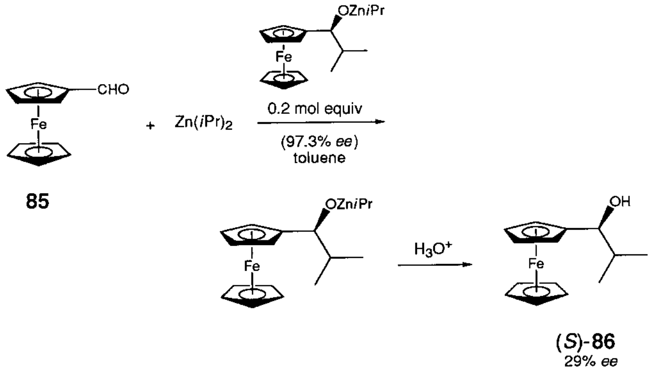
In that context a (+)-NLE superposed onto the autocatalytic reaction could be a convenient way to both amplify the initial *ee* value and to maintain it at a high level through the whole course of the autocatalytic reaction. There are quite a few identified asymmetric autocatalytic reactions.[78] Addition of a dialkylzinc compound to aromatic aminoaldehydes was the reaction pioneered by Soai et al. in the search of autocatalytic systems. In 1990 they discovered that pyridyl alcohol **84** is able to catalyze asymmetrically its own formation (Scheme 14).[80] The important point is that (*R*)-alcohol **84** (86% *ee*) catalyzes formation of (*R*)-**84**, although with a low enantioselectivity (35% *ee*, calculated by removal of the contribution of the initial catalyst).



Scheme 14. Autocatalysis in the addition of diisopropylzinc to pyridine-3-carbaldehyde (**83**).

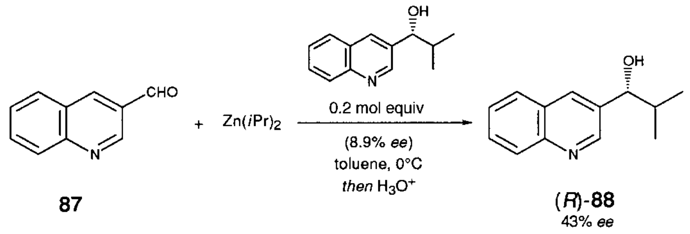
Subsequent investigations of Soai et al. on various types of aromatic aldehydes allowed the *ee* value of the product to be increased, which was also obtained with the same absolute configuration as the initiator. Ferrocene carboxaldehyde (**85**, Scheme 15) and diisopropylzinc in the presence of 0.2 mol equivalent of alcohol (*S*)-**86** (97.3% *ee*) gave 4.75 times more alcohol (*S*)-**86** (29% *ee*).[81]

A significant improvement was made recently in the reaction of quinoline-3-carboxaldehyde (**87**) with diisopropyl



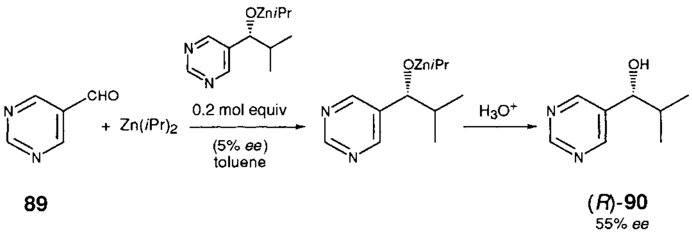
Scheme 15. Autocatalysis in the addition of diisopropylzinc to ferrocene-carbaldehyde (**85**).

zinc catalyzed by alcohol (*R*)-**88** (Scheme 16).[82] By optimization of the experimental conditions (1.2 mol equivalent of $Zn(iPr)_2$ instead of 2 mol equiv, a proper dilution to give a 4 mM concentration of the initial catalyst) it was discovered that **88** (93.6 % *ee*) replicates 3.2 times into **88** (89.7 % *ee*).[83a] These experimental conditions were selected to study the influence of the initial *ee* value of **88** on the *ee* value of the additional **88** produced; in this particular case there is a strong (+)-NLE. For example 8.9 % *ee* of **88** generates 2.8 times more **88** (43.3 % *ee*).



Scheme 16. Autocatalysis in the addition of diisopropylzinc to quinoline-3-carbaldehyde (**87**).

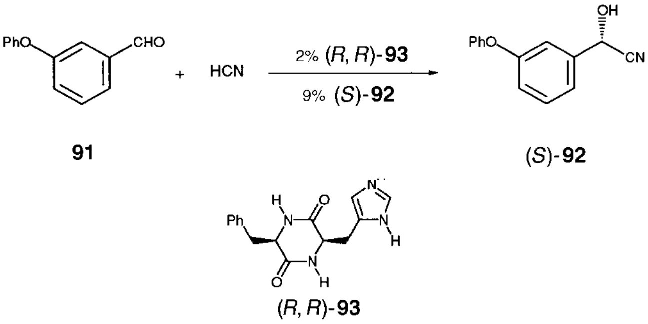
A further investigation has been conducted by using 5-pyrimidyl carboxaldehyde (**89**) and the alcohol **90** (Scheme 17).[84] Even with an initial *ee* of 2 % for the **90** formed, a plot of the *ee* value of newly formed **90** (ee_{prod}) versus the *ee* of the starting catalyst **90** (ee_{aux}) showed a typical (+)-NLE, with a strong amplification. The authors also made a correlation between their experimental data by taking the enantiomer ratios instead of the *ee*'s as parameters.[85] The above experiments have been performed by taking an initial catalyst of low *ee* and reusing the resulting product (with amplified *ee*) as a catalyst in a new reaction. By such a cycle of reactions the authors could use a sample of 2 % *ee* and reached a level of 88 % *ee* in five consecutive cycles. When the same procedure was applied to quinoline carboxaldehyde (**87**), by using the alcohol **88** with an initial 8.9 % *ee*, the enantiomeric excess obtained for (*R*)-**88** at the end of the cycle was 88 % as well (Scheme 16).[83a] A one-pot asymmetric autocatalytic reaction with a remarkable amplification (from 0.2 % *ee* to 90 % *ee*) was obtained recently in the formation of **90** by a special experimental procedure.[83b]



Scheme 17. Autocatalysis in the addition of diisopropylzinc to pyrimidyl-5-carbaldehyde (**89**).

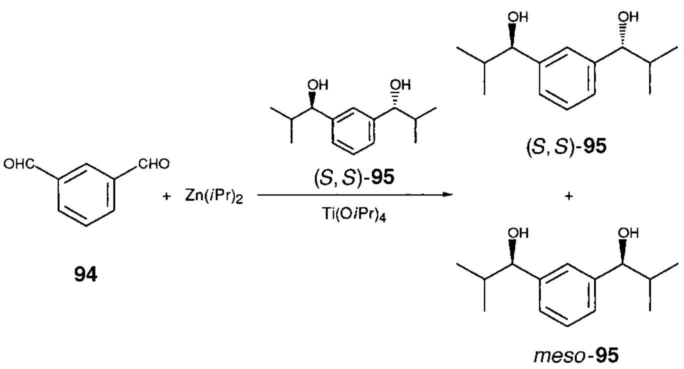
A catalytic enantioselective autoinductive reaction is a process that may be of interest to propagate high *ee*'s. This process is based on stereoselective reactions in which the products initially formed may influence the stereoselectivity of the proceding reaction (catalytic or stoichiometric). Albert and Wynberg coined the expression "enantioselective" autoinduction during their studies of a stoichiometric enantioselective reaction.[88]

