Pergamon

Tetrahedron: Asymmetry, Vol. 8, No. 18, pp. 2997–3017, 1997

Printed in Great Britain
PII: S0957-4166(97)00375-3
0957-4166/97 $17.00 + 0.00

TETRAHEDRON: ASYMMETRY REPORT NUMBER 28

Nonlinear stereochemical effects in asymmetric reactions †

Martín Avalos, Reyes Babiano, Pedro Cintas,* José L. Jiménez and Juan C. Palacios
Departamento de Química Orgánica, Facultad de Ciencias, Universidad de Extremadura, E-06071 Badajoz, Spain

Contents

1. Introduction and background

As the new century draws ever nearer the search for the origin of molecular handedness is still a fascinating challenge, not only to look to the future but also to reflect on the achievements of the 20th century. Although numerous biotic and abiotic hypotheses have been proposed,[1] in particular those that suppose a gradual selection of one enantiomer from a racemic mixture, many scientists are convinced that some theories are somewhat speculative and will probably be impossible to verify experimentally.

In a preliminary approach, one can suppose that some processes of chiral selection or enantiodifferentiation arise from diastereomeric interactions of a racemic mixture thus causing enhancements of the enantiomeric excess (*ee*). In other words, there could be a nonlinear relationship between optical purity and enantiomeric excess. Horeau was probably the first person to recognize the importance of such interactions of a racemic mixture in the liquid phase.[2] Although the nature of these interactions is not fully understood, it is now well established that racemates often behave as eutectics and this fact accounts for the different properties for a racemic mixture or a pure enantiomer.[3] In the absence of a chiral reagent it is also possible that an enantiomerically pure compound and a racemic mixture exhibit different chemical rates, and eventually, afford a different product distribution.[4] Both the self-induced NMR anisochrony and the measurable differences in reactivity account for enantiomer discrimination as a consequence of aggregation or formation of conglomerates which are homochiral or heterochiral associates, and therefore nonracemic, not enantiopure samples leading to diastereoisomeric transition states.[3,5]

While enantiomeric discrimination is only significant by forming heterochiral associates,[6] one can expect that a chiral ligand, not necessarily in enantiopure form, capable of forming homo- and heterochiral associates with a metal center, may lead to high levels of asymmetric induction by enantiomer discrimination. In such a case a nonlinear relationship (NLE)[7] between the *ee* of the

† Dedicated to Henri Kagan for his pioneering contributions in this area and on the occasion of his 67th birthday.

* Corresponding author. Email: pecintas@unex.es

product and the *ee* of the chiral ligand may occur. As we shall see this has been well documented with metal catalysts suitable for asymmetric reactions. There has been a tendency to denote some of these nonlinear processes under the terms of *chiral amplification* or *chiral multiplication*. Although these terms have already been coined, their use is somewhat misleading as they are not meant to imply a departure from linearity. Strictly speaking, any asymmetric catalytic reaction, with linear or nonlinear effects, involves an amplification since one chiral catalyst molecule can create millions of chiral product molecules, being therefore the most desirable and the most challenging among the types of asymmetric reactions.[8] A further drawback is the fact that, from a practical viewpoint, the efficiency of the chiral multiplication can be defined as the quotient: [(major isomer−minor isomer) in moles]/moles of (chiral auxiliary).[9] This dimensionless number denotes the substrate/catalyst mole ratio and a high value of the latter is a requirement for achieving a practical asymmetric synthesis. Nevertheless an estimation of the catalytic process based on such a factor can be less intuitive than the *ee* of the product. On the other hand, cholesteric mesophases (liquid crystals) of very high optical rotation may be utilized to amplify very small optical rotations or to detect them in very small amounts of a sample. These chiroptical methods are often referred to as *chirality amplification*,[10] though in many cases the optical activity is solely due to a chiral solute or solvent rather than to specific solute–solvent interactions. Anyway and in order to avoid misinterpretations, the term *amplifying effect* as described in the literature will be freely utilized through this text.

The aim of this report is to provide a critical vision of the unexpected nonlinear correlations found in asymmetric transformations, rather than an exhaustive compilation of unconnected experiments. It also discusses how this issue bears upon the oligomeric structure of catalysts and their diastereomeric interactions. It provides an overview of the technical literature as well as analytical commentaries on its significance. Although the best examples of nonlinear effects are provided by asymmetric catalysis, unexpected enhancements of stereoselectivity have also been found in chiral autocatalysis and this aspect will also be discussed in some detail.

2. Nonlinear effects in catalysis

2.1. *Conceptual considerations*

The utilization of a chiral auxiliary, either in a stoichiometric or catalytic fashion, has become a common practice in asymmetric synthesis. Such auxiliaries can be obtained as a single enantiomer from chiral natural products (e.g. carbohydrates, amino acids, etc) or by resolution techniques. Unfortunately, their enantiopurity is not always 100% and auxiliaries of different optical purities are frequently used.

Ideally, the enantioselectivity of an asymmetric reaction ($ee_{product}$) can be correlated with the *ee* of the auxiliary by means of Eq. 1

$$ee_{product} = ee_o ee_{aux} \tag{1}$$

where ee_o is the enantiomeric excess of the auxiliary when used in enantiopure form. In other words, the theoretical optical yield of the reaction can be calculated according to Eq. 2

$$ee_o = ee_{product}/ee_{aux} \tag{2}$$

A simple plot of $ee_{product}$ versus ee_{aux} is depicted in Figure 1. Three types of correlations may then be found: a linear effect (straight line 1), a positive nonlinear effect (curve 2), and a negative nonlinear effect (curve 3).

It should be emphasized strongly that these curves are ideal cases of NLE and borderline situations, even combinations of linear and nonlinear relationships can be encountered. As mentioned, catalytic reactions for which the catalyst involves two or more chiral ligands that are not enantiomerically pure are prone to NLE, that is, the enantiomeric excess of the product will not bear a straight relationship to the enantiomeric excess of the catalyst. This is the situation where two enantiomeric chiral ligands (L_R or L_S) are attached to a metal center (M) to afford ML_2 complexes as reactive species. Obviously, other achiral ligands may also be present such as hydrogen, halogen, alkoxy, which is otherwise

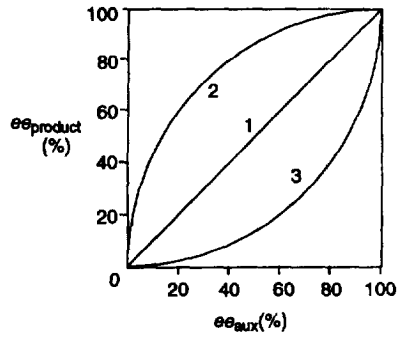


Figure 1.

the real situation of most catalysts. In addition, coordination of chiral ligands can also create a new chiral center on the metal. In a simplified case, however, with two chiral ligands, three complexes are possible: ML_RL_R, ML_SL_S, and ML_RL_S. If we suppose that L_R is in excess and the stability constant for the *meso* complex ML_RL_S is greater than that of the chiral complexes, then ML_RL_R and ML_RL_S will be the major catalytic species. Furthermore, if the *meso* complex ML_RL_S is the most active catalyst, a lower than expected *ee* will be obtained (Figure 1, curve 3). On the contrary, if the *meso* catalyst is less reactive than ML_RL_R or ML_SL_S, then the *ee* will be higher than the one calculated theoretically (Figure 1, curve 2).

It is difficult to ascertain when the first nonlinear deviations were observed because before the 1980s the enantiopurity of chiral auxiliaries was not routinely checked. Moreover, it is known that many auxiliaries are partially resolved and some naturally-occurring substances are indeed isomeric mixtures. Nevertheless, the first notorious example of a clear nonlinear effect was demonstrated by Kagan and his associates for the Katsuki–Sharpless epoxidation of geraniol with Ti(*O*-^{i}Pr)$_4$/(+)-DET/*t*-BuOOH in the ratio 1:1:2 (Eq. 3)[11]

(3)

Kagan's group studied the above reaction under the conditions described but with diethyl tartrate (DET) of different optical purities. Epoxygeraniol was obtained with greater *ee*s (positive NLE) than those correlated with the enantiomeric purity of the diethyl tartrate. Similarly, the authors also investigated the asymmetric oxidation of methyl 4-tolylsulfide into the corresponding sulfoxide by a water-modified Sharpless reagent, as well as a Robinson-type asymmetric annulation catalyzed by (*S*)-proline.[11] The former was an intriguing case since the experimental curve exhibited a negative NLE until ee_{aux}=70% and then the linearity was recovered by using diethyl tartrate of optical purity higher than 70%. In contrast, the catalytic asymmetric annulation showed always a negative nonlinearity regardless of the (*S*)-proline enantiomeric purity.

Why do NLEs occur in asymmetric catalysis? At first sight a satisfactory answer appears to be complicated. Be that as it may, Eqs 1 and 2 should now be considered as ideal expressions and experimental results are better correlated with a modified Eq. 4

$$ee_{product} = ee_o ee_{aux} f \tag{4}$$

where f is a correction factor[11,12] defined by

$$f = (1 + \beta)/(1 + g\beta) \tag{5}$$

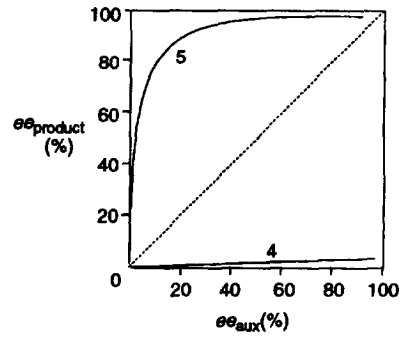


Figure 2. Limiting cases of NLEs (see text).

