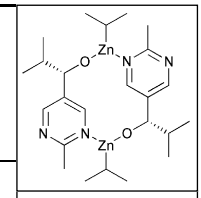
Asymmetric autocatalysis: product recruitment for the increase in the chiral environment (PRICE)



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Asymmetric catalytic reactions are possible *via* efficient transfer of the chiral environment of a reaction to the transition state. In theory any asymmetric structure may contribute to this, including the product of the reaction itself. For product influence to be significant, a nonlinear effect needs to operate, whereby one diastereomer of the product/catalyst assists the reaction, and the other does not. When these conditions are satisfied, we obtain an asymmetric autocatalytic reaction in which the enantiomeric excess of a compound (that is both product and catalyst) actually increases as the reaction iterates. It is only recently that we have seen reports of such processes. Of particular interest are Soai's reports of the alkylation of aromatic heterocycles. Such reactions, aside from their inherent interest, may offer clues into the origins of asymmetric molecular replication that predated the origin of life.

Introduction

The Nobel Prize for chemistry in 2001 was awarded to Sharpless, Knowles and Noyori for their seminal work in the area of asymmetric catalysis. Knowles first showed that it is possible to transmit stereochemical information from a chiral metal complex to an organic molecule. This fact, revolutionary at the time, is now a central feature of every undergraduate course in asymmetric synthesis. Clearly for such a process to proceed efficiently, the catalyst must accelerate the reaction, and also be chiral. The product of the reaction is chiral. It is usually assumed that the reaction product cannot catalyse the reaction itself. Is this assumption valid, or sensible? Would it not be extraordinarily useful if the product of a reaction could be recruited back into the reaction cycle, either to enhance the transmission of stereochemical information to the transition state of the reaction, or to help catalyse the reaction more efficiently (or maybe both)?

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Part 1. The road to asymmetric autocatalysis

Asymmetric autoinduction

At the outset, we need to question whether the product of a reaction may (a) catalyse that reaction, or (b) influence its stereochemical outcome. We leave the first question, that of autocatalysis, until later. The second question of whether the product of a reaction may affect the stereoselectivity of that reaction was answered in seminal work by Alberts and Wynberg as recently as 1989.[1] It was noted at the time that in asymmetric chemical processes "…the stereochemical effect *of the product* acting as a ligand in intermediate complexes has not been systematically investigated." The reaction of interest was the addition of ethyllithium to benzaldehyde (Scheme 1a). The addition of stoichiometric enantioenriched product of the reaction (**1**, deuterated to distinguish it from the alcohol product) was found to influence the enantioselectivity of the reaction. The e.e. of the product **2** was found to be 17% in favour of the same absolute configuration of the alcohol added, a fascinating result, particularly given the ubiquity of reactions such as these in the field of asymmetric synthesis.

The influence of product ligand acting to alter the stereochemical outcome of a reaction was defined as 'enantioselective autoinduction'. The product here is not a catalyst for the reaction, but is altering the stereochemical environment in the transition state of this spontaneous process. However, the same effect was also demonstrated in a catalytic process (Scheme 1b). The addition of diethylzinc to benzaldehyde is not a spontaneous reaction, but can be catalysed by orthotitinates. When such a catalyst was prepared from $TiCl_4$ and **1**, and used in the addition of diethylzinc to benzaldehyde, the product was produced in 32% e.e. again in the same absolute configuration as the Ti ligands. A similar autoinduction using titanium was reported more recently for the alkylation of aromatic dialdehydes.[2] The enantioselectivity and yield of the autoinductive addition of diethylzinc to benzaldehyde (*i.e.* in the presence of one enantiomer of the product), can be enhanced by the addition of a catalytic amount of achiral amine.[3]

Autoinduction is not limited to the alkylation of aldehydes. Wulff *et al.* reported an asymmetric autoinduction in a Diels–Alder reaction catalysed by a chiral Lewis acid complex (Scheme 2).[4] The addition of methyl acrylate to cyclopentadiene is catalysed by the aluminium complex of VAPOL ('vaulted biphenanthrol ligand,' **3**). It was found (by the analysis of aliquots of the reaction mixture) that the enantiomeric excess of the *endo* Diels–Alder product grew as the reaction progressed, *e.g.* 48% e.e. after five minutes, rising to

82% e.e. after 24 h, when the reaction was complete. The explanation suggested was that the product of the reaction (a carbonyl compound like the acrylate starting material) is coordinating to the metal centre, to form a pentacoordinate complex of the form of **6**, and that this catalytic species is more enantioselective in the Diels–Alder reaction than the initially-formed catalyst **5** in which the metal centre is not coordinated by product. This postulate was given experimental support when the reaction was run with enantiomerically pure product present at the outset (0.5 equivalents relative to the dienophile). In this case the e.e. of product was high throughout, *i.e.* the auto *induction* was not observed. A range of other, non-product, carbonyl compounds were also found to enhance the e.e. of the product in the reaction; these compounds were referred to by the authors as 'product mimics.'

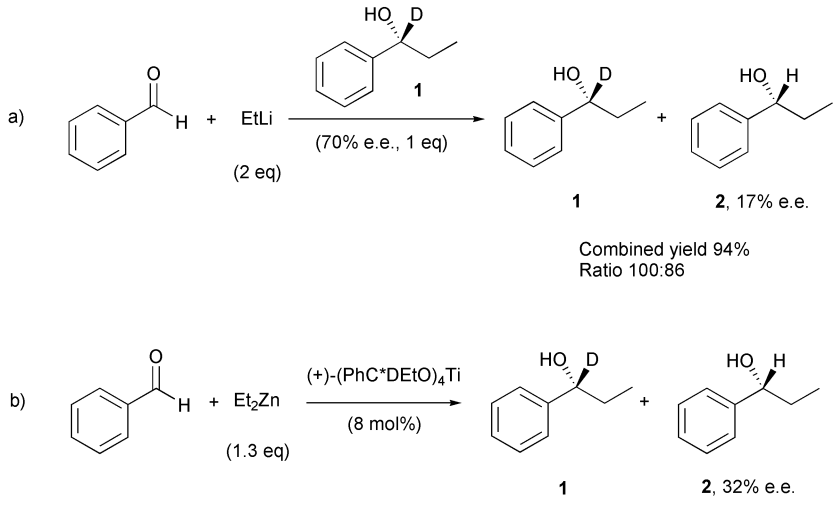
More recently a titanium complex-catalysed autoinductive aldol reaction was reported (Scheme 3),[5] widening further the range of reactions where this effect has been observed. The route to the discovery of the autoinduction in this Aldol reaction is instructive. It was known that 2-trimethylsilyloxyfuran adds to aldehydes to give the product butenolides (**7**) in good e.e. when the catalyst $BINOL_2Ti$ was employed, but in order to try to improve the yields and e.e. of the reaction, a number of other chiral activating additives were examined. It was found that the addition of a chiral alcohol additive (TADDOL in this case) markedly affected both the yield and e.e. of the reaction. This logically implies that the product of the reaction, **7**, also a chiral alcohol, should be investigated as a candidate 'additive.' Indeed, when the reaction is run with the $BINOL_2Ti$ catalyst, but in the presence of a small amount of **7**, the same product is formed quantitatively, and with the same absolute configuration. However, if the enantiomer of the product is employed as additive, then while the reaction yield remains the same, the product e.e. drops dramatically.