The first example of enantioselective autoinduction in a catalytic reaction seems to be the report of Danda et al.[89] on the formation of cyanhydrine in the presence of small amounts of cyclic dipeptide **93** (Scheme 18). The authors found that the initial catalyst **93** is replaced in situ by the combination of **93** with product **92**. This has been established by adding a small amount of (*S*)-**92** with high *ee* value to the cyclic dipeptide **93** (enantiopure or of small *ee* value) at the beginning of the reaction. It is the enantiomeric purity of (*S*)-**92** that is the stereocontrolling factor on the catalytic production of cyanohydrine (*S*)-**92**. For example, in a given set of experimental conditions 0.022 mol equivalent of catalyst (*R,R*)-**93** (2 % *ee*) gave product (*S*)-**92** (81.6 % *ee*) in 43 % yield from the corresponding aldehyde **91**. The initially added (*S*)-**92** acts as a chiral co-catalyst. Interestingly, the catalyst prepared from **93** (66.8 % *ee*) and (*S*)-**92** (92.0 % *ee*) was able to generate (*S*)-**92** in 89 % yield with 96.0 % *ee* (which is higher than the *ee* of both components of the catalyst). The mechanistic details of the reaction, which works in heterogeneous conditions as a gel are not well understood, several mechanisms have been proposed.[90]



Scheme 18. Autoinduction in cyanohydrine formation in the presence of a cyclic dipeptide (**93**) (toluene, 5 °C).

Soai et al. recently studied a catalytic enantioselective reaction with autoinduction in the particular case of addition of diisopropylzinc on an aromatic dialdehyde **94** (Scheme 19).[91] The catalyst is a chiral titanium complex



Scheme 19. Autoinduction in the double addition of diisopropylzinc with **94**.

presumably with a 1:2 stoichiometry, formed from the combination of $Ti(OiPr)_4$ with the chiral diol **95**. This chiral catalyst is different from the chiral zinc alkoxide which is derived from **95**, hence the expression "autoinduction". Here again the absolute configuration of the product **95** is the same as for the initiator **95** engaged in the catalyst. Unfortunately the product is obtained in lower *ee* value (30% *ee*) than the initial *ee* value of **95** (> 99% *ee*), together with a large amount of *meso* diol.[92]

In conclusion asymmetric autocatalysis seems to be a promising area of investigation, as stated earlier by Wynberg.[93] The possibility of asymmetric amplification has been well established recently[84] and seems a consequence of the intervention of positive nonlinear effects (most presumably by a reservoir effect, see Section 2.2).[94]

3. Stoichiometric Asymmetric Synthesis

3.1. Principles

A chiral reagent may be prepared by modification of an achiral reagent with a chiral auxiliary X_c that will be bound covalently (**96**) or not (**97**) to the reagent Y (Figure 60). A chiral silane R^*_3SiH (R^* = chiral group) or the combination *sec*-BuLi, sparteine (for asymmetric deprotonation) are examples of chiral reagents of type **96** ($Y-X_c$) or **97** ($Y\cdots X_c$).

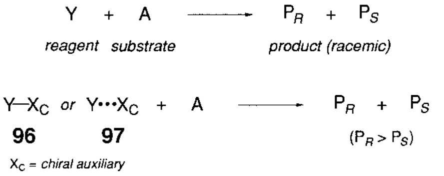


Figure 60. Formation of covalently bound (**96**) or associated (**97**) species in noncatalyzed asymmetric synthesis.

Two basic situations are described in Figure 61. In the first case reagent $Y-X_c$ (**96**) is transformed into an inert by-product $Z-X_c$, the auxiliary is then removed from the reaction simultaneously to the formation of the product. When reagent $Y\cdots X_c$ (**97**) is used it may behave as above if the by-products $Z\cdots X_c$ and $Z\cdots \bar{X}_c$ retain their structures and do not exchange the X_c and $\bar{X}_c$ fragments with the reagents. If there are some exchanges of these groups (for example, as chiral ligands of some organometallic compounds) one may end up in the situation of asymmetric catalysis where there is a fast exchange of ligands (see Section 2). The enantioselectivity of the reaction must be independent of the conversion, with or without NLE that arises from the the number of X_c groups around Y, and of the relative reactivities of the diastereomeric species. One expects the same general behavior and the same models as discussed in Section 2.

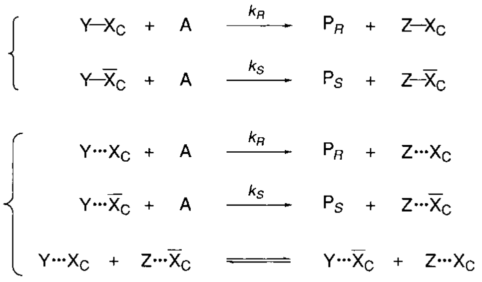


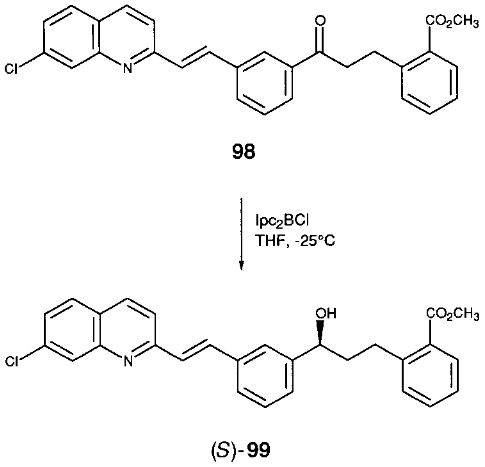
Figure 61. Two possible pathways in the noncatalyzed asymmetric synthesis. Xc and $\bar{X}_c$ = chiral intermediates of opposite configuration, Z = reagent that replaces Y.

The covalent reagent **96** gives a different scenario. If it involves only one X_c group the initial enantiomer ratio will remain constant during the course of the reaction and no NLE will appear. If this reagent gives rise to some aggregation one finds again the general features discussed for catalytic reactions (Section 2), some diastereomeric aggregates may be unreactive and the reaction will proceed through a monomeric reagent or a given diastereomer. NLE will be produced by a reservoir effect or through the $(ML)_n$ model.[96] The nonlinear effect will depend on conversion because the enantiomeric composition of the reagent should change if diastereomeric aggregates are of different reactivities. For example, if an heterochiral dimer is less reactive, the reaction will start with a (+)-NLE and in the latter stages of the reaction it will very much slow down with the generation of the racemic product. A constant (+)-NLE is expected if a large excess of reagent (in respect to substrate) is used. A reactive heterodimer will provide a strong (−)-NLE, and an excess of reagent will enhance this trend.

A special case, which is worth mentioning, is the use of a chiral reagent obtained by the permanent linking of two chiral fragments X_c to the achiral reagent Y. If the enantiopure reagent $Y(X_c)_2$, or $Y(\bar{X}_c)_2$, or the mixture of these enantiomeric reagents can be used in asymmetric synthesis, one would expect perfect linearity (unless aggregation occurs). However if the chiral reagent is prepared by the reaction of a mixture of X_c and $\bar{X}_c$ with Y there is the possibility that some heterochiral reagent $Y(X_c)(\bar{X}_c)$ will be generated. We then have a mixture of diastereomeric reagents in which the more reactive diastereomer has a chance to operate during part of the reaction, and provide an invariant NLE.