In Eq. 5 β stands for the relative amounts of the *meso* and homochiral complexes [β=a/(b+c)], whereas g expresses the relative reactivities of the *meso* and homochiral catalysts [$g=k_{RS}/k_{RR}$ or k_{RS}/k_{SS}]. These considerations are unavoidable since an asymmetric catalysis should necessarily be based on a kinetic scheme involving equilibria between free ligands and complexed species.

Coming back to Eq. 5, the linear correlation takes place when $f=1$, i.e. only when β=0 (there is no *meso* catalyst) or g=1 (the reactivities of *meso* and homochiral catalysts are identical). In all the cases in which the correction factor is not equal to 1, a departure from linearity will occur. A positive NLE requires a correcting factor >1 and this is achieved if g<1, that is the *meso* complex is less reactive than the homochiral complexes. On the other hand, g values greater than 1 will lead to a negative NLE. One can obviously deduce that the maximum departure from linearity in positive effects occurs when g=0 (no reactivity of the *meso* complex).

Once the thermodynamic equilibrium is reached, the equilibrium constant could be expressed as a function of the distribution of complexes: $K=a^2/bc$. Therefore a combination of a small g value and a large K (low reactivity and high concentration of *meso* complex) will give the highest positive nonlinearity.

There are some considerations that should be taken into account. Firstly, the above model assumes a fast ligand exchange between all the reactive complexes involving two chiral ligands, L_R and L_S. Complexes thus formed are irreversibly converted into products. The complex of higher reactivity will ultimately determine the type of nonlinear effect. Secondly, the two homochiral complexes are enantiomers and will have the same reactivity giving products with the same *ee* but of opposite configuration. In contrast, the *meso* complex ML_RL_S will provide a racemic product unless the metal itself is a stereogenic center. Moreover, if the *meso* complex is much more reactive than the chiral complexes, then $g \gg 1$ and $f \sim 0$. As a consequence the *ee* of the product will asymptotically tend to zero whatever the *ee* of the ligand (Figure 2, curve 4). Another limiting case will occur when the *meso* complex is unreactive (g=0) but it is formed preferentially and, in an irreversible fashion, from a chiral ligand, say L_R. In this particular case one of the two homochiral complexes (ML_RL_R) will not be formed. The f value will be $1/ee_{aux}$ and Eq. 4 indicates that $ee_{product}=ee_o$, that is the $ee_{product}$ will asymptotically tend to the highest value (Figure 2, curve 5).

An in-depth mathematical treatment of these considerations as well as the other cases involving higher types of catalytic species such as ML_3 or ML_4 lies beyond the purpose of this review, as they have been the subject of a detailed study.[81,12]

The fact that the asymmetric epoxidation of allylic alcohols exhibits a pronounced convexity with respect to a linear correlation clearly excludes a catalytic species involving only one tartrate ligand coordinated at the metal center. The positive NLE indicates a cooperative effect of two tartrate ligands around the titanium atom, and the *meso* complex should be less reactive (g<1) than any of the

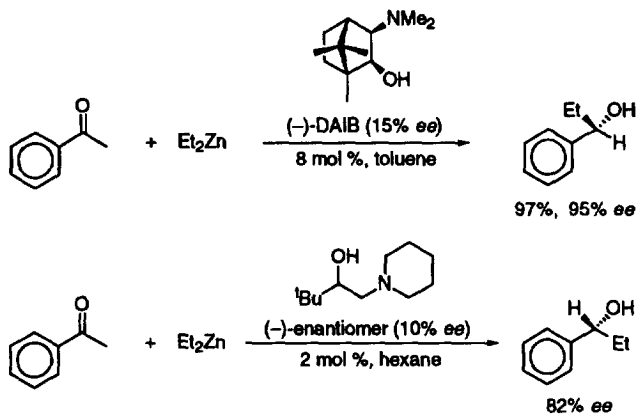
homochiral complexes. This interpretation is consistent with the mechanistic insights of the titanium-mediated asymmetric epoxidation (AE) suggesting the intermediacy of a dimeric complex in solution.[13]

The realistic situation of NLEs is however more complicated since both homo- and heterochiral complexes are present and their reactivities may not be very different. The NLEs should therefore be a consequence of the formation of diastereomeric species, either by complexation or aggregation.[12] A complementary interpretation of catalytic reactions by Sharpless and his associates, based on the concept of *ligand-accelerated catalysis*,[14] may also account for NLEs. The overall rate of product formation can be increased in the presence of the ligand (acceleration) or slowed down (deceleration). With chiral ligands the enantioselectivity can eventually be enhanced upon ligand binding. This is usually observed only in reactions proceeding through very organized transition states, which emerge from the participation of single reactive species in dynamic ligand exchange processes.[14]

The existence of an oligomeric distribution of ligands in solution implies that an analysis of the departure from linearity by chiroptical methods (e.g. optical rotation), though fast, should be considered with caution because the optical purity may not be coincidental with the enantiomeric excess. The diastereomeric species responsible for enantiomer discrimination will affect the effective concentration of the enantiomerically pure ligand. Moreover, the magnitude and wavelength of the Cotton effect, which accounts for the optical activity, will differ for homo- and heterochiral associates.[15]

2.2. *Synthetic applications*

One of the most striking examples of NLEs is provided by the enantioselective addition of dialkylzincs to aldehydes catalyzed by amino alcohols (Scheme 1).[8d,f,16–18]

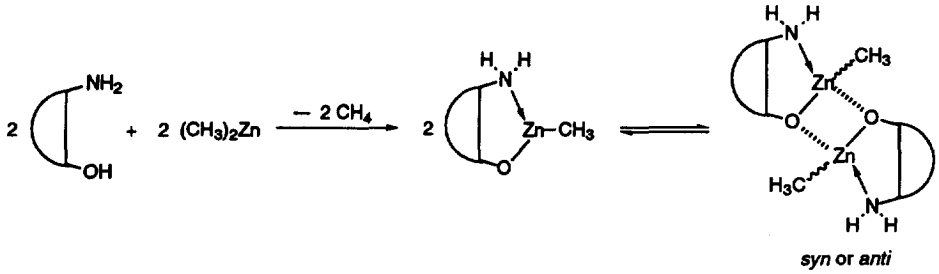


Scheme 1.

Dialkylzinc organometallics are usually inert to aldehydes in hydrocarbon solvents, but in the presence of a β-dialkylamino alcohol the addition reaction proceeds smoothly to give, after an aqueous workup, the corresponding secondary alcohol. The best chiral catalyst to achieve the enantioselective version is (2*S*)-3-*exo*-(dimethylamino)isoborneol (DAIB). Although the first paper on this relevant transformation was published in 1986,[16] almost simultaneously with Kagan's paper,[11] the process was recognized as a chiral multiplication by Oguni and coworkers, who proposed the same asymmetric amplification.[17] Improved amplification and a deeper mechanistic investigation were provided later by Noyori and his group.[18,19]

The catalytic efficiency is particularly remarkable since when 100 mol% of the amino alcohol is added to organozinc no alkylation was observed, while a catalytic amount (2–8 mol%) afforded the alkylated product in high yield. The positive NLEs are clearly visualized in Scheme 1. Thus ethylation of benzaldehyde with DAIB in 15% *ee* gives the alkylation product in 95% *ee*, very close to the 98% *ee* obtained with DAIB in enantiomerically pure form.

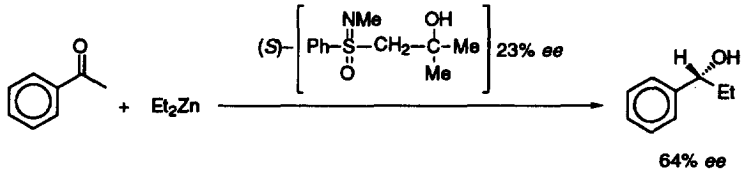
The reaction occurs through an alkylzinc alkoxide, generated from the dialkylzinc and DAIB after elimination of an alkane moiety. This tricoordinate zinc alkoxide undergoes further dimerization to form a chiral or achiral dimer, *syn*- or *anti*-, respectively (Scheme 2).



Scheme 2.

An *ab-initio* molecular orbital study on the reaction mechanism[20] evidences that the *anti* dimer is more stable than the *syn* isomer by 3 kcal/mol, as a consequence of the relative stabilities of the *syn*- and *anti*-5/4/5 tricyclic skeletons. The heterochiral dimer is therefore more stable than the homochiral compounds and authors suggest that this thermodynamic difference, along with the reaction conditions, are the origin of the enantiodifferentiation.

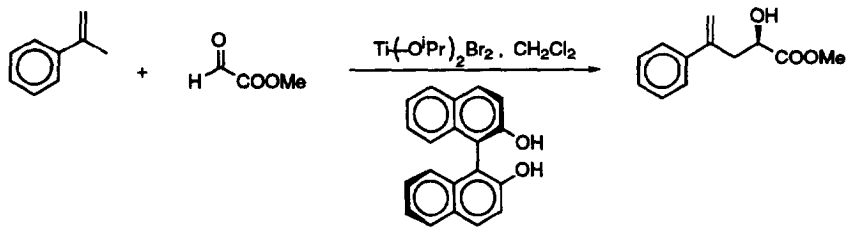
Since these pioneering works, deviations from linearity have been observed in a few types of synthetically useful enantioselective reactions. The amplifying effect observed in the addition of organozincs to aldehydes catalyzed by sterically congested β-amino alcohols,[16–18] can be complemented by the use of optically active β-hydroxy sulfoximines.[21,22] Catalytic amounts (5–10 mol%) *accelerate* the ethylation of aldehydes affording the alkylated products up to 88% *ee*. When (*S*)-β-hydroxy sulfoximines were used, the major secondary alcohol obtained was invariably the (*S*)-enantiomer. Scheme 3 depicts the NLE observed with a β-hydroxy sulfoximine of 23% *ee* affording an alcohol with 64% *ee*. The authors were also able to characterize a dimeric zinc alkoxide by X-ray diffraction analysis.[21] Again, the NLE is consistent with the formation of homochiral dimers ruling out the intermediacy of monomeric species in solution.