Influence of the product: hydrocyanation

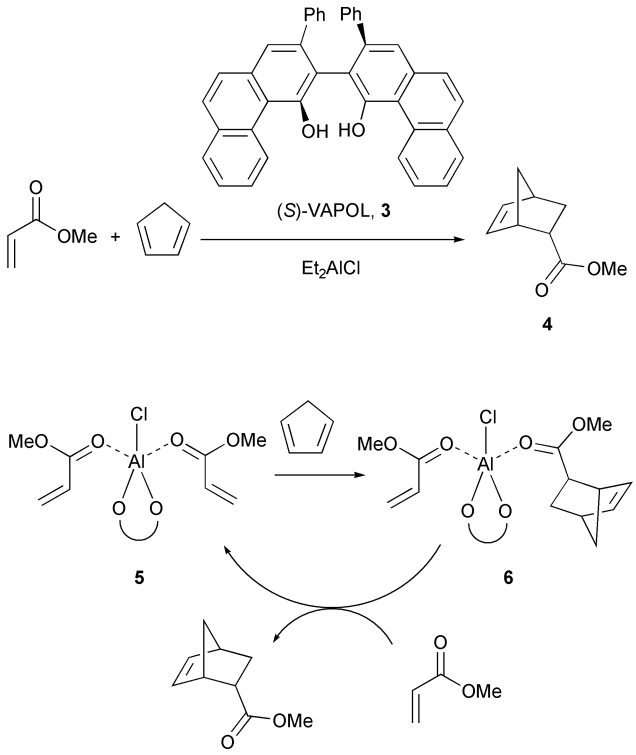
A striking demonstration of enantioselective autoinduction was reported by Danda *et al*. in 1991.[6] The reaction concerned was the asymmetric hydrocyanation of an aromatic aldehyde catalysed by a cyclic dipeptide (Scheme 4). This reaction was the first metal-free example of enantioselective autoinduction, and is perhaps striking in that it resembles the kind of process one might imagine occurring in a biochemical primordial soup. When the achiral aldehyde **8** was reacted with hydrogen cyanide in the presence of the dipeptide catalyst **9**, it was found that the e.e. of the product **10** increased with increasing conversion. If the reaction was run instead with a small amount of (*S*)-**10** (in 92% e.e.) present at the outset, then the e.e. of the product remained high (*ca.* 96%) throughout the reaction. If (*R*)-**10** was used as this initial seed instead, then the reaction proceeded similarly to the first case where only the dipeptide was the catalyst.

Clearly the (*R*,*R*)-**9**–(*S*)-**10** diastereomeric interaction is producing a species that is particularly efficient at catalysing the reaction to give (*S*)-**10**. This conclusion is supported by the observation of amplification of chirality when enantioimpure dipeptide was employed. Thus when the catalyst used was (*R*,*R*)-**9** in only 2% e.e. with an initial seed of (*S*)-**10** in 92% e.e., (*S*)-**10** was formed in 82% e.e. (at 43% conversion); in contrast when the same reaction was run without any initial seed of product, (*S*)-**10** was formed in only 3% e.e., and indeed the reaction only proceeded to 4% conversion in the same time. The product on its own (**10** without **9**) is not an active catalyst, *i.e.* this is not an autocatalytic reaction (where **10** alone would be sufficient to catalyse the reaction). It was shown that the dipeptide forms a (*R*,*R*)–(*S*,*S*) dimer that is catalytically inactive, but which is able to dissociate in the presence of (*S*)-**10** to give the super-catalyst (*R*,*R*)-**9**–(*S*)-**10**. This was supported by the isolation of a catalytically active gel from a preparation of racemic **10** and enantiopure (*R*,*R*)-**9** containing a ratio of 93 : 7 (*S*)-**10** : (R)-**10**. The dipeptide is preferentially sequestering one enantiomer of the product for the formation of the super-catalyst. When this gel was employed as the catalyst in the hydrocyanation of **8**, the product (*S*)-(**10**) was formed with 97% e.e. Of course conversely the enantiomeric catalyst (*S*,*S*)-**9** can associate with (*R*)-**10** to generate a similarly effective catalyst for the production of (*R*)-**10**; thus addition of either product enantiomer is the deciding factor in which enantiomer is preferentially produced when near-racemic dipeptide is used. This is therefore a very pronounced case where the product of a reaction is influencing the course of that reaction.

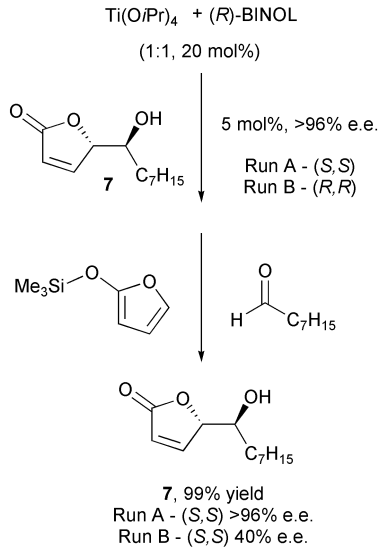
The mechanism of this reaction has been the focus of some interest. The catalytically active gels isolated by Danda *et al*. have been the subject of further investigation since the method of preparation of the catalyst is important to the efficiency of the process.[7] Efficient hydrocyanation is achieved when the dipeptide is prepared in heterogeneous form. Unfortunately the active catalyst also exhibits low crystallinity. Clearly this makes the issue of the mechanistic details of the reaction less tractable. Comparison of candidate catalyst structures and transition states should ideally take into account effects of neighbouring functional groups, as well as how the dipeptide components fit together, rather than being a simpler analysis of isolated dipeptide molecules. The problem parallels that of elucidating the interactions occurring in an enzyme's active site. That a subtle interplay of intermolecular hydrogen bonding is crucial



Scheme 1 First demonstration of asymmetric autoinduction.



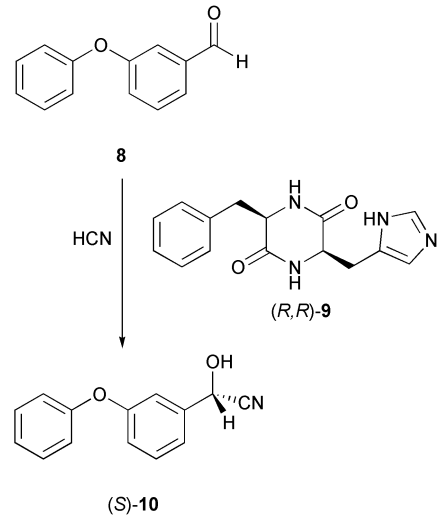
Scheme 2 Asymmetric autoinduction in the Diels–Alder reaction.



Scheme 3 Asymmetric autoinduction in an aldol reaction.

to the mechanism is supported by elimination of enantioselectivity in the hydrocyanation reaction in solvents (such as methanol) in which the dipeptide is fully soluble. The reaction is known to be second order and this is further supported by poor enantioselectivities obtained when polymer-bound enantiopure dipeptides were employed as catalysts, where hydrogen bonding between dipeptides is presumably prevented.[8] An understanding of the mechanistic details of the parent reaction, as well as the nature of the influence of the product in the production of the super-active catalyst, remains elusive. A variety of different aldehydes have been shown to display similar enantioselective autoinduction.[9] The influence of other (non-product cyanohydrin) additives to improve enantioselectivity, and the kinetics of the reaction have also been investigated.[9]

There are two crucial points to notice about the dipeptide-catalysed hydrocyanation reaction. Firstly, though this is not



Scheme 4 Asymmetric autoinduction in the dipeptide-catalysed hydrocyanation of aldehyde **8**.

strictly an autocatalytic reaction, the involvement of the product can enhance the enantioselectivity of the process. Secondly, however, it was observed that interactions between molecules in the reaction mixture assisted the desired reaction or suppressed the undesired one, and that this allowed asymmetric amplification. Could such a process operate in an autocatalytic reaction, to allow the reproduction and asymmetric amplification of a chiral molecule?

The principle of antagonism

Frank was the first to suggest that this process, whereby the desired reaction is assisted, or the undesired reaction is suppressed, is a necessary condition of asymmetric amplification in an autocatalytic reaction.[10] He referred to such a suppression process as 'antagonism.' At the time, no autocatalytic reactions were known. Frank analysed a simple autocatalytic reaction in which two enantiomers of a molecule are produced, and when a term is introduced that represents mutual inactivation or destruction, a growth (or decay) of the e.e. of one can occur exponentially.