3.2. Asymmetric Reaction of Boron Compounds

Until now there were very few experimental data on NLE in stoichiometric asymmetric synthesis. One of the first examples seems to be an asymmetric synthesis at Merck in 1994 of an alcohol, which is a useful intermediate in the synthesis of a LTD_4 antagonist.[98, 99] It was found that Ipc_2BCl, prepared from (−)-α-pinene and BH_2Cl, reduced the ketone **98** to give alcohol **99** in 97% *ee* or 95% *ee* with (+)-α-pinene of 98% *ee* or 70% *ee* (Figure 62). It was hypothesized that three reagents (two homochiral and one *meso*) are in statistical distribution, with the *meso* borane being very sluggish to react. More recently the authors studied in detail the relationships between the *ee* value of the alcohol **99** and the *ee* value of the α-pinene (Figure 62). There is a good agreement between the calculated curve and experimental data, when the hypothesis of a statistical distribution and an



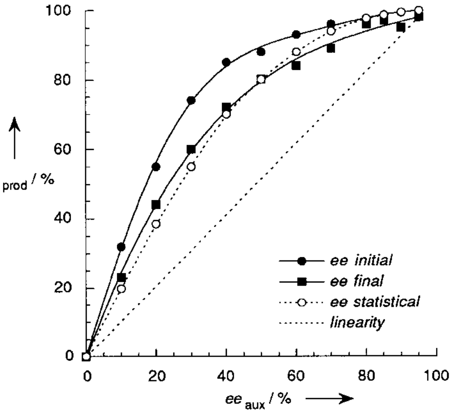
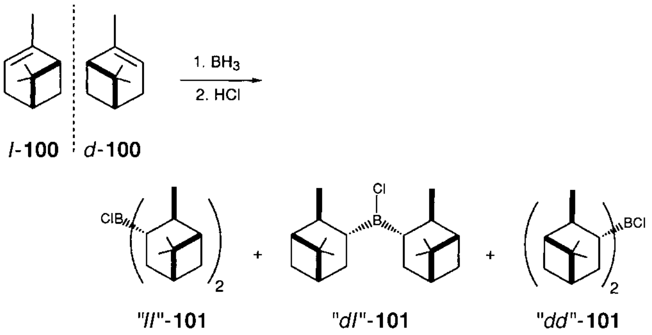


Figure 62. (+)-NLE in Ipc$_2$BCl reduction of the ketone **98**. Ipc = isopinocampheyl.

unreactive *meso* Ipc$_2$BCl is employed.[99] However, a quite large deviation has been observed at low conversion giving a higher *ee* value of **99** than after complete reduction.

In 1995 Kagan and Girard studied the asymmetric reduction of acetophenone by Ipc$_2$BCl (4 equiv) by using a reagent derived from (−)-α-pinene (**100**).[100] Ipc$_2$BCl was prepared according to the procedure of Brown and Joshi.[101] The way the reagent was synthesized was very important for the outcome of the reduction of acetophenone (**102**, Scheme 20). The separate preparation of Ipc$_2$BCl (**101**) from enantiopure α-pinenes gave "*ll*"-**101** and "*dd*"-**101**, which were then mixed in various amounts to reach the desired *ee*$_{aux}$. The other procedure starts from a mixture of (−)- and (+)-α-pinene in the required *ee*'s (*l*- and *d*-**100**) to give rise to the formation of three boranes: "*ll*"-**101,** "*dd*"-**101** and "*dl*"-**101.** The first procedure gave perfect linearity between *ee*$_{aux}$ and *ee*$_{prod}$ (Figure 63 a), while the second method generated a strong (+)-NLE, the asymmetric amplification being especially good above 30% *ee* for α-pinene (Figure 63 b). The linear relationship indicates that each of the enantiomeric reagents acts independently in the reduction process. The (+)-NLE is in agreement with a very low reactivity of the *meso* reagent "*dl*"-**101**, which is presumably formed in quite a large amount.



Scheme 20. Homochiral ("*ll*"- and "*dd*"-**101**) and heterochiral ("*dl*"-**101**) reagents generated during the formation of Ipc$_2$BCl (**101**).

As an added proof, the recent study by the Merck group demonstrated that the *ee* value of their reduction product was time-dependent.[102] The NLE was indeed more pronounced at lower conversion than after completion of the reaction. The curves however keep the same shape during the course of the reduction; which is close to the calculated curve based on a statistical distribution of the pinene on the boron atom. Kagan and Girard also presented another study where the stoichiometry of Ipc$_2$BCl (**101**) was varied from one to four equivalents.[103] The curves had the same shape, but the NLE increased with the amount of reductant used. These complementary results suggest that a higher *ee* value at the beginning

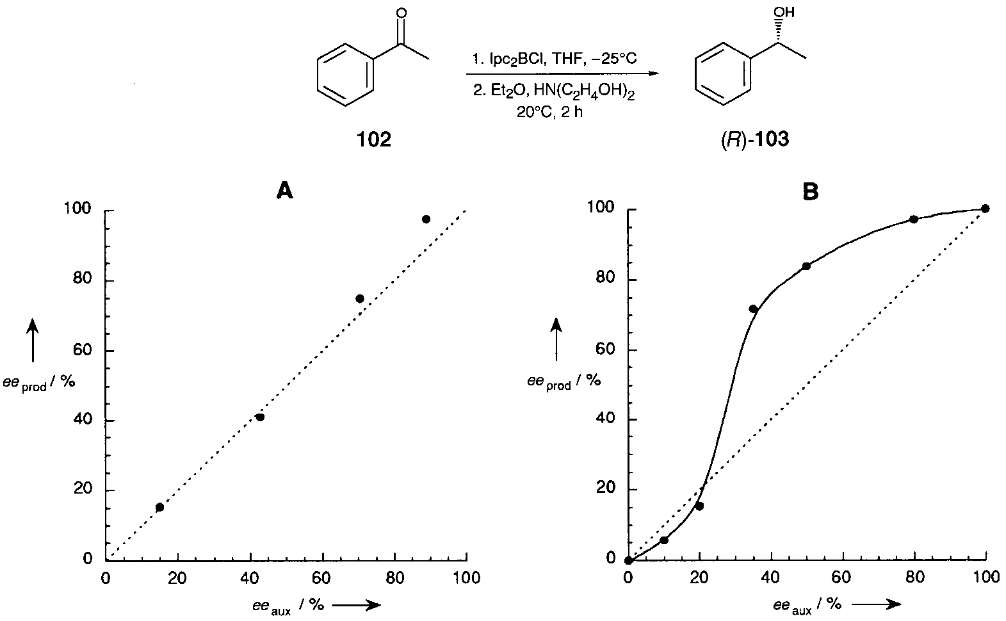


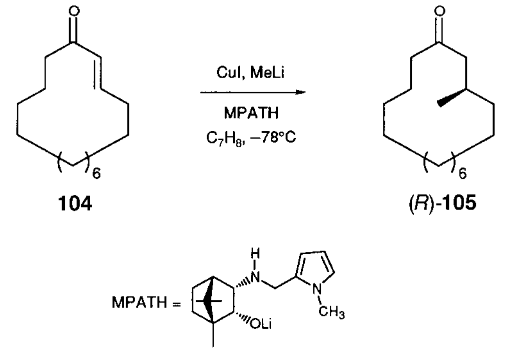
Figure 63. Variation in the *ee* value of (*R*)-**103** with the *ee* value of α-pinene (see text for further details).

of the reaction will be provided by the more reactive homochiral species or by the use of a larger quantity of reagent. But as soon as the amount of this species drops, with time or by using less reagent, the "unreacting" heterochiral borane becomes involved in the reduction, which lowers slightly the *ee* value of the product.