Scheme 3.

Mikami and his group have described NLEs in asymmetric ene reactions,[23] in particular the carbonyl-ene reaction with glyoxylate catalyzed by chiral titanium complexes,[24,25] which constitutes an efficient route to the asymmetric preparation of α-hydroxy esters.[26] Thus a positive NLE was observed by using 1 mol% of a chiral titanium catalyst, generated from a partially resolved (*R*)-BINOL plus Ti(*O*-^{i}Pr)$_2$Br$_2$ in CH_2Cl_2 and in the presence of 4 Å-MS (molecular sieves). Results clearly indicate that the use of BINOL in 30–40% *ee* is sufficient to provide *ee*s comparable to those of enantiomerically pure (*R*)-BINOL (Scheme 4).[25]

This remarkable NLE was interpreted as a result of the different catalytic activity of the diastereoisomeric (*R*),(*R*) and (*R*),(*S*) dimers of BINOL. In line with this surmise, kinetic studies demonstrated that the catalytic activity (in terms of reaction rates) by the chiral catalyst containing 100% *ee* of BINOL is 35 times greater than that of the complex with a racemic ligand. It therefore appears evident that the catalyst generated from racemic BINOL is not a mixture of homochiral dimers (*R*),(*R*)- and

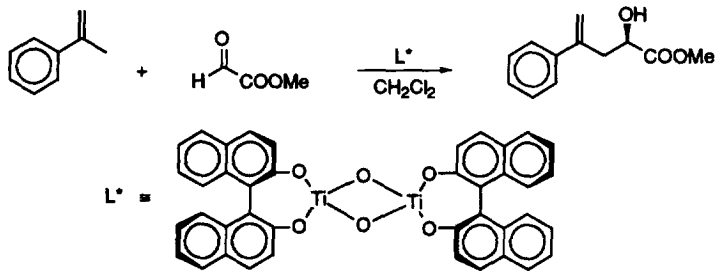


(*R*)-BINOL (%*ee*)	Product Yield (%)	Product *ee* (%)
33	92	91
47	88	93
67	96	94.5
100	98	94.5

Scheme 4.

(*S*),(*S*)-BINOL, which would otherwise provide the same extent of catalytic activity. The heterochiral (*R*),(*S*) dimer should be more stable and hence less reactive, while further experiments indicated the fast dissociation of the homochiral (*R*),(*R*) dimer to afford a monomeric complex with titanium and glyoxylate. This may account for the higher NLE at lower concentrations of the chiral titanium catalyst. In addition, authors also considered the intermediacy of a trinuclear complex, derived from (*R*)- and (*S*)-ligands, as an alternative pathway.[25]

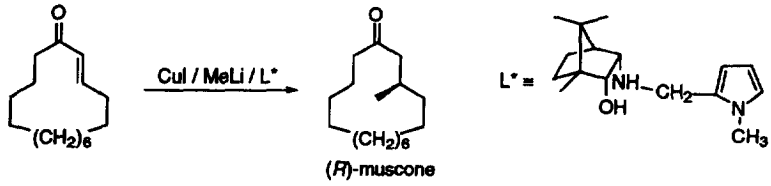
When the isolation of the chiral titanium dihalide catalyst, formed from (*R*)-BINOL and Ti(*O*-^{i}Pr)$_2$X$_2$ in the presence of 4 Å-MS, was performed by azeotropic removal with toluene, it resulted in the unexpected formation of a chiral titanium μ-oxo complex.[27] Such an (*R*)-complex even in 0.2 mol% catalyzes the glyoxylate-ene reaction leading to the ene products up to 98.7% *ee* (Scheme 5). A positive NLE was clearly visible in the glyoxylate-ene reaction with α-methylstyrene consistent with the different reactivity ($K=k_{homo}/k_{hetero}=9$) between the homo- and heterochiral titanium μ-oxo complexes.



Scheme 5.

Conjugate addition reactions constitute a lively scenario where NLEs are frequently found. An interesting amplification has been detected in the asymmetric synthesis of (*R*)-muscone by conjugate addition of a chiral alkoxydimethylcuprate to a macrocyclic enone, (*E*)-cyclopentadec-2-enone.[28] The convexity was clearly seen at *ees* of the chiral ligand greater than 60%, while negative effects were observed at lower *ees* (Scheme 6).

Assuming that organocuprates may exist as dimers in solution, the NLE can be explained by considering the different reactivity of the diastereoisomeric homo- and heterochiral dinuclear complexes. Thus, the proposed structure for the homochiral alkoxydimethylcuprate dimer (Figure 3) possesses chiral C_2 symmetry.



L* (% *ee*)	(*R*)-muscone (%*ee*)
20	6
50	33
60	76
80	93
100	100

Scheme 6.

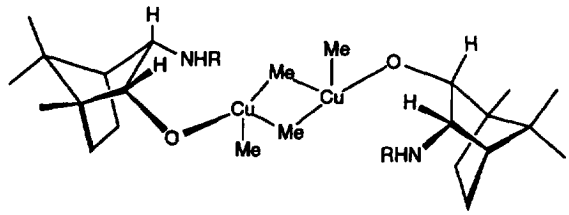
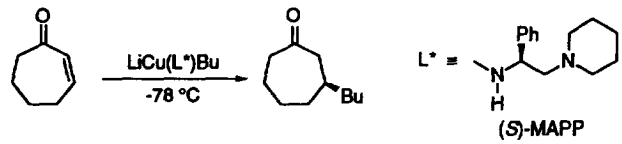


Figure 3.

A similar chiral amplification was also observed by Rossiter and his group in the synthesis of 3-butyl cycloheptanone.[29] Likewise, enantioselective conjugate addition of chiral organocuprates to 2-cycloheptenone was examined.[30,31] Chiral amidocuprates of general formula LiCu(L*)R were used, where L* was either (*R*)- or (*S*)-*N*-methyl-1-phenyl-2-(1-piperidinyl)ethaneamine (MAPP) with R=methyl, *n*-butyl, or phenyl (Scheme 7). The reaction is largely influenced by the solvent, Cu(I) salt, ligand, and the presence of an additive (TMSCl or cyanide), which have a profound effect on the reactivity and selectivity.



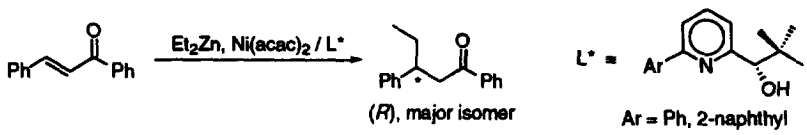
(*S*)-MAPP (%*ee*)	Product (%*ee*)
56	81
78	88
84	94
>99	96

Scheme 7.

The reaction is run and quenched at −78°C in diethyl ether and, under these circumstances, it gives a product with a higher *ee* than that of the ligand. This suggests that MAPP-cuprates may be reacting as dimers, and therefore both enantiomers of MAPP self-assemble to form a statistical mixture of (*R*),(*R*), (*S*),(*S*), and (*R*),(*S*) dimeric organocuprates. The heterochiral *meso* complex is believed to be unreactive as modeling studies reveal an extra steric crowding around the binding/catalytic site.[30]

Tanaka and coworkers also observed a complex correlation between $ee_{product}$ and ee_{aux} for the reaction of a chiral alkoxymethylcuprate with (*E*)-2-cyclopentadecenone.[32] Cuprates of low optical purity gave a negative NLE which became positive for *ee*s >55%. Similarly, in the addition of ^{i}PrMgCl to 2-cycloheptenone catalyzed by a copper(I) thiolate complex derived from a chiral mercaptoaryl oxazoline as ligand,[33] a negative NLE was found, the *ee* of the product being lower than that of the ligand. However the lack of information about the reaction mechanism and the catalyst structure precludes an interpretation of such an effect.

Nickel complexes with optically active pyridine ligands catalyze the conjugate addition of diethyl zinc to chalcone giving alkylated products with *ee*s up to 86%. A positive NLE has been observed with ligand of low optical purity.[34] Reactions were conducted in the presence of 1 mol% of nickel(II) acetylacetonate, [Ni(acac)$_2$], and 20 mol% of chiral ligand to give a catalytic system for the addition of Et_2Zn to chalcone. A nonlinear relationship between the *ee* of the ligand and the *ee* of the product was observed, but the amplification is only noticeable when using ligand of low enantiomeric purity. With higher optical purities the *ee* of the ligand and the *ee* of the product became comparable (Scheme 8).



L* (Ar = Ph, %*ee*)	Product (% yield)	Product (%*ee*)
10	61	44
12	74	48
32	77	66
54	81	74
74	77	80
92	77	82
98	75	82

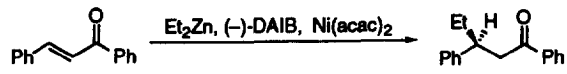
Scheme 8.

In addition, it was observed that the *ee* of the product was also dependent on the metal/ligand ratio and increases with the amount of ligand, up to 86% *ee* using 30 mol% of chiral ligand (Ar=Ph) having 92% *ee*. Remarkably, the amplification is also stronger at higher catalyst concentration. Thus the best enantioselectivity was reached using 4 mol% of Ni(acac)$_2$ and 40 mol% of chiral ligand with 16% *ee*, while lower enantioselectivities were obtained with the same ligand and a lower concentration of catalyst. Again the departure from linearity was rationalized assuming that the active catalytic species is derived from a less stable homochiral complex, whereas the *meso* (*R*),(*S*) complex is less reactive.