Consider an asymmetric autocatalytic reaction (Fig. 1). The achiral starting material (**X**) may be transformed into the product of the reaction **A** or **B** (reaction cycle I), which are enantiomers. The reaction is catalysed by enantiopure **A** at the outset (but of course could also be catalysed by its enantiomer **B** were that to be present, with the same efficiency). The reaction is efficient (100% yield, 99% enantioselective, giving 98% e.e.). The result of the first round of catalysis, where 100 molecules of **X** are reacted, is 100 molecules of **A** (we should include the molecule of **A** present at the outset) and one of **B**. If we iterate this reaction, as an autocatalytic reaction would, and use the products of the first round as the catalyst for the next, then there are four possible reaction paths in reaction cycle II. We may calculate the number of molecules produced by each reaction path by considering the product of the number of molecules of substrate used (10000 in this case, to preserve the same ratio of substrate to catalyst as we had in round 1), the relative enantioselectivities of the two catalysts (99% likely to produce itself with the same absolute configuration, 1% likely to produce itself with the opposite absolute configuration), and the probability that the substrate will encounter either in the reaction mixture (given that there are 100 molecules of **A** and 1 of **B**), and the results are shown. We calculate (again including the initial catalyst present in the final tally) that we produce 9903 molecules of **A** and 198 of **B**, which is an e.e. of 96%. This degradation of e.e. is inexorable as the reaction continues to

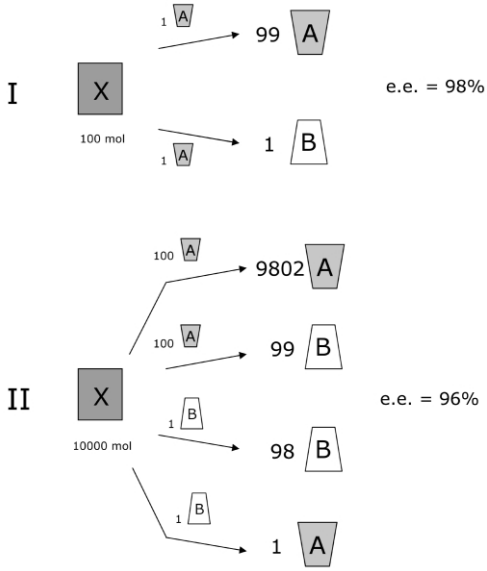


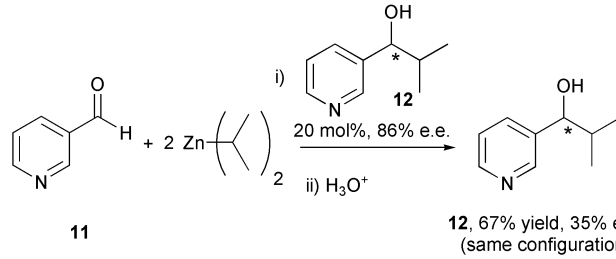
Fig. 1 Schematic of an autocatalytic reaction not exhibiting Frank's antagonistic principle. The substrate **X** is converted to enantiomeric products **A** and **B** with 99% and 1% efficiency respectively with A as catalyst in round I. In round II, the 'impurity' of **B** formed in first step results in its rapid amplification. The e.e. of product in such a reaction inexorably decreases.

iterate, with the consequence that any autocatalytic reaction of this sort goes to the racemate over time, no matter how efficient it is.

Frank showed that with the introduction of an antagonistic term this is no longer the case. *If it is possible to suppress one reaction pathway relative to the other, then the e.e. can grow rapidly as the autocatalytic reaction iterates*. Clearly what was observed in the non-autocatalytic dipeptide-catalysed hydrocyanation of benzaldehydes discussed above was a reaction displaying a similar process, where one diastereomeric complex between product and dipeptide results in a catalyst with enhanced activity, whereas the other diastereomeric interaction does not. It will be interesting to see whether such an association in non-autocatalytic cases is common (but as yet unnoticed). At the time of Frank's paper, however, no autocatalytic reaction had been observed, let alone one that demonstrated antagonism. In a fascinating taunt to the experimentalists, Frank concluded "A laboratory demonstration may not be impossible."

First demonstrations of autocatalysis

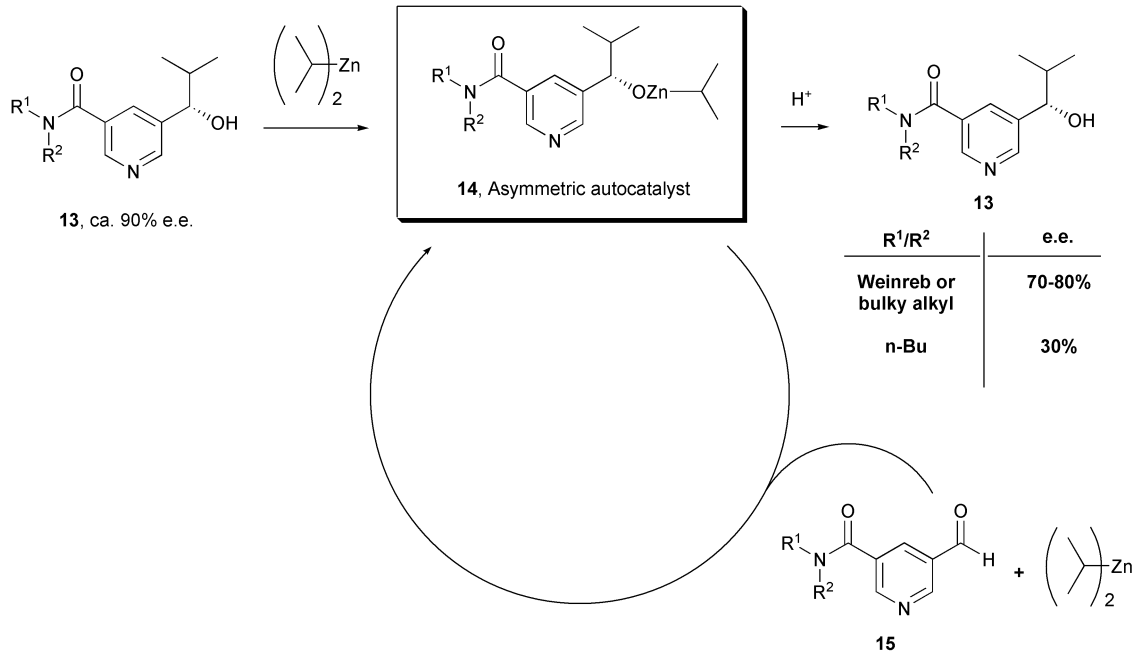
A practical demonstration of asymmetric autocatalysis in fact had to wait several decades. In 1990, Soai reported that the addition of dialkylzincs to pyridine-3-carbaldehyde (**11**) was catalysed by the product of the reaction (**12**), and that the product obtained was enriched in the same enantiomer as the catalyst (*i.e.* after one takes into account the contribution of the original catalyst in the final product mixture, Scheme 5).[11] Thus



Scheme 5 Soai's initial demonstration of an autocatalytic reaction.

when **12** was used as catalyst (20 mol%), the addition of diisopropylzinc was found to add to the aldehyde to generate the product/catalyst in 35% e.e. Slightly lower values were obtained with the corresponding ethylation and methylation reactions. While the active catalytic species was purported to be the zinc alkoxide of the product, no mechanism was given for how the enantioautoinduction occurs.