Apart from mechanistic interest, the possibility of creating a strong (+)-NLE in Ipc_2BCl reductions allows the expensive enantiopure α-pinene to be avoided, and instead cheaper α-pinene of *ee*'s lower than 90% can be used.[98, 99]

3.3. Cuprate Addition

Tanaka et al. studied an asymmetric synthesis of muscone **105** by the 1,4-addition of a methylcuprate complexed by the chiral bidentate ligand MPATH to the enone **104**.[104] An interesting NLE was observed, the data given in the paper allows to draw a two-shaped curve (Figure 64). The authors postulated the formation of dimeric species such as **106**. The curve was accurately reproduced by using the $(ML)_4$ model, which could mean the involvement of an aggregation of dimers.[31]



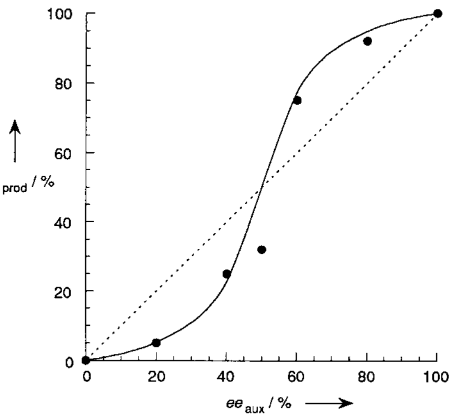
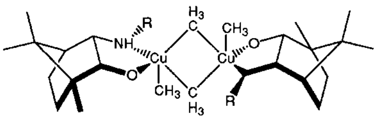
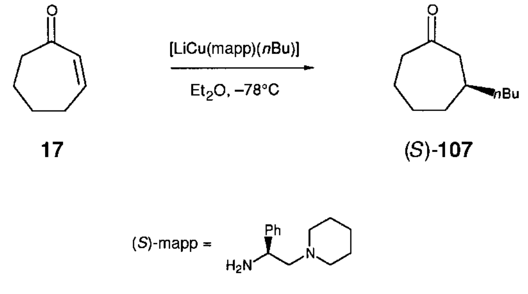


Figure 64. Two-shaped NLE curve observed in the synthesis of muscone (**105**) from **104**.



106

Rossiter et al. observed a (+)-NLE in the asymmetric addition of a *n*-butylcuprate to 2-cycloheptenone (**17**) by using the lithium salt of an aminoalcohol chiral ligand, (*S*)-mapp (Figure 65).[105] The authors assumed a statistical distribution of ligands into dimers such as the unreactive *meso* dimer **108**. Calculations are in good agreement with these hypotheses. For example, enantiopure ligand in this case gave 96% *ee* of product, while the (*S*)-MAPP at 56% *ee* provided a product with 81% *ee* (instead of 54% *ee* for linearity and 81.9% *ee* calculated with the above hypotheses). When the reaction was performed in diethyl ether with additives such as HMPA or solvents such as THF, which break the dimeric structure by lithium solvation, suppression of the enantioselectivity, presumably by generation of non-enantioselective monomers, was observed (HMPA = hexamethylphosphoramide). The cases of 1,4-additions of Grignard reagents in the presence of catalytic amounts of chiral copper complexes were discussed in Section 2.3.3.



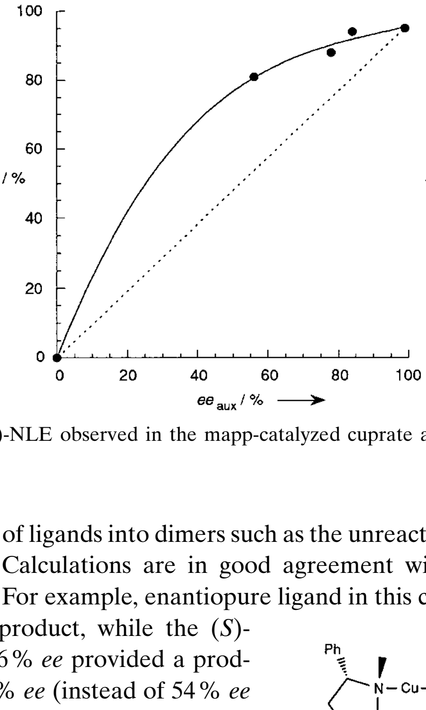
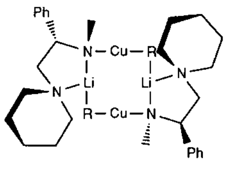


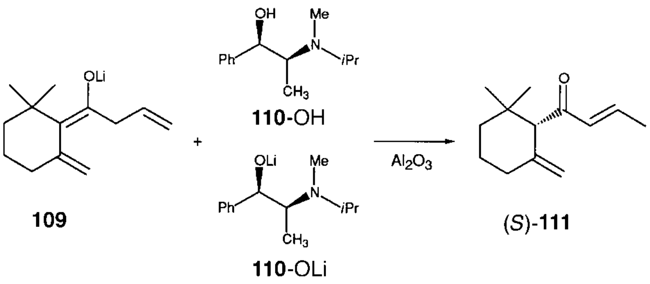
Figure 65. (+)-NLE observed in the mapp-catalyzed cuprate addition to **17**.



108

3.4. Asymmetric Protonation

A (+)-NLE has been observed in the asymmetric protonation of a lithium enolate **109** to (*S*)-γ-damascone ((*S*)-**111**) by a 1:2 mixture of the amino alcohol **110**-OH and its corresponding lithium alkoxide **110**-OLi (Scheme 21).[106] The use of an enantiopure protonating agent (100 % *ee*) gave the product **111** with 75 % *ee*, while the use of 50 % *ee* mixture of **110** gave the product with the same 50 % enantiomeric excess. The chiral protonating agent was proposed to form a complicated and dimeric structure, which is in agreement with the observed nonlinear effect prevailing in the present case.

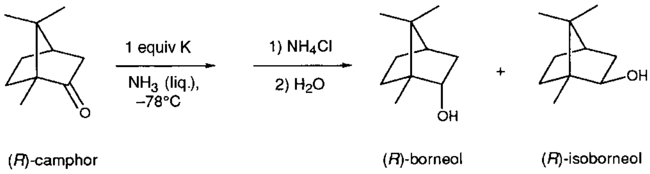


Scheme 21. Asymmetric protonation of **110** to (*S*)-γ-damascone (**111**).

4. Diastereoselective Reactions

In this section the reactions of chiral substrates that give rise to isolable diastereomers are considered. The reactions may be realized with an achiral or a chiral reagent, or with a chiral catalyst. If during the course of the reaction some aggregation occurs it may generate perturbations, as observed in enantioselective reactions. These perturbations should be reflected by nonlinearities between the diastereomeric excess and the *ee* value of the substrate or the reagent. Until now there were very few reports in that area. Wynberg and Feringa discovered that the $LiAlH_4$ reduction of racemic or enantiopure camphor gave different values for the isoborneol/borneol ratio[16] (see Section 1) but there were no data with camphor of intermediate *ee*'s, and then no knowledge of the variation of *de* of the product with the *ee* of the camphor.

Rautenstrauch et al. carefully investigated the reduction of camphor by potassium in liquid ammonia (Scheme 22).[107] They looked at the diastereomeric composition of the resulting alcohols (*dc*, percentage of the major diastereomer) as a function of the enantiomeric composition (*ec*, percentage of the major enantiomer) of camphor. Surprisingly, borneol is the major product when one starts from racemic camphor, while borneol slightly predominates if enantiopure camphor is the starting material.



Scheme 22. Reduction of (*R*)-camphor by potassium in liquid ammonia.