In a related work, chiral Ni(II)–amino alcohol complexes catalyzed the enantioselective conjugate addition of Et_2Zn to chalcones.[35] Catalysts were prepared *in situ* from Ni(acac)$_2$ and chiral amino alcohols such as (−)-DAIB. When the latter was employed with varying degrees of *ee*, a positive NLE was observed (Scheme 9).

Nevertheless, the positive effect was found by using (−)-DAIB with low *ee* while for *ee*s >50% a decrease in the *ee* of the product became visible. Remarkably, the nonlinear relationship was also dependent on the ligand-to-nickel ratio. Thus, the data depicted in Scheme 9 were collected when the amount of ligand was kept constant (16 mol%) and 1 mol% of Ni(acac)$_2$ was used. Higher amounts of Ni(acac)$_2$ resulted in lower *ee*s of product.

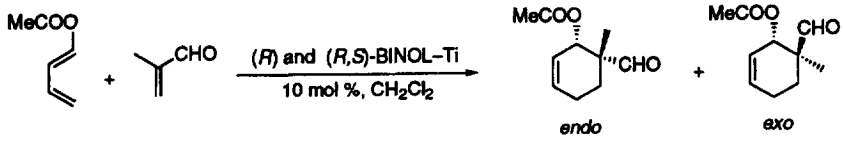
Despite the intrinsic interest of cycloadditions, few examples of NLEs have been reported for this kind of reactions. The first case was described by Iwasawa *et al.* in the Diels–Alder reaction of isoprene with a heterocyclic methyl ester catalyzed by a chiral titanium complex.[36] The latter, generated from Ti(*O*-^{i}Pr)$_2$Cl$_2$ and a tartrate-based 1,4-diol, was characterized by NMR spectrocopy.



(–)-DAIB (%*ee*)	Product (%*ee*)
12.5	21
25	34
37.5	45
50	50
75	62
100	72

Scheme 9.

A binaphthol–titanium complex also catalyzes asymmetric Diels–Alder cycloadditions.[37] In following their previous accomplishments on enantioselective carbonyl-ene reactions,[23,26] Mikami and coworkers prepared the (*R*)-BINOL–Ti complex in the presence of 4 Å-MS, which was further utilized to catalyze the Diels–Alder reaction of 5-hydroxynaphthoquinone (juglone) with butadienyl acetate. Although the reaction was completely *endo*-selective, the adduct was obtained in only 9% *ee*. Under the same conditions the parent naphthoquinone gave the cycloadduct in 85% *ee*. This indicates that the free hydroxyl group of juglone is responsible for the low *ee* presumably because of the specific complexation to the titanium atom. Such a binding is facilitated by 4 Å-MS (a Na^+-zeolite) releasing NaCl after the binding of BINOL–$TiCl_2$ and juglone. Accordingly, a complex was made from MS-free BINOL–$TiCl_2$ and then used in the cycloaddition. The resulting adduct was now obtained in high yield and high optical yield (76–96% *ee*) thus evidencing the dramatic effect of MS. The MS-free complex shows also an amplifying effect for the hetero-Diels–Alder reaction of different alkoxybutadienes with methacrolein (Scheme 10).



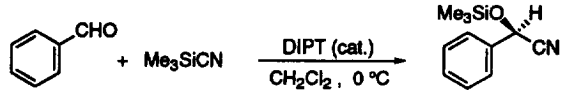
Catalyst (% *ee*)	*endo* : *exo*	*endo* (% *ee*)
33	99:1	50
50	99:1	74
68	99:1	80
100	99:1	94

Scheme 10.

The positive NLE becomes evident only when the catalyst is prepared by mixing (*R*)-BINOL and racemic BINOL as depicted in Scheme 10. Kinetic studies also demonstrated that the reaction rate with (*R*)-BINOL is approximately five times greater than that of the racemic mixture under the same conditions. On the contrary, a linear, even slightly negative, relationship was found when the chiral catalyst was prepared by mixing different amounts of (*R*)- and (*S*)-BINOL. This proves again the distinctive character of racemates affording an oligomeric distribution in which the more stable and hence less reactive dimer will be prevalent.

Optically active cyanohydrins have been obtained by asymmetric silylcyanation of aromatic aldehydes with trimethylsilyl cyanide using a modified Sharpless catalyst consisting of $Ti(O\text{-}^iPr)_4$ and chiral diisopropyl tartrate [L-(+)-DIPT].[38,39] The reaction can be achieved either in a stoichiometric

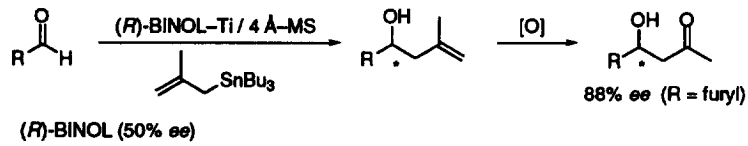
or catalytic fashion and both the enantioselectivity and reaction yield are much influenced by the solvent, the concentration of the reactants, and the nature of the catalyst. A freeze-dried catalyst with a 1:1.1 molar ratio of Ti(*O*-^{i}Pr)$_4$ and L-(+)-DIPT gave the optimum results for yield and *ee*. A positive departure from linearity could be observed in the addition of trimethylsilyl cyanide to benzaldehyde with partially resolved DIPT, albeit enriched in (*R*)-enantiomer (Scheme 11).



DIPT (% *ee*)	Product (% yield)	Product (% *ee*)
15	65	27
25	78	50
50	83	70

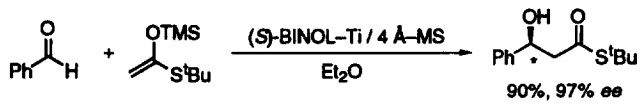
Scheme 11.

An NLE has been described in the enantioselective Lewis acid-catalyzed reaction of methallylstannane with aldehydes using chiral Lewis acid catalysts derived from Ti(*O*-^{i}Pr)$_4$ and (*R*)-BINOL.[40] This procedure enables the preparation of optically active allyl alcohols which, by further ozonolysis of the terminal vinyl moiety, are converted into products equivalent to those of an asymmetric crossed aldol reaction (Scheme 12). Using (*R*)-BINOL of 50% *ee* at −20°C, the starting aldehyde (R=furyl) was converted into a product of 88% *ee*. However, the linearity was maintained using a similar titanium catalyst at 23°C in dichloromethane solution.



Scheme 12.

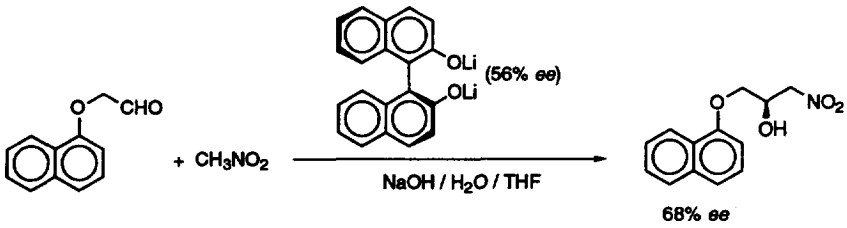
An enantioselective Mukaiyama aldol reaction has been reported using (*S*)-BINOL and Ti(*O*-^{i}Pr)$_4$ as the catalytic system.[41] There is a pronounced influence of several factors such as the solvent, catalyst concentration, and temperature which affect largely both reaction rate and enantioselectivity. Optimal conditions were established using ether as solvent at −20°C and 20 mol% of catalyst consisting of (*S*)-BINOL and Ti(*O*-^{i}Pr)$_4$ with a 1:1 stoichiometry and in the presence of 4 Å-MS (Scheme 13). The unusual concentration effects (higher amounts of catalyst decreased yields as well as diminishing the *ee*) might be eventually related to an NLE in which oligomeric species, rather than a unique monomeric structure, appear to be involved.



Scheme 13.

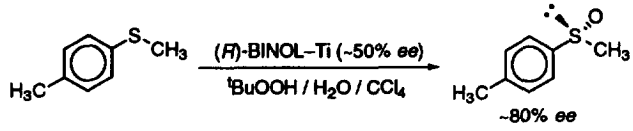
NLEs were also observed in the catalytic asymmetric nitroaldol reaction catalyzed by an optically active lanthanum complex.[42] This complex is easily generated from the inexpensive $LaCl_3 \cdot 7H_2O$, dilithium (*S*)-binaphthoxide, NaO-*t*-Bu, and a small amount of water in THF solution. The presence of water is critical and under anhydrous conditions the reaction did not proceed even at reflux. The chiral lanthanum complex prepared from enantiomerically pure (*S*)-BINOL gave the (*R*)-adduct between α-

naphthoxyacetaldehyde and nitromethane in 91% *ee*. When (*S*)-BINOL with an enantiomeric excess of 56% was used, the (*R*)-adduct was obtained with 68% *ee* (Scheme 14).



Scheme 14.

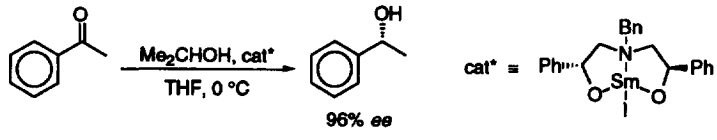
In connection with the preliminary NLE observed by Kagan *et al.* on the catalytic asymmetric oxidation of sulfides to sulfoxides,[11] Japanese authors have devised an efficient enantioselective oxidation of sulfides with *tert*-butyl hydroperoxide catalyzed by a titanium complex generated from a titanium alkoxide and (*R*)-BINOL.[43] The presence of water was essential not only to maintain the catalytic activity of the complex for a longer time but also to achieve the highest enantioselectivity. The process exhibits a notable positive NLE, the *ee* of methyl 4-tolyl sulfoxide exceeds the *ee* of the (*R*)-BINOL employed over a wide range (Scheme 15).