A structure–activity relationship study was reported on this reaction.[12] The 5-position of the catalyst/product ring was functionalised with a small number of carbamoyl derivatives (**13**, Scheme 6). In all cases the reactions demonstrated asymmetric autocatalysis in good to excellent yield, but the substituents on the nitrogen of the amide affected the efficiency of the asymmetric induction. Thus *i*-Pr groups and the Weinreb amide (*i.e.* R^1 = OMe, R^2 = Me) were found to be beneficial, but far less efficient were cases where the substituents were straight-chain alkyl groups. No rationale was suggested as to why this should be the case, and it is interesting to note that modifications at a site apparently so far from the site of the alkylation reaction might affect the enantioselectivity of the process so markedly. Soai also reported that the alkylations of bis(2-formylphenyl)ether[13] and of a ferrocenyl aldehyde[14] also proceeded *via* an asymmetric autocatalytic route.



Scheme 6 Effect of variation in substituents in Soai's first autocatalytic reaction.

The simplicity of these reactions is striking, however, and is a clear case of the product of the reaction acting as a chiral catalyst for its own formation. Significantly the e.e. of the product is lower than that of the catalyst employed. Such a process could never be the basis of an asymmetric autocatalytic system with amplification of chirality. Such a reaction is clearly not satisfying Frank's conditions for chirality amplification, either because the antagonistic principle is not fulfilled, or the sense of the enantioinduction is inefficient (or maybe both). Whilst the discovery of a truly asymmetric autocatalytic reaction is the key first stage towards such a goal, we need to understand what is missing from this reaction that prevents an increase in the e.e., and this requires a deeper understanding of the potential complexity of asymmetric processes. Only once we have addressed this missing component, can we return to consider the reaction mechanism itself.

Part II. Nonlinear effects

Nonlinear physical processes

It has been appreciated for many years that the physical properties of a chiral compound depend upon its enantiomeric purity. In 1969 it was shown that there existed a nonlinear relationship between optical rotation and e.e. for 2-methyl-2-ethyl succinic acid (**16**) measured in chloroform (Fig. 2).[15] It

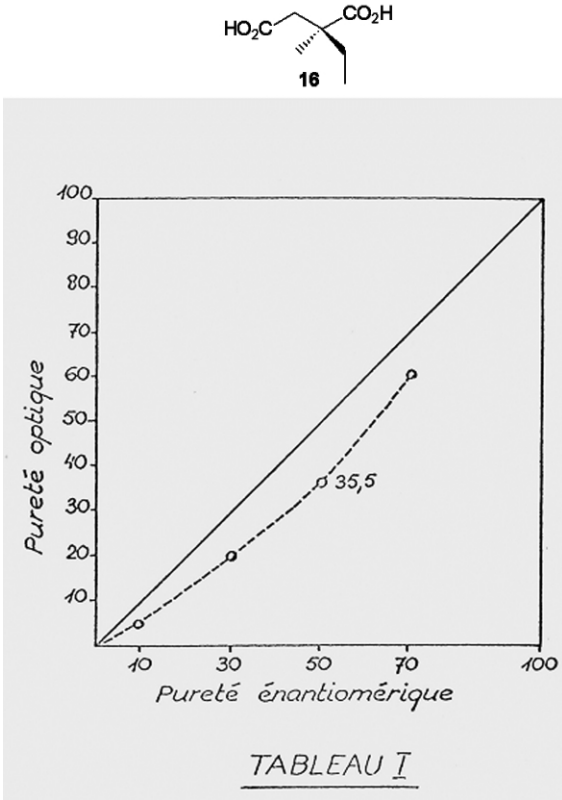
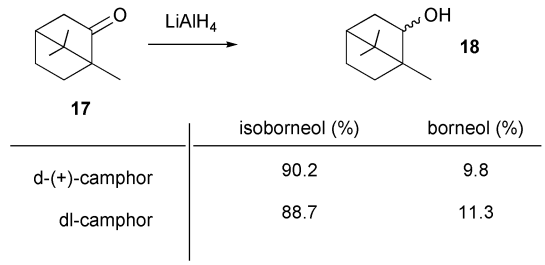


Fig. 2 Nonlinear relationship between optical rotation and e.e. for 2-methyl-2-ethyl succinic acid (straight line indicates expected linear relationship, dotted line indicates experimental values). Figure reproduced from reference 15, © 1969, with permission from Elsevier Science.

was proposed that diastereomeric interactions in solution were responsible for the deviation from linearity, and this proposal was supported by re-measuring the optical rotation in methanol, which disrupted the intermolecular hydrogen bonding, and led to the expected linear relationship. Similarly, it was shown that the NMR spectra of racemic *vs*. enantiopure dihydroquinine differed, again presumably due to hydrogen bond-mediated diastereomeric interactions.[16]

Nonlinear chemical reactions

That the chemical reactivity of a molecule could depend on its enantiomeric composition was shown by Wynberg and Feringa in 1976 (Scheme 7).[17] It was found that the reduction of



	isoborneol (%)	borneol (%)
d-(+)-camphor	90.2	9.8
dl-camphor	88.7	11.3

Scheme 7 Early demonstration of the dependence of chemical reactivity on enantiomeric excess of starting material.

camphor (**17**) gave slightly different ratios of the two possible products (borneol and isoborneol, **18**) depending on whether racemic or enantiopure camphor was employed as the starting material. The authors noted at the time: "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."

Indeed, in the later work of Alberts and Wynberg described above (Scheme 1),[1] it was noted that "In the perspective of nonlinear effects in asymmetric induction … assuming precipitation-inactivation of aggregated complexes with internal mirror planes … the optical purity of the formed product is not necessarily limited by the optical purity of the previously added product." In other words, employment of a catalyst/reagent of a certain e.e. does not have to translate linearly into the e.e. of the product of that reaction if a mechanism of suppression or activation according to the Frank model is operating. For an autocatalytic reaction to exhibit amplification of chirality, it had to be shown that a given chemical reaction could increase the e.e. of the initially-added ligand/catalyst *via* a nonlinear chemical process.

Clear empirical demonstrations of Frank's 'antagonism' were reported by Kagan in 1986.[18] Kagan observed that in a simple asymmetric reaction, a catalyst of the type Metal–Ligand (ML) would display linear enantioinduction, *i.e.* that the e.e of the catalyst–ligand complex would be linearly related to e.e. of the product of the reaction. However, in the more complex case where two ligand molecules assemble about a metal centre to generate a catalytically active dimer ML_2, that three different catalyst molecules could form, ML_RL_R, ML_SL_S, ML_RL_S, and that since the diastereomeric complexes were likely to differ in their chemical reactivity, that there is no reason to expect a linear relationship between e.e. of the catalyst and that of the product. One of the examples provided was a study of the asymmetric oxidation of sulfide **19** (Fig. 3a) using a water-modified Sharpless reagent. In this case the catalyst in question is a mixture of two equivalents of diethyl tartrate, one of water, and one of Ti(O-*i*-Pr)$_4$, producing a μ-oxotitanium dimer where two tartrate molecules are coordinated around a single titanium atom, therefore corresponding to the theoretical idea of the ML_2 system. When the oxidation reaction was performed with this catalyst containing variable enantiomeric purities of tartrate, the yields were consistently high, but a striking nonlinearity between e.e. of ligand and e.e. of product was observed in both stoichiometric and catalytic cases. Though linearity is recovered at tartrate e.e.'s above about 75%, a lower than expected e.e. of the sulfoxide is obtained when the tartrate e.e. is lower than this,

a so-called *negative nonlinear effect*. In contrast, when the Sharpless reagent was used in the asymmetric epoxidation of geraniol (**21**, Fig. 3b), a striking *positive nonlinear effect* was observed, wherein the e.e. of the epoxide was higher than that of the tartrate ligands employed in the catalyst.

Oguni reported a similar effect in the alkylation of benzaldehyde.[19] The addition of diethylzinc to benzaldehyde may be catalysed by β-aminoalcohols (Scheme 8). For example, when 2 mol% 1-piperidino-3,3-dimethyl-2-butanol (PMB, **23**) was employed in an e.e. of 10.7%, the alkylated product was obtained in 82% e.e., a very pronounced amplification. Cryoscopic molecular weight determination indicated that both enantiopure and racemic catalyst forms dimers in the presence of diethylzinc. Further, it was observed that the e.e. of the catalyst markedly affected the reaction rate, *viz*. the racemic reaction was 5.5 times slower than that with a catalyst e.e. of 60%.