In Figure 66 the *dc* of the alcohol versus *ec* of the camphor is shown. It is easy to establish that the relationships $de_{\text{product}} = EE_0 ee_{\text{substrate}}$ and $dc_{\text{product}} = EC_0 ec_{\text{Substrate}}$ are equivalent (EE_0 and EC_0 are the enantiomeric excess or the enantiomeric composition of the major alcohol derived from reduction of an enantiopure substrate).[108] There is almost a linear behavior for the diastereoselectivity of the reaction (Figure 66 a), while a strong nonlinear effect has been

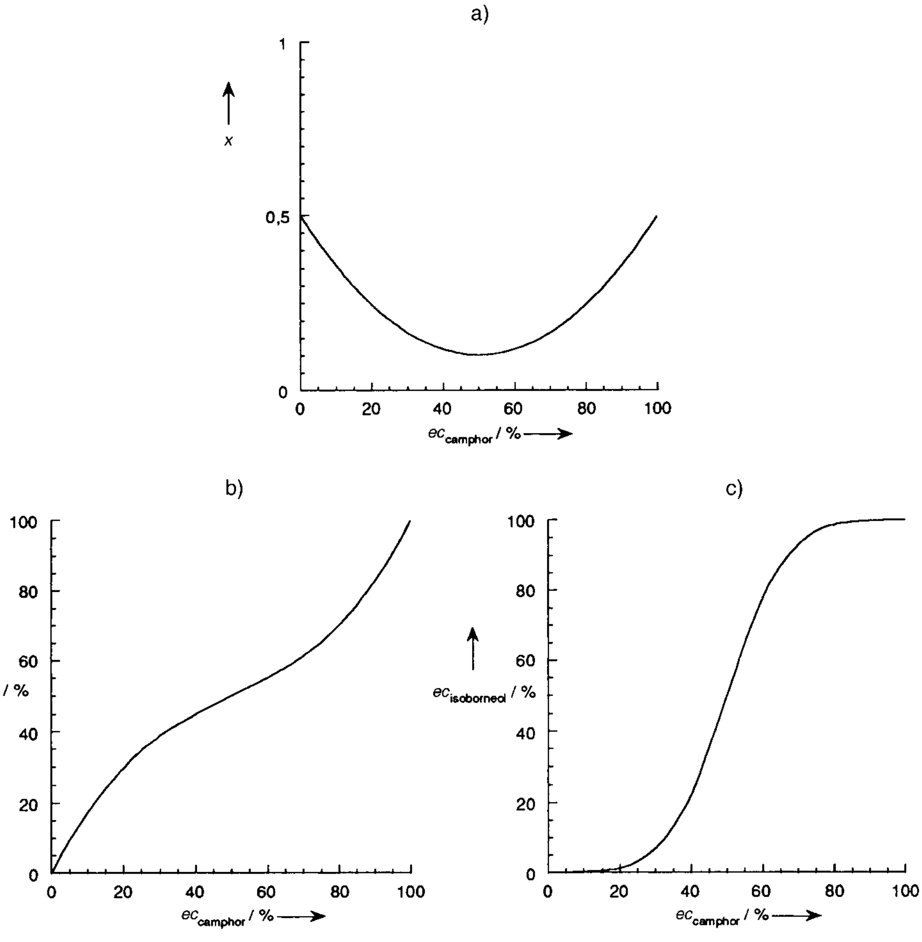
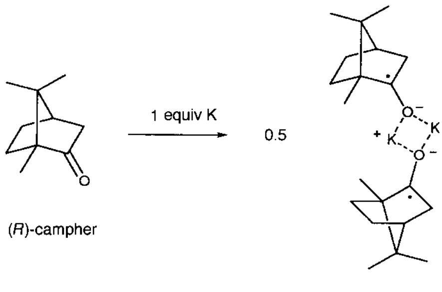


Figure 66. a) Mole fraction *x* of isoborneol and also the *ec* of b) borneol and c) isoborneol as functions of the enantiomeric composition of camphor.

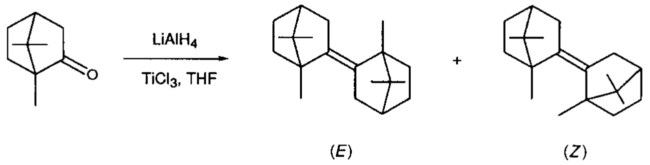
observed for the enantiomeric composition of borneol or isoborneol (Figures 66b, c). These observations have been explained by a mechanism that involves the initial formation of a ketyl anion radical (as a dimeric species). Experimental results have shown that hydrogen transfers between two dimers **A** provide (after hydrolysis) equimolar amounts of alcohols and camphor (Scheme 23). A kinetic analysis of the results is in agreement with the reaction being fourth order in camphor (second order in respect to the dimers **A**). This analysis highlights the importance of associations of lithio species for stereochemical controls. The key factor that explains the deviation from linearity is the formation of diastereomeric species **A**, which give rise to new routes in the subsequent disproportionations into products.



A

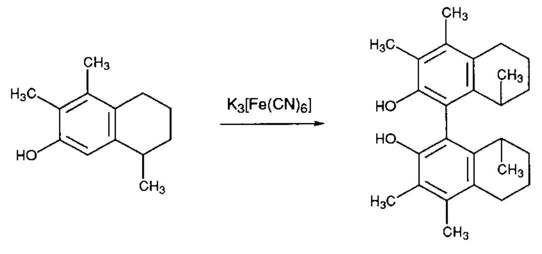
Scheme 23. The dimeric diastereomeric species **A** formed during the reduction of camphor.

The self-coupling reaction may give different products if the reactant is enantiopure or a mixture of enantiomers (homochiral or a mixture of homochiral and heterochiral coupling products are formed, respectively). Moreover the coupling reaction may create a new stereochemical unit (*E*/*Z*, *R*/*S*, *P*/*M*). It is this situation that has been investigated by Wynberg and Feringa in the case of McMurry coupling of camphor and the *ortho*-coupling of phenols with an asymmetric center[16] (Scheme 24). These reactions were only performed for 100% *ee* or 0% *ee*, and showed some stereochemical differences according to the initial *ee* value. For example, the McMurry coupling of enantiopure camphor gave homochiral dimers (*E*/*Z* = 1.68). McMurry coupling of racemic camphor provided homochiral dimers (*E*/*Z* = 1.67) and heterochiral dimers (*E*/*Z* = 2.9) in a ratio of 1.8:1



Scheme 24. McMurry coupling of camphor.

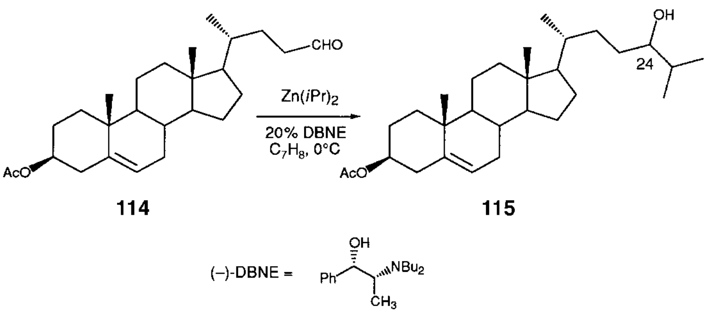
The oxidative coupling of enantiopure (*S*)-phenol **112** (Scheme 25) led to only one (> 97.5%) configuration for the new atropoisomeric unit **113** (*P*), while the coupling of racemic **112** gave the following distribution of **113**: (*S*,*S*,*P*) + (*R*,*R*,*M*)/(*S*,*S*,*M*) + (*R*,*R*,*P*)/(*R*,*S*,*P*) + (*R*,*S*,*M*) in the relative ratio of 66.0:7.9:26.1. In the above reactions, as well as in the reduction of camphor by $LiAlH_4$, it would be of interest to follow the various diastereoselectivities as a function of the enantiomeric excess of the substrate.



112 **113**

Scheme 25. Oxidative coupling of a phenol derivative **112**.

The condensation of a reagent (chiral or not) with a chiral substrate with the creation of an asymmetric center may also give rise to nonlinear effects if there is an external chiral auxiliary (in stoichiometric or catalytic amounts). A reagent control has been observed by Tanaka et al. in the catalyzed addition of diisopropylzinc on the steroid **114** (Scheme 26).[109]



Scheme 26. DBNE-catalyzed addition of diisopropylzinc to the steroid **114**.