Scheme 15.

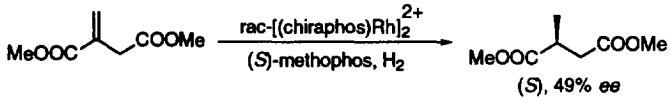
This result contrasts with the negative NLE observed previously using a modified Sharpless reagent consisting of Ti(*O*-^{i}Pr)$_4$/(+)-DET/CH_2Cl_2-H_2O,[11] indicating that both catalytic systems should be structurally different. From a mechanistic viewpoint, the authors also determined that the *ee* of the sulfoxide was dependent on the reaction time rather than the reaction temperature. The 50% *ee* obtained at the initial reaction stage improved over time to 96% *ee*. This means that a subsequent kinetic resolution of the sulfoxide may follow the asymmetric oxidation, thus further enhancing the *ee* of the product.

The Meerwein–Ponndorf–Verley reduction of aryl methyl ketones can be conducted with extreme enantioselectivity by a chiral 1:1 samarium–ligand complex.[44] The latter was prepared from a (*R*,*R*)-ligand which was deprotonated with *n*-BuLi and then complexed with SmI_3 in THF. The soluble catalyst at 5 mol% catalyzes the reduction of ketones to give (*R*)-alcohols in high yields and up to 97% *ee*. The best hydride source was provided by 2-propanol and other lanthanides (NdI_3, YI_3, and TbI_3) gave optimum selectivities as well. When an enantiomerically pure ligand was employed, the product was formed in 96% *ee* (Scheme 16), while an enantioenriched ligand (80% *ee*) gave also the product in the same (95% *ee*) optical yield. This amplifying effect is consistent with a scenario in which homo and heterodimers are formed allowing (*R*,*R*)-SmI complex to kinetically dominate the reaction.



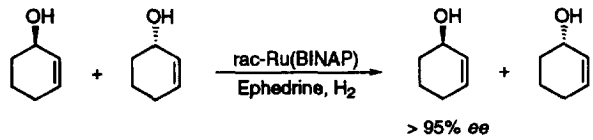
Scheme 16.

Although the synthetic results exposed above clearly illustrate the effectivity and economy of using partially resolved ligands, the most promising perspectives, particularly on an industrial scale, emerge from cases in which optically active compounds can be formed with racemic catalysts. The term *chiral poisoning* has been coined for this effect where a chiral substance deactivates one enantiomer of the racemic catalyst.[45–49] Thus it is possible to perform an asymmetric hydrogenation starting from racemic diphosphines by kinetic resolution with a small amount of a chiral dehydrophenylalanine derivative.[46] Maruoka and Yamamoto utilized a small amount of 3-bromocamphor to resolve a racemic organoaluminum complex, which further catalyzed a hetero-Diels–Alder cycloaddition giving a product with 82% *ee*.[47] A nonlinear amplification has also been demonstrated by Faller and Parr in the asymmetric hydrogenation of dimethyl itaconate to give optically active dimethyl methylsuccinate.[48] Hydrogenation using an enantiomerically pure (*R*,*R*)-chiraphos rhodium complex affords the (*S*)-methylsuccinate in >98% *ee*. Then authors reasoned that an economical and convenient strategy might involve the utilization of racemic $[(\text{chiraphos})\text{Rh}]_2^{2+}$ in the presence of a chiral poison which would preferentially sequester one enantiomer of the catalyst, so that there could be no longer equal amounts of $[(R,R)\text{-chiraphos}]\text{Rh}^+$ and $[(S,S)\text{-chiraphos}]\text{Rh}^+$ in solution. Accordingly, they selected (*S*)-methophos, readily available from methionine, as the chiral poison. Hydrogenation with (*S*)-methophos alone gives dimethyl methylsuccinate in less than 2% *ee*. Obviously racemic $[(\text{chiraphos})\text{Rh}]_2^{2+}$ gives the product in 0% *ee*. However, hydrogenation with *rac*-$[(\text{chiraphos})\text{Rh}]_2^{2+}$ plus (*S*)-methophos produces dimethyl methylsuccinate in 49% *ee*, thus enhancing dramatically the enantioselectivity (Scheme 17).



Scheme 17.

Similarly, (1*R*,2*S*)-ephedrine, a chiral amino alcohol readily available in enantiomerically pure form and in low cost, is an effective poison in the kinetic resolution of allylic alcohols using racemic BINAP instead of the expensive (*R*)-BINAP.[49] Thus (*R*)-2-cyclohexenol can be obtained in >95% *ee* using a racemic BINAP–Ru catalyst with (1*R*,2*S*)-ephedrine (Scheme 18).

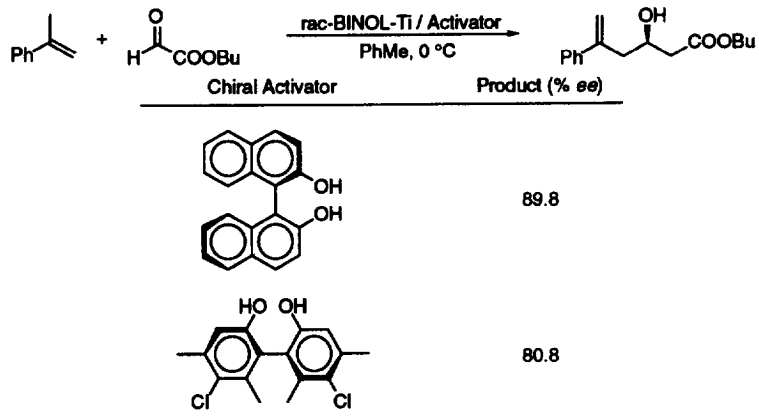


Scheme 18.

When pure (*R*)-BINAP is used, (*S*)-2-cyclohexenol is obtained in >95% *ee*. This indicates that (*R*)-BINAP–Ru catalyst hydrogenates (*R*)-2-cyclohexenol much faster than its (*S*)-enantiomer. With ephedrine, the (*R*)-2-cyclohexenol is obtained with high enantioselectivity and the poison is therefore deactivating the (*R*)-BINAP–Ru enantiomer of the racemate.

An elegant asymmetric synthesis by *enantiomer-selective activation* of racemic catalysts has recently been devised by Mikami and Matsukawa for carbonyl-ene reactions.[50] This concept is however opposite to asymmetric catalysis with a chiral poison or deactivator, since the chiral activator selectively, or preferentially, activates one enantiomer of the racemic catalyst. The activating strategy usually proceeds much faster and yields higher *ee*s of the products than that of chiral poisoning.

A catalytic system consisting of *rac*-BINOL and $\text{Ti}(O\text{-}^i\text{Pr})_4$ and an additional catalytic amount of (*R*)-BINOL or (*R*)-5,5′-dichloro-4,4′,6,6′-tetramethylbiphenol (5-chloro-BIPOL) as chiral activators, can be utilized for the enantioselective carbonyl-ene reaction with glyoxylate to give (*R*)-ene products in high *ee* (Scheme 19).



Scheme 19.

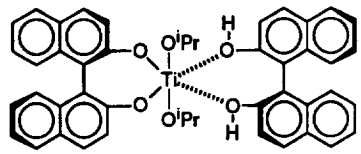
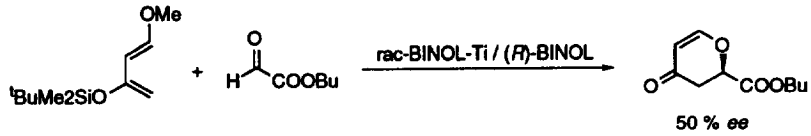


Figure 4.

It should be noted that the addition of (*S*)-BINOL resulted in lower chemical and optical yields. Interestingly, racemic BINOL can also be used as an activator for the (*R*)-BINOL–Ti catalyst, giving an enhanced level of enantioselectivity (96% *ee*). NMR spectra analyses suggest a molecular assembly of monomeric and hexacoordinated (*R*),(*R*) complexes (Figure 4).

A further exemplification of the great advantage of this strategy is provided by a Diels–Alder reaction with glyoxylate (Scheme 20).[50] An enantiomerically pure BINOL–Ti catalyst gave only 5% *ee* of the product, while starting from *rac*-BINOL–Ti and adding just 0.5 mol% of (*R*)-BINOL the *ee* increased to 50%, a relevant NLE.



Scheme 20.

The aforementioned situations of selective activation/deactivation can be rationalized in terms of the so-called '*reservoir effect*', occurring when diastereoisomeric complexes are formed inside the catalytic cycle or at its periphery.[12] Starting from one mole of a partially resolved chiral ligand, having ee_{aux}, it is possible the formation of catalytically active species and inactive complexes not involved in the catalytic cycle. We denote α the fraction of the latter complexes and ee_{res} the enantiomeric excess of these unproductive species. This means that a part of the *ee* is stored in a reservoir, and this effect modifies the *ee* of the ligand available to form the active catalyst. In other words, the ee_{aux} will be transformed into an effective *ee* (ee_{eff}). A simple equation relates these parameters:[12]

$$ee_{eff} = (ee_{aux} - \alpha ee_{res})/(1 - \alpha) \quad (6)$$

where $(1-\alpha)$ obviously indicates the molar fraction of catalytically active species. Graphical plots of ee_{eff} versus ee_{aux} give rise to straight lines of different slopes for a range between α=0.0 and α=1.0.