Noyori reported a highly efficient method for the asymmetric alkylation of benzaldehyde in 1986.[20] Several catalysts gave good results, but in particular, (−)-3-exo-(dimethylamino)isoborneol (DAIB, **24**) gave the alkylated product in virtually quantitative yield and very high (*ca.* 98%) e.e. (Scheme 9). It was shown that the required stoichiometry of zinc to aldehyde in this reaction was 2:1. In 1989, Noyori reported a nonlinear effect for the reaction when it was carried out with enantioimpure catalyst.[21] The same reaction, run with 8 mol% catalyst in 15% e.e., gave the product in virtually the same e.e. of 95%, an extraordinary amplification of chirality.

Through an exquisitely detailed analysis of this process it was found[21] that interactions between catalyst molecules and the organometallic reagent were artificially enhancing the e.e. of the active catalytic species through the formation of a stable heterodimer (Fig. 4, (*R*)-**27** omitted for clarity). It was shown that the ligands formed diastereomeric complexes in solution as part of an orthogonal equilibrium to the reaction cycle. The homochiral and heterochiral complexes that result (**26**) differ in their thermodynamic stabilities, simply through steric congestion.[22,23] The effect of this is to artificially alter the e.e. of the active catalytic species (**25**, which is monomeric in the ligand) in the reaction mixture. Since the heterochiral ligand dimer is more stable than the homochiral, a low e.e. in ligand may translate into a high e.e. in the active catalytic species of the reaction *in situ*. This in turn generates a high e.e in the product of the catalytic reaction. This gives rise here to a very pronounced positive nonlinear effect, a potentially very useful outcome. It should be noted that the mechanism of the nonlinear effect in Noyori's reaction does not involve a dimeric catalyst, but rather a dimeric pre-catalyst.

The early Soai work (Scheme 5) is interesting from this perspective. In the Noyori reaction, the nonlinear effect relies on the chelation of a metal between oxygen and nitrogen by the catalyst. In the Soai reaction such chelation is not possible due to the geometrical constraints of the planar aromatic heterocycle, and so a mechanism similar to the Noyori mechanism cannot be invoked. However, since the product e.e. is lower than the starting material e.e., a positive nonlinear effect of any significance cannot be operating in this case. By contrast, Bolm has described a system that bears close resemblance to the Soai system, where substituted pyridine **28** (Scheme 10) was found to exhibit a strong nonlinear effect in the alkylation of benzaldehyde.[24] Careful analysis of the catalytic species concerned revealed the same hetero- *vs*. homodimeric stability differences as was seen in the Noyori example, and clearly this is possible as the pyridine nitrogen and the oxygen substituents are able to coordinate zinc to generate such dimers. An examination of the related alkylation of bromopyridine-

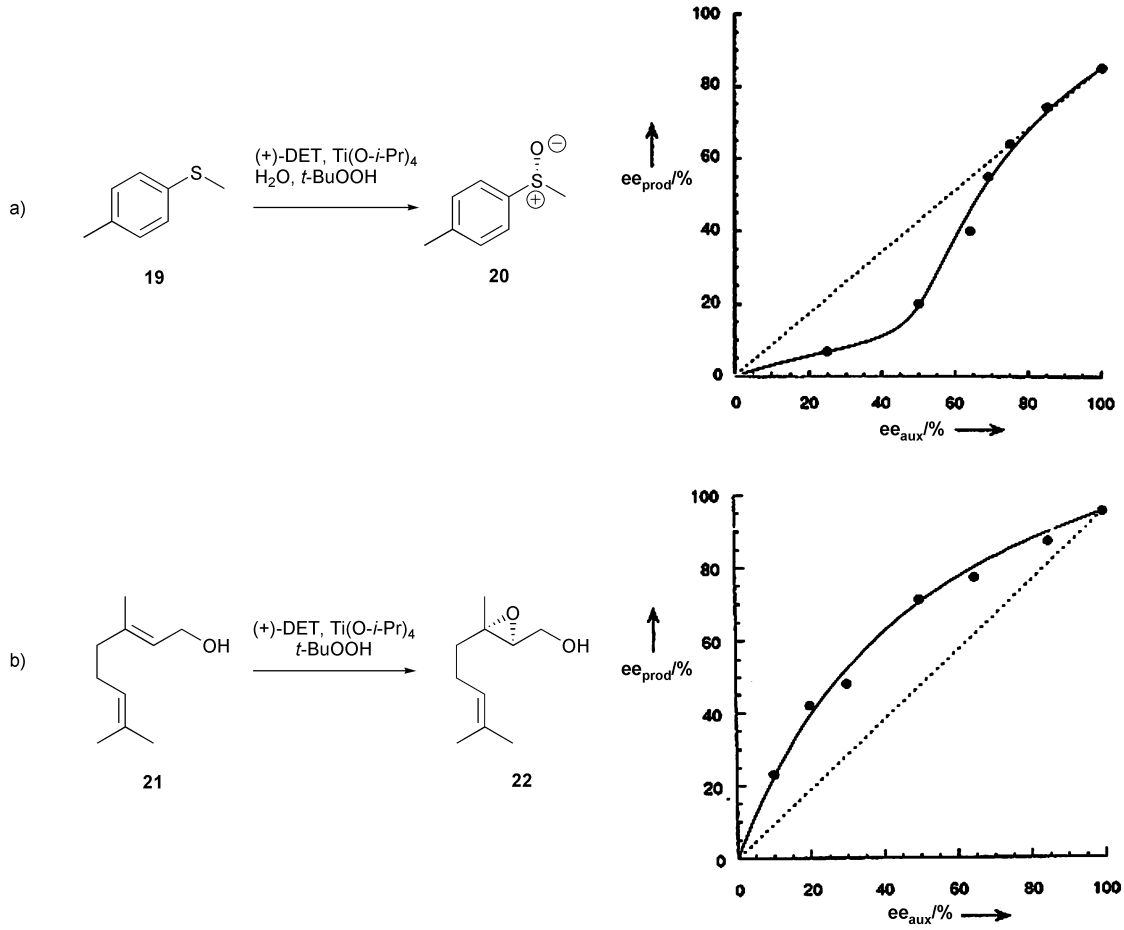
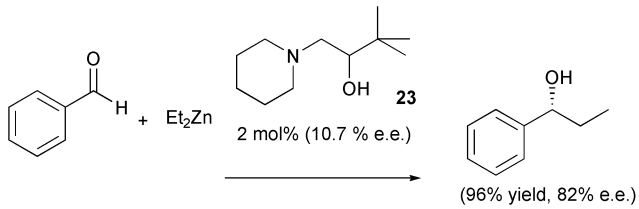
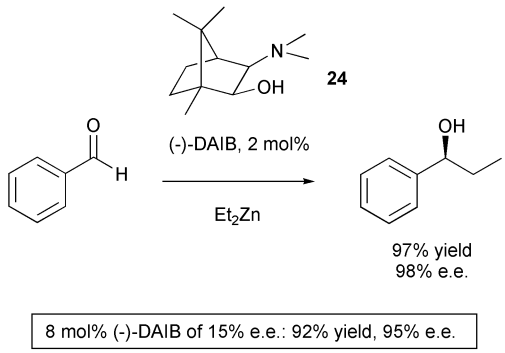


Fig. 3 Two of Kagan's early examples of nonlinear effects in asymmetric chemical reactions (figures reproduced from reference 25 © 1998 with permission from Wiley-VCH).



Scheme 8 Oguni's report of a nonlinear effect in the alkylation of benzaldehyde.