The chiral catalyst (a β-aminoalcohol of various *ee*'s) controls the configuration at C_{24}. The diastereoselectivity of the reaction is not proportional to ee_{aux}. The catalyst (−)-DBNE (100% or 21% *ee*) gave a product **115** with 24-(*R*) configuration (97.0% *de* in both cases) while with (+)-DBNE (100%) the (*S*)-product **115** (87% *de*) was obtained. These data are indicative of a positive nonlinear effect (asymmetric amplification) under reagent control.[110]

5. Summary and Outlook

In only a ten year period nonlinear effects have established themselves as an ubiquitous phenomenon in asymmetric reactions, especially in enantioselective catalysis. It provides a simple and additional tool to detect and to discuss aggregation and self-assemblies that may arise in given reactions. The generation of diastereomeric species is the key feature that gives deviation from linearity. Asymmetric amplification characterizes a (+)-NLE and is a useful property for a reacting system since enantioselectivity is higher than expected, which allows the convenient use in some cases of enantiomerically impure chiral auxiliaries. It also paves the way to the possibility to build some autocatalytic systems with autoinduction. These systems could be synthetically useful or could suggest additional models for prebiotic generation of optical activity on earth.

The presence or not of nonlinear effects may depend of the experimental conditions in the preparation of the chiral catalyst or reagent. This may also enlighten some aspects of the reaction. The basic concepts, which are the roots of the nonlinear effects in enantioselective reactions, should apply as well to kinetic resolution[47b, 111] and diastereoselective reactions, for example in the creation of a new asymmetric center in enantiopure substrates under the influence of a chiral catalyst. The diastereoselectivity of the reaction may be influenced by the enantiomeric excess of the catalyst with a deviation from linearity. The burgeoning of the reports on NLEs for a wide range of reactions show how useful this concept is, and how it provides a kind of specific signature to a given process. One may anticipate that new developments will continue to accumulate in the near future.

Funds provided by the Centre National de la Recherche Scientifique de France and Institut Universitaire de France are greatly acknowledged. C.G. wants to thank the Ministère des Affaires Étrangères de France and the Ambassade de France au Canada for the Chateaubriand fellowship, which made his post-doctoral stay possible.
The curves, schemes, and molecular structures presented here are redrawn as accurately as possible from the original papers cited in this article.

Received: July 18, 1997 [A 245 IE]
German version: *Angew. Chem.* **1998**, *110*, 3088–3127

---

[1] L. Pasteur, *C. R. Acad. Sci. Paris* **1848**, *26*, 535.

[2] The optical purity (op) has been defined as the ratio of the observed specific rotation of the compound $[\alpha]^{D}_{obs}$ divided by the specific rotation of the enantiopure compound $[\alpha]^{D}_{max}$. It is easy to establish that $op(\%) = \frac{R-S}{R+S} \times 100$ (R = mole fraction of the major enantiomer), to give a way to calculate the relative amounts of the two enantiomers. Morrison and Mosher[3] proposed the use of the expression "enantiomeric" excess (*ee*) defined as $ee(\%) = \frac{R-S}{R+S} \times 100$. This definition has the advantage that *ee* coincides with op, even when the measurement is performed by nonpolarimetric methods. (See also ref. [4] for a discussion on that topic.)

[3] J. D. Morrison, H. S. Mosher, *Asymmetric Organic Reactions*, Prentice Hall, Englewood Cliffs, **1971**, p. 10.

[4] E. L. Eliel, S. H. Wilen, L. N. Mander, *Stereochemistry of Organic Compounds*, Wiley, New York, **1994**, p. 214.

[5] A. Horeau, *Tetrahedron Lett.* **1969**, 3121.

[6] A. Horeau, J. P. Guetté, *Tetrahedron* **1974**, *30*, 1923.

[7] T. Williams, R.G. Pitcher, P. Bommer, J. Gutzwiller, M. Uskokovic, *J. Am. Chem. Soc.* **1969**, *91*, 1871.

[8] T. Katagiri, C. Yoda, K. Furuhashi, K. Ueki, T. Kubota, *Chem. Lett.* **1996**, 115.

[9] a) K. C. Cundy, P. A. Crooks, *J. Chromatogr.* **1983**, *281*, 17; b) R. Charles, E. Gil-Av, *J. Chromatogr.* **1984**, *298*, 516.

[10] W.-L. Tsai, K. Hermann, E. Hug, B. Rohde, S. S. Dreiding, *Helv. Chim. Acta* **1985**, *68*, 2238.

[11] A. Dobashi, Y. Motoyama, K. Kinoshita, S. Hara, N. Fukasaku, *Anal. Chem.* **1987**, *59*, 2209.

[12] R. Matusch, C. Coors, *Angew. Chem.* **1989**, *101*, 624; *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 626.

[13] R. M. Carman, K. D. Klika, *Aust. J. Chem.* **1991**, *44*, 895.

[14] P. Diter, S. Taudien, O. Samuel, H. B. Kagan, *J. Org. Chem.* **1994**, *59*, 370.

[15] M. Jung, V. Schurig, *J. Chromatogr.* **1992**, *605*, 161.

[16] a) H. Wynberg, B. Feringa, *Tetrahedron* **1976**, *32*, 2831; b) H. Wynberg, *Chimia* **1976**, *30*, 445.

[17] However, Izumi and Tai pointed out that the measurement of the asymmetric induction in an asymmetric synthesis may not be necessarily correlated simply to the *ee* value of the chiral auxiliary, especially in asymmetric catalysis.[18]

[18] Y. Izumi, A. Tai, *Stereo-Differentiation Reactions*, Academic Press, New York, **1977**, p. 244.

[19] C. Puchot, O. Samuel, E. Duñach, S. Zhao, C. Agami, H. B. Kagan, *J. Am. Chem. Soc.* **1986**, *108*, 2353.

[20] There are a few review articles on some aspects of nonlinear effects.[21–24] For recent highlights and discussion on NLEs, see M. Avalos, R. Babiano, P. Cintas, J. L. Jiménez, J. C. Palacios, *Tetrahedron: Asymmetry* **1997**, *8*, 2997; M. Reggelin, *Nachr. Chem. Tech. Lab.* **1997**, *45*, 392, 622; D. G. Blackmond, *J. Am. Chem. Soc.* **1997**, *119*, 12934.

[21] R. Noyori, M. Kitamura, *Angew. Chem.* **1990**, *30*, 34; *Angew. Chem. Int. Ed. Engl.* **1990**, *30*, 49.

[22] R. Noyori, *Asymmetric Catalysis in Organic Synthesis*, Wiley, New York, **1994**, pp. 273–297.

[23] C. Bolm in *Advanced Asymmetric Synthesis* (Ed. G. R. Stephenson), Blackie Academic and Professional, New York, **1996**, pp. 9–26.

[24] H. B. Kagan, C. Girard, D. Guillaneux, D. Rainford, O. Samuel, S. Y. Zhang, S. H. Zhao, *Acta Chem. Scand.* **1996**, *50*, 345.

[25] a) U. Eder, G. Sauer, P. Wiechert, *Angew. Chem.* **1971**, *83*, 492; *Angew. Chem. Int. Ed. Engl.* **1971**, *10*, 496; b) Z. G. Hajos, D. Parrish, *J. Org. Chem.* **1974**, *39*, 1615.

[26] a) C. Agami, C. Puchot, *J. Mol. Cat.* **1986**, *38*, 341; b) C. Agami, *Bull. Soc. Chim. Fr.* **1988**, 499.

[27] a) K. Katsuki, K. B. Sharpless, *J. Am. Chem. Soc.* **1980**, *102*, 5974; b) M. G. Finn, K. B. Sharpless, *J. Am. Chem. Soc.* **1991**, *113*, 113.