Equation 6 clearly establishes that enhancements of *ee* (NLEs) will be possible for some combinations of ee_{res} and α.

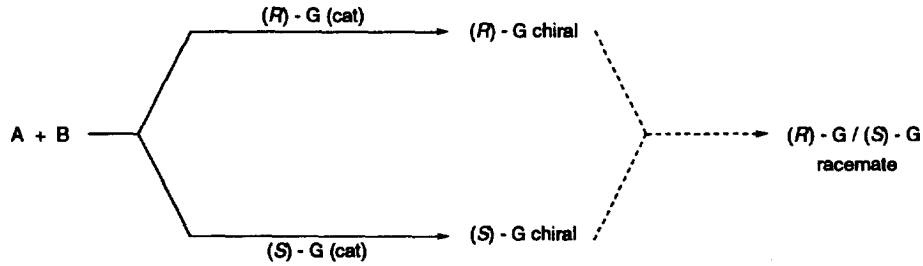
Although hard to predict, the reservoir effect will occur by formation of aggregates, such as dimers or oligomers, and thus low aggregates will behave usually as the catalytic species whereas higher order or polymeric species will remain inactive in solution. In connection with the preceding discussion, a way in which a racemic mixture can be stored is the production of a heterochiral dimer (a *meso* compound), thermodynamically stable and less active that the homochiral dimers. In the presence of a chiral substance, an *in situ* kinetic resolution will afford inactive species which are not directly involved in the catalysis, thereby changing the *ee* of the remaining ligand engaged in the catalytic cycle (chiral poisoning).

3. Chiral autocatalysis

The latest release and one of the most challenging and exciting endeavors in asymmetric reactions is chiral autocatalysis, i.e. the product itself catalyzes its own asymmetric synthesis.[51] In an asymmetric autocatalytic reaction the structures of the chiral catalyst and the product are the same, so that the reaction does not require the removal of the chiral catalyst from the product. These processes are obviously susceptible to NLEs since an optically active product with a very low *ee* can further produce molecules with high *ee*, and it is quite plausible to anticipate that such transformations could be relevant in the prebiotic era on Earth.

The first question to be addressed concerns the appropriate use of the term autocatalysis. This does not mean, neither is it equivalent to, self-replication in which a molecule acting as a template drives its own formation.[52] In many cases, there is not a true autocatalysis (*vide infra*), although the product can affect the stereochemical outcome of a preexisting catalysis.

In the early fifties, Frank developed a theoretical model for what he called *spontaneous asymmetric synthesis*.[53] In this hypothesis Frank described how two achiral substances react to form a couple of enantiomers, (*R*) and (*S*), each of which catalyzes its own formation (Scheme 21). This does not mean that the autocatalytic process can create optically active molecules from achiral substances (a distinctive point with absolute asymmetric synthesis). In fact, unless a kinetic resolution may exist the autocatalysis will lead to a racemic mixture. Nonetheless, if the reaction catalyzed by the (*R*)-enantiomer proceeds faster than that of the (*S*)-enantiomer, the overall effect is the reduction of the catalytic activity of the latter and new molecules of the (*R*)-enantiomer would be rapidly formed. This accounts for a large enantioselection, even though the desired enantiomer would have initially a low *ee*. More importantly, a small amount of a chiral substance could generate a large quantity of product in an autocatalytic reaction.



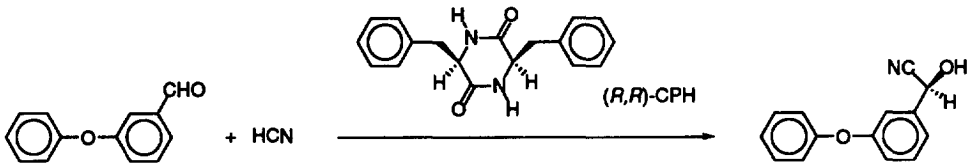
Scheme 21.

Despite these promising considerations, the implications and potentiality of chiral autocatalysis as a means of propagation of optical activity were recognized much later.[54] The first experimental observations that suggest any kind of interaction between the product and ML_n species to generate new catalysts were found by Alberts and Wynberg in the asymmetric addition of organolithium compounds to benzaldehyde,[55] where chiral lithium alcoholates presumably catalyze the reaction affecting the

stereochemical course. Again, the result appears to be consistent with the formation of aggregates of the product with some of the reactants. It is known that alkali metal compounds in solution can form aggregates whose reactivities differ from those of the parent reagents.[56] An interesting case was also found during the Birch-type reduction of enantiomerically pure or racemic camphor with potassium in liquid ammonia.[57] The ratio of the corresponding alcohols as well as their *ee*s could not be linearly related to the *ee* of the camphor. This may be due to the formation of discrete potassium-ketyl aggregates.

Since the product itself is not operating as a catalyst, Alberts and Wynberg called the process *enantioselective autoinduction*. Since then, the term autoinduction has been utilized in the literature in order to avoid the confusion with autocatalysis in which the product itself is the catalytic species. However, the way in which the product induces the formation of a new catalyst, thereby enhancing the *ee* of the product is unclear, and in the absence of mechanistic evidences the term autoinduction may certainly be speculative.

An outstanding example of autoinduction was reported by Danda and coworkers in the asymmetric hydrocyanation of 3-phenoxybenzaldehyde catalyzed by cyclodipeptides, such as cyclo[(*R*)-phenylalanyl-(*R*)-histidyl], (*R*,*R*)-CPH.[58a] This chiral dipeptide alone had little catalytic activity initially and only a prolonged reaction time increased the *ee* of the resulting (*S*)-cyanohydrin (Scheme 22). Moreover, when a small amount of the latter was present prior to the addition of HCN, the *ee* of the product was formed with an almost constant 96%. This demonstrates that the (*S*)-product is not a catalyst but its interaction with the catalyst ensures a high enantiomeric excess.



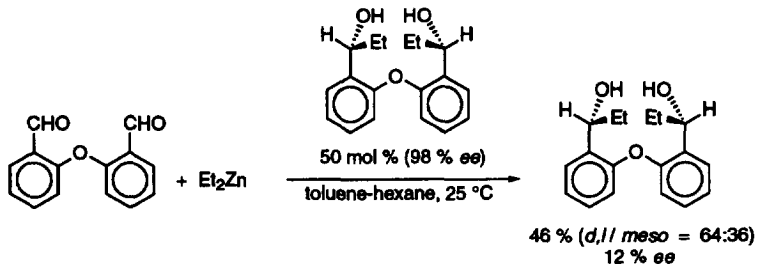
Scheme 22.

Interestingly, the initial presence of a small amount of (*S*)-cyanohydrin led to the formation of this product in a high *ee* (82–97% *ee*) and regardless of the optical purity of the (*R*,*R*)-catalyst. Thus a poorly resolved catalyst in only 2% *ee* but in the presence of a small amount of (*S*)-cyanohydrin (4.4 mol%, 92% *ee*) led to the formation of the latter in 81.6% *ee*. The same (*R*,*R*)-catalyst (2% *ee*) but with the other (*R*)-enantiomer (4.4 mol%, 84.9% *ee*) gave the (*R*)-cyanohydrin in 74% *ee*. Seemingly, the absolute configuration of the product is not determined by the configuration of the catalyst but rather by that of the added product.[58b] Authors suggest that an (*R*,*R*)-catalyst/(*S*)-cyanohydrin complex works as the active catalyst and they were also able to isolate a gel containing both compounds from the reaction mixture.[58a]

While the latter assumption might be tentative, other authors tried to elucidate the mechanism of the asymmetric hydrocyanation of aldehydes with cyclopeptides by structural and computational studies.[59] The study concludes that a heterogeneous hydrogen-bonded polymer of CPH is probably the reactive form of the catalyst where two imidazole bases function as the reactive sites. The attractiveness of such simple cyclodipeptides is that they mimic the structurally complex oxynitrilase enzymes, and both of them catalyze the hydrocyanation of aldehydes with almost the same enantioselectivity. Small quantities of alcohol or other protic compounds (e.g. the cyanohydrin) disrupt partially the hydrogen bonds, thereby modifying the secondary structure of peptides but still preserving the polymeric arrangement. The partial breaking down of the cyclopeptide polymer would therefore result in oligomers or dimers, partially soluble in the reaction medium, acting as the true catalysts that improve the enantioselectivity. This is also supported by the fact that large amounts of a protic solvent, methanol, diminish the enantioselection and no autoinduction is observed. Although the additive for

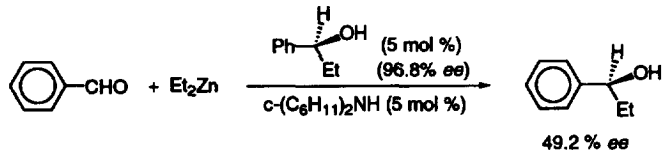
the autoinduction phenomenum may not necessarily be chiral, up to now it is unclear why the addition of a cyanohydrin with an opposite configuration to that of the product does not affect the autoinduction.