Scheme 9 Very pronounced positive nonlinear effect for the alkylation of benzaldehyde reported by Noyori.

carbaldehyde **29** revealed only very weak *autocatalytic* activity, however.

Kagan has formalised nonlinear effects mathematically. The results describe well what is now a substantial number of examples of nonlinear processes operating in a wide variety of reactions.[25]

For example, Kagan's report of the Sharpless epoxidation of geraniol (Fig. 3) may be described by the widely-applicable ML_2 model.[18] Consider a reaction involving a metallic centre (M) and two chiral ligands L_R and L_S (Scheme 11). As mentioned above, three complexes may then form: ML_RL_R, ML_SL_S and ML_RL_S in relative concentrations *x*, *y* and *z*. Let us then assume that the reaction proceeds with a final irreversible step with psuedo-first order rate constants k_{RR}, k_{SS} and k_{RS}. k_{SS} must have the same value as k_{RR}, and the *meso* species ML_RL_S produces racemic product. Kagan derived an expression for the e.e. of the product of the reaction (ee_{prod}) as a function of the e.e. of the ligand (or auxiliary) added (ee_{aux}) and the e.e. that would be obtained with enantiopure ligand (ee_o). The two novel descriptors which appear in this equation are β (which equals $z/(x + y)$ which is the relative amounts of the complexes formed), and g (which equals k_{RS}/k_{RR}, *i.e.* the relative reactivities of the hetero- and homochiral complexes). Importantly therefore, β and g become invariant features of the reaction under consideration, and their values may be found by curve fitting of the data obtained when we compare ee_{prod} with ee_{aux}.

This model implies that if no *meso* catalyst is formed (*i.e.* $\beta = 0$) or if the heterochiral and homochiral catalysts are equally reactive (*i.e.* $g = 1$) then we expect a linear relationship between the e.e. of the ligand and that of the product, which is the usual situation for an asymmetric process. In any other case we expect nonlinear behaviour. For example, if the heterochiral complex is less reactive than the homochiral one (*i.e.* $g < 1$) then the modifier $(1 + \beta)/(1 + g\beta)$ will be greater than 1 and a positive nonlinear effect will be observed. Kagan has amply demonstrated that such a model fits experimental data for the relevant reactions well.[25] Further, the model has been extended to more complex cases where the catalyst is of the form ML_n. For example, Kagan suggested the unusual shape of the curve obtained in the asymmetric oxidation of methyl-4-tolyl sulfide (above) may be described by an ML_4 model,[25] and recently the first experimental example of an ML_3 system has been reported.[26]

Blackmond has shown that such an analysis may be successfully extended towards an accurate prediction of the rates of such reactions.[27] For example, this approach was

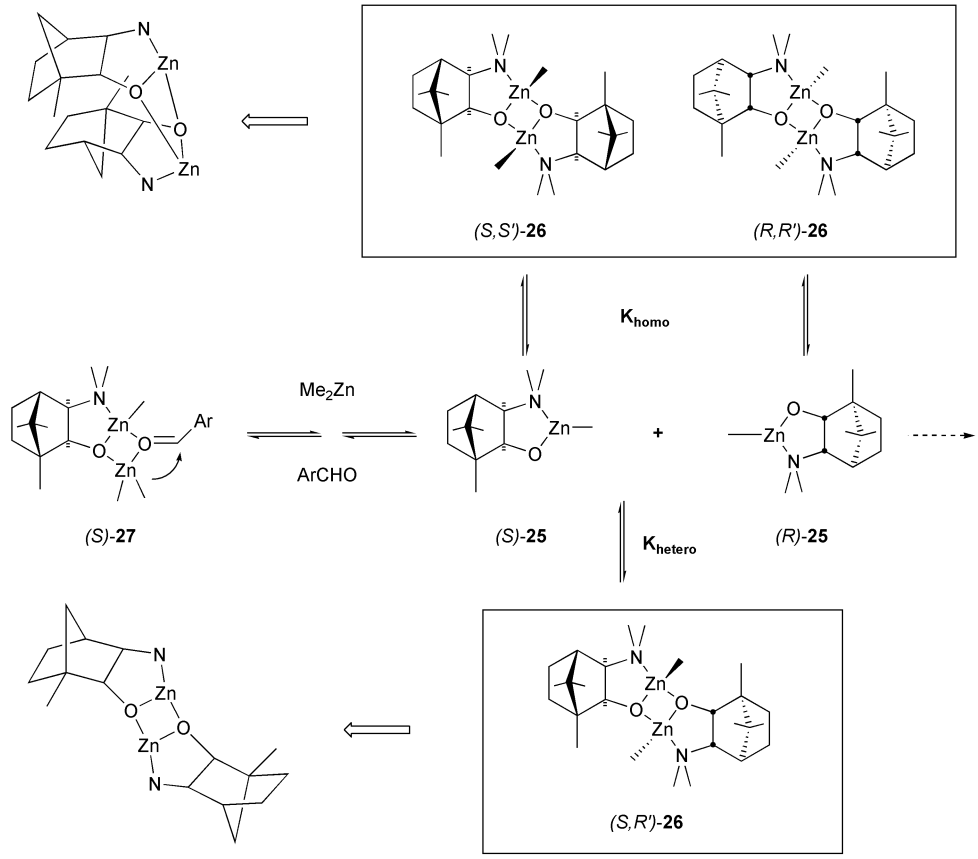
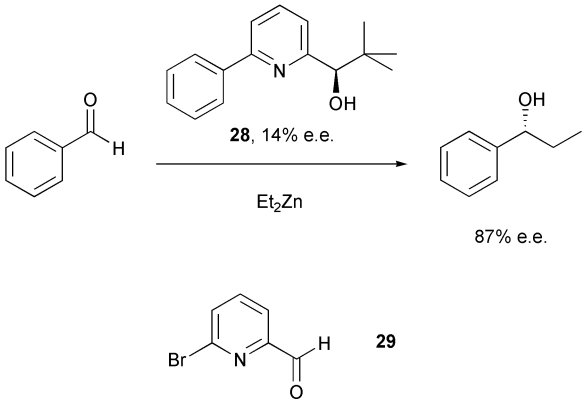
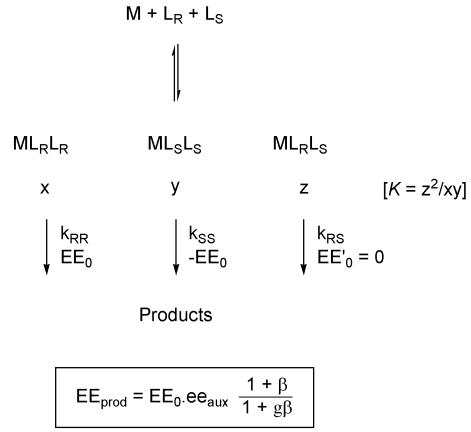


Fig. 4 Mechanism of nonlinear effect in the Noyori reaction.



Scheme 10 Nonlinear catalytic reaction reported by Bolm.



Scheme 11 Kagan's description of an ML_2 system.

applied to the asymmetric epoxidation of geraniol discussed previously.[28] An analysis of observed enantioselectivity data with the measured values of reaction rate allows for an independent confirmation of the models proposed by Kagan. A particularly striking result of such an analysis is the inevitable fall in reaction rate as ee_{aux} decreases; in other words *a positive nonlinear effect comes at the cost of a reduced reaction rate*. In the case where a heterochiral complex is less reactive than a homochiral (generating a positive nonlinear effect), the overall reaction rate (to which the *meso* complex contributes) will inevitably be lower, and this effect will grow as *g* decreases. The practical implication is then that an asymmetric autocatalytic reaction exhibiting a very strong positive nonlinear effect can be impractical for producing reaction product in a reasonable timeframe. In contrast, a reaction exhibiting a negative nonlinear effect can generate product very quickly, but of course with a lower e.e. than the initial ligand e.e.