[28] N. Oguni, Y. Matsuda, T. Kaneko, *J. Am. Chem. Soc.* **1988**, *110*, 7877.

[29] P. Pitchen, E. Duñach, M. N. Deshmukh, H. B. Kagan, *J. Am. Chem. Soc.* **1984**, *106*, 8188.

[30] For a simulation of the curve of Figure 5 under the assumption of a dimeric titanium species with four DET, see ref. [31].

[31] D. Guillaneux, S. H. Zhao, O. Samuel, D. Rainford, H. B. Kagan, *J. Am. Chem. Soc.* **1994**, *116*, 9430.

[32] a) M. Kitamura, S. Okada, R. Noyori, *J. Am. Chem. Soc.* **1989**, *111*, 4028; b) M. Yamakawa, R. Noyori, *J. Am. Chem. Soc.* **1995**, *117*, 6327; see also [21, 22].

[33] C. Bolm, G. Schlingloff, K. Harms, *Chem. Ber.* **1992**, *125*, 1191.

[34] K. Fitzpatrick, R. Hulst, R. M. Kellog, *Tetrahedron: Asymmetry* **1995**, *6*, 1861.

[35] a) C. Bolm, *Tetrahedron: Asymmetry* **1991**, *2*, 701; b) C. Bolm, M. Ewald, M. Felder, *Chem. Ber.* **1992**, *125*, 1205; c) C. Bolm, M. Felder, J. Müller, *Synlett* **1992**, 439.

[36] A. H. M. de Vries, J. F. G. A. Jansen, B. L. Feringa, *Tetrahedron* **1994**, *50*, 4479.

[37] Q.-L. Zhou, A. Pfaltz, *Tetrahedron* **1994**, *50*, 4467.

[38] G. van Koten, *Pure Appl. Chem.* **1994**, *66*, 1455.

[39] a) M. Terada, K. Mikami, T. Nakai, *J. Chem. Soc. Chem. Commun.* **1990**, 1623; b) K. Mikami, M. Terada, S. Narisawa, T. Nakai, *Synlett* **1992**, 255; c) K. Mikami, M. Terada, *Tetrahedron* **1992**, *48*, 5671; d) K. Mikami, *Adv. Asymmetric Synth.* **1995**, *1*, 1.

[40] M. Terada, K. Mikami, *J. Chem. Soc. Chem. Commun.* **1994**, 833.

[41] D. Kitamoto, H. Imma, T. Nakai, *Tetrahedron Lett.* **1995**, *36*, 1861.

[42] a) M. Hayashi, T. Matsuda, N. Oguni, *J. Chem. Soc. Chem. Commun.* **1990**, 1364; b) M. Hayashi, T. Matsuda, N. Oguni, *J. Chem. Soc. Perkin Trans.* **1992**, 3135.

[43] a) G. E. Keck, D. Krishnamurthy, M. C. Grier, *J. Org. Chem.* **1993**, *58*, 6543; b) G. E. Keck, D. Krishnamurthy, *J. Am. Chem. Soc.* **1995**, *117*, 2363.

[44] J. W. Faller, D. W. I. Sams, X. Liu, *J. Am. Chem. Soc.* **1996**, *118*, 1217.

[45] P. Bedeschi, S. Casolari, A. L. Costa, E. Tagliavini, A. Umani-Ronchi, *Tetrahedron Lett.* **1995**, *36*, 7897.

[46] D. R. Gauthier, Jr, E. M. Carreira, *Angew. Chem.* **1996**, *108*, 2521; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2363.

[47] a) N. Komatsu, M. Hashizume, T. Sugita, S. Uemura, *J. Org. Chem.* **1993**, *58*, 4529; b) N. Komatsu, M. Hashizume, T. Sugita, S. Uemura, *J. Org. Chem.* **1993**, *58*, 7624.

[48] H. B. Kagan, J.-C. Fiaud, *Top. Stereochem.* **1988**, *18*, 249.

[49] C. Zondervan, B. L. Feringa, *Tetrahedron: Asymmetry* **1996**, *7*, 1895.

[50] N. Iwasawa, Y. Hayashi, H. Sakurai, K. Narasaka, *Chem. Lett.* **1989**, 1581.

[51] J. Irurre, C. Alonso-Alija, A. Fernández-Serrat, *Afinidad* **1994**, *51*, 413.

[52] K. Mikami, Y. Motoyama, M. Terada, *J. Am. Chem. Soc.* **1994**, *116*, 2812.

[53] S. Kobayashi, H. Ishitani, M. Araki, I. Hachiya, *Tetrahedron Lett.* **1994**, *35*, 6325.

[54] D. Seebach, R. Dahinden, R. E. Marti, A. K. Beck, D. A. Plattner, F. N. M. Kühnle, *J. Org. Chem.* **1995**, *60*, 1788.

[55] M. Shimizu, Y. Ukaji, K. Inomata, *Chem. Lett.* **1996**, 455.

[56] H. Sasai, T. Susiki, N. Itoh, M. Shibasaki, *Tetrahedron Lett.* **1993**, *34*, 851.

[57] D. A. Evans, S. G. Nelson, M. R. Gagné, A. R. Muci, *J. Am. Chem. Soc.* **1993**, *115*, 9800.

[58] K. B. Hansen, J. L. Leighton, E. N. Jacobsen, *J. Am. Chem. Soc.* **1996**, *118*, 10924.

[59] M. Yamaguchi, T. Shiraishi, M. Hirama, *J. Org. Chem.* **1996**, *61*, 3520.

[60] B. Schmidt, D. Seebach, *Angew. Chem.* **1991**, *103*, 1383; *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 1321.

[61] a) C. Bolm, J. Müller, G. Schlingloff, M. Zehnder, M. Neuburger, *J. Chem. Soc. Chem. Commun.* **1993**, 182; b) C. Bolm, J. Müller, *Tetrahedron* **1994**, *50*, 4355.

[62] P. I. Dosa, J. C. Ruble, G. C. Fu, *J. Org. Chem.* **1997**, *62*, 444.

[63] M. Bougauchi, S. Watanabe, T. Arai, H. Sasai, M. Shibasaki, *J. Am. Chem. Soc.* **1997**, *119*, 2329.

[64] T. Schwenkreis, A. Berkessel, *Tetrahedron Lett.* **1993**, *34*, 4785.

[65] C. Bolm, F. Bienewald, *Angew. Chem.* **1995**, *107*, 2883; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2640.

[66] D. Seebach, R. E. Marti, T. Hintermann, *Helv. Chim. Acta* **1996**, *79*, 1710.

[67] S. E. Denmark, B. L. Christenson, S. P. O'Connor, *Tetrahedron Lett.* **1995**, *36*, 2219.

[68] a) J. W. Faller, J. Parr, *J. Am. Chem. Soc.* **1993**, *115*, 804; b) J. W. Faller, M. R. Mazzieri, J. T. Nguyen, J. Parr, M. Tokunaga, *Pure Appl. Chem.* **1994**, *66*, 1463; c) D. P. Fairlie, B. Bosnich, *Organometallics* **1988**, *7*, 936; e) D. P. Fairlie, B. Bosnich, *Organometallics* **1988**, *7*, 946; f) S. H. Bergens, P. Noheda, J. Whelan, B. Bosnich, *J. Am. Chem. Soc.* **1992**, *114*, 2121.

[69] K. Burgess, W. A. van der Donk, *Inorg. Chim. Acta* **1994**, *220*, 93.

[70] a) M. Kitamura, S. Suga, M. Niwa, R. Noyori, *J. Am. Chem. Soc.* **1995**, *117*, 4832; b) M. Kitamura, M. Yamakawa, H. Oka, S. Suga, M. Niwa, R. Noyori, *Chem. Eur. J.* **1997**, *2*, 1173.