Soai and his group reported the first asymmetric autocatalytic reaction between 3-pyridinecarboxaldehyde and dialkylzincs via the zinc alkoxides of chiral 3-pyridylalkyl alcohols as autocatalysts.[60] Similarly, this Japanese group has also described an asymmetric autocatalytic synthesis of chiral diols by reaction of dialdehydes with Et_2Zn and where zinc alkoxides of chiral diols served as asymmetric autocatalysts.[61] Thus, Et_2Zn was added to a mixture of starting dialdehyde and chiral (*S,S*)-diol in 98% *ee*. HPLC analysis revealed the formation of a mixture of (*S,S*)-, (*R,R*)-, and the *meso* diols. Taking into account the amount of the recovered catalyst, the newly formed diol was obtained in 46% yield as a 64:36 *d,l/meso* mixture and with 12% *ee* (Scheme 23). This result proves again the effectiveness of the autocatalytic system even though the induced *ee*s are relatively low. Since the prevalent enantiomer has the same configuration as that of the chiral diol, it is plausible to suppose that the intermediate chiral bis(alkylzinc alkoxides), generated *in situ*, work as autocatalysts. With the same methodology, a further autocatalytic synthesis of a chiral ferrocenyl alcohol has been reported.[62]



Scheme 23.

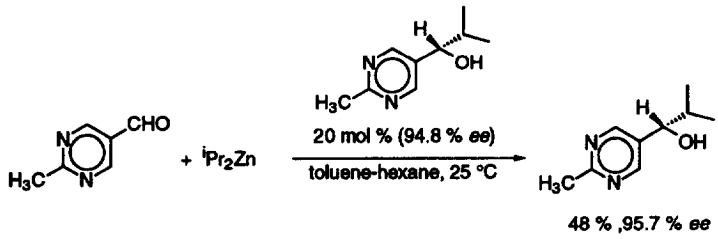
A related autocatalysis is the asymmetric synthesis of optically active alcohols, where these substances function as chiral catalysts together with a catalytic amount of amine.[63] Thus, (*R*)-1-phenylpropan-1-ol catalyzes its own synthesis in the addition of benzaldehyde to Et_2Zn (Scheme 24). When (*R*)-1-phenylpropan-1-ol is used alone, both the chemical yield and enantioselectivity were low (39.5% yield and 14.3% *ee*), while the presence of a catalytic amount of amine (primary, secondary, or tertiary) increased yields and *ee*s. The greatest effect was observed with dicyclohexylamine affording the (*R*)-alcohol in 49.2% *ee*.



Scheme 24.

The above examples exhibit a pronounced negative nonlinearity (the product has a much lower *ee* than that of the catalyst), which could at first sight suggest that an autocatalytic reaction is not convenient for achieving asymmetric transformations. Very recently, however, Frank's dream became true when it was showed that a (*S*)-pyrimidyl alcohol (20 mol%, 94.8% *ee*) catalyzed its synthesis, via the reaction between the corresponding pyrimidyl aldehyde and diisopropylzinc, leading to the product in 48% yield and 95.7% *ee* (Scheme 25).[64,65]

Likewise, Frank's predictions on the amplifying effect of autocatalysis were demonstrated as well.[64] Starting from 20 mol% of the (*S*)-alcohol and only in 2% *ee*, the first autocatalysis gave the alcohol in 10% *ee*. Subsequent reaction cycles increased the *ee* from 10 through 57 to 81, and finally to 88%



Scheme 25.

ee. Thus, an exponential increase is reached after only four reaction cycles. As mentioned previously, the chiral intermediates should be the corresponding zinc alkoxides, albeit the exact structure, either dimeric or oligomeric, must be elucidated to understand the mechanism and in the search of conclusions for future research.

4. Conclusions

Nonlinear effects in asymmetric reactions, once considered an exotic feature, are an extremely clever and thought-provoking approach to these important transformations. An in-depth study of these processes reveals that, in the presence of chiral ligands, the preferential enantiomer recognition may be attributed to the differential reactivity and stability of homo- and heterochiral catalytic complexes formed by ligand exchange. The existence of an NLE may reveal mechanistic insights concerning the nature of catalytic species involved. The overall amplifying effect can be harnessed as an efficient and economical process that enables the utilization of partially resolved ligands, even as a racemic mixture. Likewise, a negative effect can be important when using poorly resolved ligands as a trace of the undesired enantiomer will lower the enantioselectivity of the catalyst. There could also be cases in which optically pure auxiliaries lead to homochiral catalysts giving a racemic mixture whereas heterochiral complexes are enantioselective.

Autocatalysis has also emerged as a phenomenom that accounts for the unexpected selectivities of certain enantio- and diastereoselective reactions where the nature of the catalyst can be modified by the product. Remarkably, autocatalysis constitutes an example of atom economy reactions where all the reactants and catalysts are converted into products without further byproducts. At this stage a crucial question is unavoidable: could nonlinear effects be important in the prebiotic age for enantiomer differentiation? Further refinements will doubtless be a stimulus for future research and contribute to a better understanding of asymmetric reactions.

5. Note added in proof

After the acceptance of this account, some important papers on NLEs have been published. Thus, Mikami and his group have reported on tandem and two-directional asymmetric catalysis of the Mukaiyama aldol reaction.[66] Likewise, Matsukawa and Mikami have emphasized the importance of chiral activators in the asymmetric catalytic Diels–Alder reactions by titanium(IV) complexes.[67] Soai and coworkers have described an asymmetric autocatalytic reaction in which a chiral zinc alkoxide self-replicates by the addition of 5-carbamoylpyridine-3-carbaldehyde and diisopropylzinc.[68] A very recent communication describes the application of asymmetric amplification through achiral auxiliaries for the synthesis of 2-deoxy- or 4-deoxy-carbohydrates.[69]

Acknowledgements

We are grateful to Professor Laurence D. Barron for his valuable comments and suggestions on chiral autocatalysis and the effects of falsely chiral influences. Thanks are also due to Professors Koichi Mikami and Bryant E. Rossiter who have kindly provided us copies of their works. The authors

also acknowledge the DGICYT (PB95-0259-CO2-01) and the Junta de Extremadura-Fondo Social Europeo (EIA94-32) for financial support.

References

1. a) Mason, S. F. *Molecular Optical Activity and the Chiral Discriminations* Cambridge University Press, Cambridge, 1982. b) Bonner, W. A. *Top. Stereochem.* **1988**, *18*, 1–96. c) Inoue, Y. *Chem. Rev.* **1992**, *92*, 741–770.
2. a) Horeau, A. *Tetrahedron Lett.* **1969**, 3121–3124. b) Horeau, A.; Guetté, J. P. *Tetrahedron* **1974**, *30*, 1923–1931.
3. For an excellent and comprehensive survey on stereoisomer discrimination, properties of racemates and of their enantiomers: Eliel, E. L.; Wilen, S. H. *Stereochemistry of Organic Compounds* Wiley, New York, 1994, Chapter 6, pp. 153–295.
4. a) Wynberg, H.; Feringa, B. *Tetrahedron* **1976**, *32*, 2831–2834. b) Wynberg, H.; Lorand, J. P. *J. Org. Chem.* **1981**, *46*, 2538–2542. c) Okada, M.; Sumitomo, H.; Atsumi, M. *J. Am. Chem. Soc.* **1984**, *106*, 2101–2104. d) Grassi, M.; Di Silvestro, G.; Farina, M. *Tetrahedron* **1985**, *41*, 177–181.
5. a) Kabachnik, M. I.; Mastryukova, T. A.; Fedin, E. I.; Vaisberg, M. S.; Morozov, L. L.; Petrovskii, P. V.; Shipov, A. E. *Russ. Chem. Rev.* **1978**, *47*, 821–844. b) Dobashi, A.; Saito, N.; Motoyama, Y.; Hara, S. *J. Am. Chem. Soc.* **1986**, *108*, 307–308.
6. Luchinat, C.; Roelens, S. *J. Am. Chem. Soc.* **1986**, *108*, 4873–4878.
7. From now on we will use the acronym NLE to denote a nonlinear stereochemical effect. Do not confuse this term with NLO (nonlinear optical effect), which has been largely popularized and states that molecules with large hyperpolarizabilities are liable to have nonlinear optical properties.
8. There are numerous and excellent reviews on catalytic asymmetric reactions, some of them describing examples of NLEs: a) Kagan, H. B. *Bull. Soc. Chim. Fr.* **1988**, 846–853. b) Brunner, H. *Synthesis* **1988**, 645–654. c) Ojima, I.; Clos, N.; Bastos, C. *Tetrahedron* **1989**, *45*, 6901–6939. d) Noyori, R. *Chem. Soc. Rev.* **1989**, *18*, 187–208. e) Brown, J. M.; Davies, S. G. *Nature* **1989**, *342*, 631–636. f) Noyori, R.; Kitamura, M. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 49–69. g) Catalytic Asymmetric Synthesis, *Tetrahedron: Asymmetry* (Special Issue); Brown, J. M., Ed., **1991**, *2*, 481–732. h) Kagan, H. B.; Riant, O. *Chem. Rev.* **1992**, *92*, 1007–1019. i) *Catalytic Asymmetric Synthesis* Ojima, I., Ed., VCH, Weinheim, 1993. j) Noyori, R. *Asymmetric Catalysis in Organic Synthesis* Wiley, New York, 1994. k) Bolm, C. in *Advanced Asymmetric Synthesis* Stephenson, G. R., Ed., Blackie Academic and Professional, New York, 1996, pp. 9–26. l) Kagan, H. B.; Girard, C.; Guillaneux, D.; Rainford, D.; Samuel, O.; Zhang, S. Y.; Zhao, S. H. *Acta Chem. Scand.* **1996**, *50*, 345–352.
9. Takaya, H.; Ohta, T.; Sayo, N.; Kumobayashi, H.; Akutagawa, S.; Inoue, S.-I.; Kasahara, I.; Noyori, R. *J. Am. Chem. Soc.* **1987**, *109*, 1596–1597.
10. a) Rinaldi, P. L.; Naidu, M. S. R.; Conaway, W. E. *J. Org. Chem.* **1982**, *47*, 3987–3991. b) Ref. 3, Chapter 13, pp. 1057–1059. c) See also: Dagani, R. *Chem. Eng. News* **1996**, *Sept. 23*, 17–18.
11. Puchot, C.; Samuel, O.; Duñach, E.; Zhao, S.; Agami, C.; Kagan, H. B. *J. Am. Chem. Soc.* **1986**, *108*, 2353–2357.
12. Guillaneux, D.; Zhao, S.-H.; Samuel, O.; Rainford, D.; Kagan, H. B. *J. Am. Chem. Soc.* **1994**, *116*, 9430–9439.
13. Finn, M. G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1991**, *113*, 113–126.
14. Berrisford, D. J.; Bolm, C.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1059–1070.
15. For a discussion, see Ref. 3, Chapter 6, pp. 217–221.
16. Kitamura, M.; Suga, S.; Kawai, K.; Noyori, R. *J. Am. Chem. Soc.* **1986**, *108*, 6071–6072.
17. Oguni, N.; Matsuda, Y.; Kaneko, T. *J. Am. Chem. Soc.* **1988**, *110*, 7877–7878.
18. Kitamura, M.; Okada, S.; Suga, S.; Noyori, R. *J. Am. Chem. Soc.* **1989**, *111*, 4028–4036.
19. For an excellent criticism: Noyori, R. *Chem. Eng. News* **1997**, *March 31*, 4.
20. Yamakawa, M.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 6327–6335.