A further model was introduced by Kagan to account for the nonlinear effect observed in the Noyori reaction (Scheme 9). This was required since in the ML_2 model described above, it is assumed that the catalyst is present simply as catalytically active dimers. In the case of the Noyori reaction, the active catalyst is monomeric in the ligand, and there is an equilibrium between dimeric and monomeric species. Kagan's 'reservoir effect' model describes this situation,[25] wherein two groups of catalytic species may be formed in a reaction: one consisting of the reservoir of inactive catalytic aggregates (such as the dimers in the Noyori case) with ee_{res}, and the other as catalytically active species with an effective enantiomeric excess ee_{eff} (Fig. 5). That we refer to the active catalyst as having an 'effective' enantiomeric excess is due to sequestration of a portion of ligand by the reservoir. We saw this previously in Fig. 4, where the thermodynamic stability of the heterochiral DAIB–Zn complex effectively removes this species from consideration,

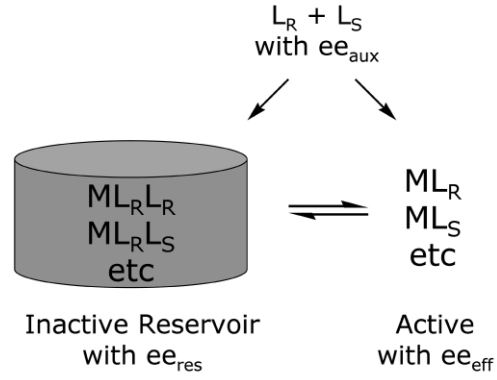


Fig. 5 Kagan's 'reservoir effect model' to explain nonlinear effects.

leaving an artificially enriched monomeric complex population. (The nonlinear effect may be viewed in this light as a convenient *in situ* purification of the enantiopure catalyst, which effectively decreases the amount of catalyst actually carrying out the reaction.) Kagan showed that such a model can be used to explain a wide variety of nonlinear effects, and that similarly useful data may be extracted.

Noyori modelled the reaction described in Fig. 4 according to this model.[29] A steady state approximation was applied to the reactive complex (**27** in Fig. 4), and the step that gives the ligand-bound product (*i.e.* the actual alkylation step) is treated as irreversible and rate-limiting. It was shown that the crucial boundary condition for nonlinearity is when $K_{homo} = 2K_{hetero}$, in that when $K_{homo} > 2K_{hetero}$, the chirality of the product is amplified. The extent of the nonlinear effect in this reaction was also found to depend on factors other than the catalyst e.e., such as the concentration of reagents. Noyori further showed that this reaction could not be analysed according to Kagan's ML_2 model where independent chiral and achiral catalytic cycles are in competition. Rather the reaction is correctly analysed by the reservoir model with a monomeric chiral catalyst complex.

The quantitative model developed by Noyori describes the reaction well during its initial stages. As product accumulates, however, the model must be modified to take account of product inhibition. The thermodynamic driving force of the reaction is the formation of a highly stable tetrameric alkoxide product.[23] The accumulation of this tetramer influences the equilibria between monomeric and dimeric complexes **25** and **26**, and the effect is to reduce the amplification of chirality at this stage. Enantioselectivity is hence also dependent on extent of conversion. Noyori showed that the model requires such a modification.[29]

That the product of this reaction can influence the non-linearity of the process was then tested experimentally. Blackmond has addressed the kinetics of a number of complex reactions by employing reaction calorimetry.[27] This simple approach allows the study of reaction rate directly by monitoring the heat flow from the reaction vessel, and the nature of the technique allows a large number of data to be acquired per reaction (typically one data point every few seconds), thereby generating a revealing account of reaction progress. To study the effect of product inhibition in the Noyori alkylation, diethylzinc was used in excess, with aliquots of benzaldehyde injected sequentially, with the reaction being catalysed by an enantiopure analogue of Noyori's DAIB ligand.[30] In other words successive reaction cycles take place in the presence of increasing quantities of reaction product. Blackmond clearly showed that by the fourth reaction cycle, the kinetics deviate from those expected if one assumes product inhibition is not operating. By incorporating a term in the rate expression to take account of both the product binding constant and the concentration of product, a rate expression was found that more accurately represented the observed data. The wider implication of this work is interesting. If one assumes that the product of the

reaction does not influence a nonlinear reaction, this can lead one to erroneous values for the equilibrium constants for formation of the inactive dimers—the incorrect model attempts to compensate for the observed data by altering these values. This would lead one to erroneous conclusions about the relative concentrations of the active monomeric catalysts, and therefore a misunderstanding of the scale of the nonlinear effect. More generally, we should be aware of the possibility of product inhibition in cases where enantioselectivity is found to be a function of conversion.

In the preceding discussion of nonlinear effects, we have observed that diastereomeric interactions between catalyst molecules can result in an effective enantiomeric excess of the active catalyst that is higher than the e.e. of the monomeric ligand added to the reaction mixture. Similar effects are possible if chiral *reagents* are employed in a reaction. In such a case, the effective enantiomeric excess of the reagent will depend upon the e.e. employed, but also on the reaction coordinate (*i.e.* conversion) since the chiral reagent is of course consumed as the reaction proceeds. The reported case was the use of the reagent *B*-chlorodiisopinocamphenylborane (Ipc_2BCl), employed in the reduction of ketone **30** to **31** (Scheme 12), which is employed in the synthesis of a medicinally important compound by an industrial group.[31] The reagent is prepared using the naturally-occurring compound α-pinene. It was found that use of α-pinene of 70% e.e. gave the product alcohol in 95% e.e., whereas use of virtually enantiopure α-pinene (99% e.e.) gave the same product in 98% e.e., only a small increase. α-Pinene in 70% e.e. is approximately 25 times cheaper than the enantiopure material, and thus is an enormous saving in cost for this process, particularly given that this is a reagent, and therefore has to be used in quantity. This benefit has to be weighed against the additional cost incurred by using a reagent that exhibits such behaviour. Blackmond has shown the reaction may be analysed with a modified ML_2 model (the ML_2 model itself cannot be applied since it does not allow for alteration in enantioselectivity with reaction coordinate).[32] Since the reducing agent in this case forms a much less reactive *meso* dimer, much of the reagent is unreactive, necessitating the use of excess reagent to allow the process to operate in a reasonable timeframe. Further, if stoichiometric reagent were used, no amplification of e.e. would occur, since once the reactive reagent has performed the reaction, the *meso* dimer will eventually react in the usual way, obliterating the nonlinear phenomenon.

A digression into the implications of nonlinear effects has been necessary to explain possible mechanisms by which Frank's principle of antagonism may be realised. We have seen that complex interactions in a reaction mixture are able to suppress the formation of one enantiomer of a reaction product, and we have seen dramatic illustrations of the amplification in e.e. that may arise. Might it be possible to couple a nonlinear effect with an autocatalytic reaction, in order to allow a molecule to replicate itself with an amplification in chirality?

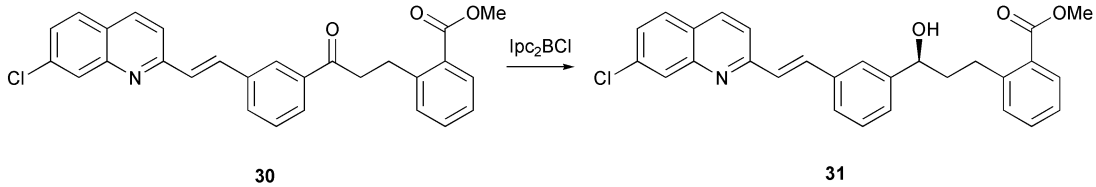
Part III. Asymmetric autocatalysis with amplification of chirality

As described above, Soai was the first to report an asymmetric autocatalytic reaction (Scheme 5), and several other systems were shown to exhibit such behaviour, as described in Section 1.[33] In all cases, though, despite the reactions being asymmetric and autocatalytic, the e.e.'s were shown to decrease, in line with an absence of Frank's antagonistic principle.