[71] The authors used Equations (8) and (9) to draw the calculated curves: where ν_0^A and ν_0^B are the initial rates of pure cat_{A^-}- and cat_{B^-}-catalyzed reactions proceeding with enantioselectivities of ee_A and ee_B, respectively. The abscissa or the graphics are catalyst composition expressed as $100\,cat_A/[cat_A]+[cat_B]$ or $100\,cat_B/[cat_A]+[cat_B]$.

$$ee_{ber} = \frac{ee_A \nu_0^A [cat_A] + ee_B \nu_0^B [cat_B]}{[cat_A] + [cat_B]} \tag{8}$$

$$\nu_{0,ber} = \frac{\nu_0^A [cat_A] + \nu_0^B [cat_B]}{[cat_A] + [cat_B]} \tag{9}$$

[72] S. Y. Zhang, C. Girard, H. B. Kagan, *Tetrahedron: Asymmetry* **1995**, *6*, 2637.

[73] K. B. Sharpless, W. Amberg, Y. L. Bennani, G. A. Crispino, J. Hartung, K.-S. Jeong, H.-L. Kwong, K. Morikawa, Z.-M. Wang, X.-L. Zhang, *J. Org. Chem.* **1992**, *57*, 2768.

[74] E. J. Corey, M. C. Noe, *J. Am. Chem. Soc.* **1993**, *115*, 12579.

[75] a) M. A. Giardello, V. P. Conticello, L. Brard, M. R. Gagné, T. J. Marks, *J. Am. Chem. Soc.* **1994**, *116*, 10241; b) P.-F. Fu, L. Brard, Y. Li, T. J. Marks, *J. Am. Chem. Soc.* **1995**, *117*, 7157.

[76] F. C. Frank, *Biochim. Biophys. Acta* **1953**, *11*, 459.

[77] M. Calvin, *Chemical Evolution*, Clarendon, London, **1969**, Chap. 7.

[78] For a recent highlight on asymmetric autocatalysis with amplification of chirality, see ref. [79a]. For a possible asymmetric autocatalytic system (liquid phase autoxidation) see ref. [79b].

[79] a) C. Bolm, F. Bienewald, A. Seger, *Angew. Chem.* **1996**, *108*, 1767; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1657 and references therein; b) T. Buhse, D. Lavabre, J. C. Micheau, W. Thiemann, *Chirality* **1993**, *5*, 341.

[80] K. Soai, S. Niwa, H. Hori, *J. Chem. Soc. Chem. Commun.* **1990**, 983.

[81] K. Soai, T. Hayase, K. Takai, *Tetrahedron: Asymmetry* **1995**, *6*, 637.

[82] T. Shibata, K. Choji, T. Hayase, Y. Aizu, K. Soai, *Chem. Commun.* **1996**, 751.

[83] a) T. Shibata, K. Choji, T. Hayase, Y. Aizu, K. Soai, *Chem. Commun.* **1996**, 1235; b) T. Shibata, T. Hayase, J. Imamoto, K. Soai, *Tetrahedron: Asymmetry* **1997**, *8*, 1717.

[84] K. Soai, T. Shibata, H. Marioka, K. Choji, *Nature* **1995**, 767.

[85] For advantages or disadvantages of the use of the enantiomeric ratio (*er*) in stereochemical problems or Horeau amplification, see refs. [86, 87].

[86] H. B. Kagan, *Rec. Trav. Chim. Pays-Bas* **1995**, *114*, 203.

[87] V. Rautenstrauch, *Bull. Soc. Chim. Fr.* **1994**, *131*, 515.

[88] a) A. H. Alberts, H. Wynberg, *J. Am. Chem. Soc.* **1989**, *111*, 7265; b) A. H. Alberts, H. Wynberg, *J. Chem. Soc. Chem. Commun.* **1990**, 453.

[89] H. Danda, H. Nishikawa, K. Otaka, *J. Org. Chem.* **1991**, *56*, 6740.

[90] Y. Shvo, M. Gal, Y. Becker, A. Elgavi, *Tetrahedron Lett.* **1996**, *7*, 911, and references therein.

[91] K. Soai, Y. Inoue, T. Takahashi, T. Shibata, *Tetrahedron Asymmetry* **1996**, *7*, 13355.

[92] The interpretation of the reaction is complicated here by the possibility of a double asymmetric reaction.[87]

[93] H. Wynberg, *Chimia* **1989**, *43*, 150.

[94] A qualitative model for asymmetric autocatalytic processes has been proposed by Bailey.[95] It is based on the ML_2 model,[31] the reaction involving the formation of L. As discussed above it is possible to introduce a (+)-NLE, which makes this system useful for self-replication of chirality.

[95] P. D. Bailey, *J. Chem. Soc. Chem. Commun.* **1995**, 1707.

[96] Equations based on competitive reactions of Figure 60 have been developed to describe the various cases where stoichiometric asymmetric synthesis can give rise to NLE.[97]

[97] C. Girard, H. B. Kagan, manuscript in preparation.

[98] a) A. O. King, E. G. Corley, R. K. Anderson, R. D. Larsen, T. R. Verhoeven, P. J. Reider, Y. B. Xiang, M. Belley, Y. Leblanc, M. Labelle, P. Prasit, R. J. Zamboni, *J. Org. Chem.* **1993**, *58*, 3731; b) I. Shinkai, A. O. King, R. D. Larsen, *Pure Appl. Chem.* **1994**, *66*, 7551.

[99] Initial reports from Merck[98] indicated that NLE was observed for one value of *ee* of pinene. An excellent and complete study was published later.[102]

[100] C. Girard, H. B. Kagan, *Tetrahedron :Asymmetry* **1995**, *6*, 1881.

[101] H. C. Brown, N. N. Joshi, *J. Org. Chem.* **1988**, *53*, 4059.

[102] M. Zhao, A. O. King, R. D. Larsen, T. R. Verhoeven, P. J. Reider, *Tetrahedron Lett.* **1997**, *38*, 2641.

[103] C. Girard, H. B. Kagan, *Tetrahedron: Asymmetry* **1997**, *23*, 3851.

[104] K. Tanaka, J. Matsui, Y. Kawabata, H. Suzaki, A. Watanabe, *J. Chem. Soc. Chem. Commun.* **1991**, 1632.

[105] a) R. E. Rossiter, M. Eguchi, A. E. Hernandes, D. Vickers, J. Medich, J. Marr, D. Heninis, *Tetrahedron Lett.* **1991,** *32*, 3973; b) R. E. Rossiter, G. Miao, N. M. Swingle, M. Eguchi, A. E. Hernandez, R. G. Patterson, *Tetrahedron: Asymmetry* **1992**, *3*, 231.

[106] a) C. Fehr, J. Galindo, *J. Org. Chem.* **1988**, *53*, 1828; b) C. Fehr, J. Galindo, *Helv. Chem. Acta* **1995**, *78*, 539; c) C. Fehr, *Angew. Chem.* **1996**,*108*, 2726; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2567.

[107] V. Rautenstrauch, P. Mégard, B. Bourdin, A. Furrer, *J. Am. Chem. Soc.* **1992**, *114*, 1418.

[108] For the advantages and disadvantages of the use of *ee*, *ec*, or *er* in various problems, see ref. [86].

[109] M. Okamoto, M. Tabe, T. Fujii, T. Tanaka, *Tetrahedron: Asymmetry* **1995**, *6*, 767.

[110] S. Masamune, W. Choy, J. S. Petersen, L. R. Sita, *Angew. Chem.* **1985**,*97*, 1; *Angew. Chem. Int. Ed. Engl.* **1985**, *24*, 1.

[111] C. Girard, T. Luukas, H. B. Kagan, unpublished results.