21. Bolm, C.; Müller, J.; Schlingloff, G.; Zehnder, M.; Neuburger, M. *J. Chem. Soc., Chem. Commun.* **1993**, 182–183.
22. Bolm, C.; Schlingloff, G.; Harms, K. *Chem. Ber.* **1992**, *125*, 1191–1203.
23. For a review on asymmetric ene reactions in organic synthesis: Mikami, K.; Shimizu, M. *Chem. Rev.* **1992**, *92*, 1021–1050.
24. Mikami, K.; Nakai, T. *J. Chem. Soc., Chem. Commun.* **1990**, 1623–1624.
25. Mikami, K.; Terada, M. *Tetrahedron* **1992**, *48*, 5671–5680.
26. Mikami, K.; Terada, M.; Narisawa, S.; Nakai, T. *Synlett* **1992**, 255–265.
27. Terada, M.; Mikami, K. *J. Chem. Soc., Chem. Commun.* **1994**, 833–834.
28. Tanaka, K.; Matsui, J.; Kawabata, Y.; Suzuki, H.; Watanabe, A. *J. Chem. Soc., Chem.Commun.* **1991**, 1632–1634.
29. a) Rossiter, B. E.; Eguchi, M.; Hernández, A. E.; Vickers, D.; Medich, J.; Marr, J.; Heninis, D. *Tetrahedron Lett.* **1991**, *32*, 3973–3976. b) For an excellent review on asymmetric conjugate additions: Rossiter, B. E.; Swingle, N. M. *Chem. Rev.* **1992**, *92*, 771–806.
30. Rossiter, B. E.; Miao, G.; Swingle, N. M.; Eguchi, M.; Hernández, A. E.; Patterson, R. G. *Tetrahedron: Asymmetry* **1992**, *3*, 231–234.
31. Rossiter, B. E.; Eguchi, M.; Miao, G.; Swingle, N. M.; Hernández, A.E.; Vickers, D.; Fluckinger, E.; Patterson, R. G.; Reddy, K. V. *Tetrahedron* **1993**, *49*, 965–986.
32. Tanaka, K.; Matsui, J.; Suzuki, H. *J. Chem. Soc., Perkin Trans. 1* **1993**, 153–157.
33. Zhou, Q.-L.; Pfaltz, A. *Tetrahedron* **1994**, *50*, 4467–4478.
34. a) Bolm, C. *Tetrahedron: Asymmetry* **1991**, *2*, 701–704. b) Bolm, C.; Zehnder, M.; Bur, D. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 205–207.
35. De Vries, A. H. M.; Jansen, J. F. G. A.; Feringa, B. L. *Tetrahedron* **1994**, *50*, 4479–4491.
36. Iwasawa, N.; Hayashi, Y.; Sakurai, H.; Narasaka, K. *Chem. Lett.* **1989**, 1581–1584.
37. Mikami, K.; Motoyama, Y.; Terada, M. *J. Am. Chem. Soc.* **1994**, *116*, 2812–2820.
38. Hayashi, M.; Matsuda, T.; Oguni, N. *J. Chem. Soc., Chem. Commun.* **1990**, 1364–1365.
39. Hayashi, M.; Matsuda, T.; Oguni, N. *J. Chem. Soc., Perkin Trans. 1* **1992**, 3135–3140.
40. Keck, G. E.; Krishnamurthy, D.; Grier, M. C. *J. Org. Chem.* **1993**, *58*, 6543–6544.
41. Keck, G. E.; Krishnamurthy, D. *J. Am. Chem. Soc.* **1995**, *117*, 2363–2364.
42. Sasai, H.; Suzuki, T.; Itoh, N.; Shibasaki, M. *Tetrahedron Lett.* **1993**, *34*, 851–854.
43. Komatsu, N.; Hashizume, M.; Sugita, T.; Uemura, S. *J. Org. Chem.* **1993**, *58*, 4529–4533.
44. Evans, D. A.; Nelson, S. G.; Gagné, M. R.; Muci, A. R. *J. Am. Chem. Soc.* **1993**, *115*, 9800–9801.
45. Alcock, N. W.; Brown, J. M.; Maddox, P. J. *J. Chem. Soc., Chem. Commun.* **1986**, 1532–1533.
46. Brown, J. M.; Maddox, P. J. *Chirality* **1991**, *3*, 345–354.
47. Maruoka, K., Yamamoto, H. *J. Am. Chem. Soc.* **1989**, *111*, 789–790.
48. Faller, J. W.; Parr, J. *J. Am. Chem. Soc.* **1993**, *115*, 804–805.
49. Faller, J. W.; Tokunaga, M. *Tetrahedron Lett.* **1993**, *34*, 7359–7362.
50. Mikami, K.; Matsukawa, S. *Nature* **1997**, *385*, 613–615.
51. For a brief survey: Bolm, C.; Bienewald, F.; Seger, A. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1657–1659.
52. a) Mason, S. F. *Chemical Evolution: Origins of the Elements, Molecules, and Living Systems* Clarendon Press, Oxford. b) Wintner, E. A.; Conn, M. M.; Rebek, Jr., J. *Acc. Chem. Res.* **1994**, *27*, 198–203.
53. Frank, F. C. *Biochim. Biophys. Acta* **1953**, *11*, 459–463.
54. a) Wynberg, H. *Chimia* **1989**, *43*, 150–152. b) See also: Soai, K.; Niwa, S. *Chem. Rev.* **1992**, *92*, 833–856.
55. a) Alberts, A. H.; Wynberg, H. *J. Am. Chem. Soc.* **1989**, *111*, 7265–7266. b) Alberts, A. H.; Wynberg, H. *J. Chem. Soc., Chem. Commun.* **1990**, 453–454.
56. Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1624–1654.
57. Rautenstrauch, V.; Mégard, P.; Bourdin, B.; Furrer, A. *J. Am. Chem. Soc.* **1992**, *114*, 1418–1428.

58. a) Danda, H.; Nishikawa, H.; Otaka, K. *J. Org. Chem.* **1991**, *56*, 6740–6741. b) Very recently it has also been demonstrated that the added cyanohydrin *does not have to be* the same as the product cyanohydrin. Thus in the conversion of cyclohexanecarboxaldehyde to its (*S*)-cyanohydrin, the addition of 8 mol% of (*S*)-benzaldehyde cyanohydrin raised the *ee* from 42% to 67%: Kogut, E. F.; Thoen, J. C.; Lipton, M. A. Abstract presented at the 213th ACS National Meeting in San Francisco; for a comment see Stinson, S. C. *Chem. Eng. News* **1997**, *April 28*, 26–27.
59. Shvo, Y.; Gal, M.; Becker, Y.; Elgavi, A. *Tetrahedron: Asymmetry* **1996**, *7*, 911–924.
60. Soai, K.; Niwa, S.; Hori, H. *J. Chem. Soc., Chem. Commun.* **1990**, 982–983.
61. Soai, K.; Hayase, T.; Shimada, C.; Isobe, K. *Tetrahedron: Asymmetry* **1994**, *5*, 789–792.
62. Soai, K.; Hayase, T.; Takai, K. *Tetrahedron: Asymmetry* **1995**, *6*, 637–638.
63. ShengJian, L.; Yaozhong, J.; Aiqiao, M.; Guishu, Y. *J. Chem. Soc., Perkin Trans. 1* **1993**, 885–886.
64. Soai, K.; Shibata, T.; Morioka, H.; Choji, K. *Nature* **1995**, *378*, 767–768.
65. Shibata, T.; Morioka, H.; Hayase, T.; Choji, K.; Soai, K. *J. Am. Chem. Soc.* **1996**, *118*, 471–472.
66. Mikami, K.; Matsukawa, S.; Nagashima, M.; Funabashi, H.; Morishima, H. *Tetrahedron Lett.* **1997**, *38*, 579–582.
67. Matsukawa, S.; Mikami, K. *Tetrahedron: Asymmetry* **1997**, *8*, 815–816.
68. Shibata, T.; Morioka, H.; Tanji, S.; Hayase, T.; Kodaka, Y.; Soai, K. *Tetrahedron Lett.* **1996**, *37*, 8783–8786.
69. Pauly, M. E.; Pringle, W. C.; Merlic, C. A. Abstract presented at the 213th ACS National Meeting in San Francisco, CA, April 13–17, 1997; Abstracts Book, #479.

(*Received in UK 30 June 1997; accepted 27 August 1997*)