The combination of an autocatalytic reaction with a nonlinear effect was finally reported by Soai in 1995.[34] This landmark publication demonstrated for the first time an asymmetric autocatalytic reaction with amplification of chirality. The reaction concerned (Scheme 13) was similar to those previously reported by Soai. When pyrimidine-5-carbaldehyde (**34**) was treated with diisopropylzinc in the presence of a catalytic quantity of the reaction product (**32**), the reaction reproduced the product in the same absolute configuration and with an enhanced e.e. Thus an initial 5% e.e. of (*S*)-**32** generated, after reaction of the parent aldehyde with diisopropylzinc, (*S*)-**32** in 42% yield but in an enantiomeric excess of 55%, far greater than that of (*S*)-**32** used initially. It was suggested that the zinc alkoxide of the product, **33**, was the active catalytic species in the reaction (which is clearly simply formed *in situ* when the organozinc reagent is added).

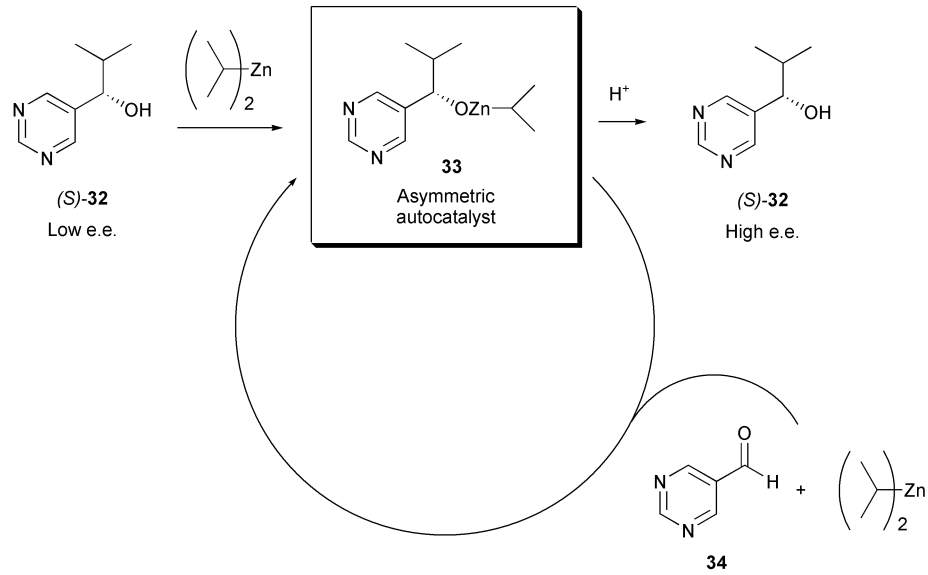
The significance of this result was spelled out by running the reaction iteratively, where the products of one reaction are used as the catalyst in the next cycle. When the reaction was performed with an initial seed of 20 mol% of **32** in only 5% e.e., and the reaction repeated three times, the e.e. of the product in the reaction mixture is seen to grow in successive steps to 39%, 76% and 85% (Fig. 6). Whilst the production of (*R*)-**32** has increased only slightly, the quantity of (*S*)-**32** has increased over four hundred-fold. The reaction also operated in the opposite configuration if (*R*)-**32** was used as the initial catalyst seed, *i.e.* the absolute configuration of the initial seed of **32** determines which enantiomer is amplified. A seed of racemic **32** generates no amplification. Since the e.e. of the reaction is not decreasing in this autocatalytic process, and in fact is seen to grow as the reaction iterates, this is the first experimental demonstration of Frank's asymmetric autocatalysis with amplification of e.e. An antagonistic mechanism, wherein either the favoured reaction is promoted or the undesired reaction is suppressed, must therefore be operating. At the time of reporting this reaction, however, Soai did not propose a mechanism of how this might be possible. We shall return to this in a moment. A synthetically attractive feature of such reactions should be noted, however, which is that the catalyst need not be separated from the product at the end of the reaction.

The same process was shown by Soai to work also with the isopropylation of the related quinoline-3-carbaldehyde (**35**), where again through a small number of iterative reaction cycles the e.e. of the product 3-quinolylalkanol could be enhanced from its initial value of 9% to 88%.[35] Interestingly an initial



Reagent e.e. (%)	Product e.e. (%)
99	98
70	95

Scheme 12 Nonlinear effect operating with a chiral reagent.



Scheme 13 Soai's landmark report of asymmetric autocatalysis with amplification of chirality.

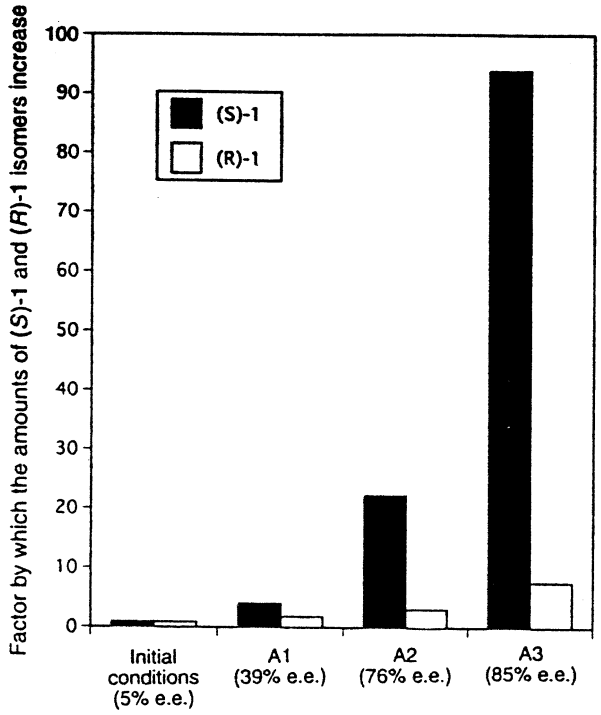
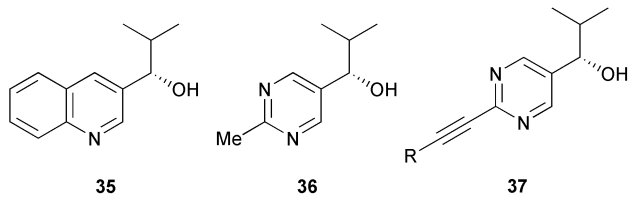


Fig. 6 The growth in enantiomeric excess as the Soai reaction iterates (reproduced from reference 34 © 1995 with permission from nature).



35 **36** **37**

report on this reaction system had used high e.e. of the product as catalyst, and had noted that there was no loss in the e.e. of the product during single reaction cycles.[36] Similarly, when the enantioselective isopropylation of pyrimidine-5-carbaldehyde used in Soai's seminal Nature paper was first reported, all reactions were run with high e.e. of autocatalyst.[37] It was shown that there was no loss in the e.e. of **32** and the related compound **36**, but the case where low e.e. is used initially was not examined. It was only when the reaction was run with low e.e. of catalyst that the extent of the amplification was spotted. This implies something quite profound about the way in which we run asymmetric reactions. In cases where a very high e.e. is reported for a standard asymmetric catalytic reaction, how do we know that the reaction is not exhibiting asymmetric autocatalysis with a nonlinear chirality amplification of this type?

Soai *et al.* optimised the yields and enantioselectivities of their alkylation reaction to exhibit 'practically perfect' asymmetric autocatalysis in the case of (2-alkynyl-5-pyrimidyl)alkanols (**37**).[38] In an initial screen of this compound class to examine the degree of asymmetric amplification it was found that variation in the R group greatly affected the amplification of e.e. in a single reaction iteration. Bulky R groups such as *tert*-butyl or trimethylsilyl, or a phenyl group gave significant amplification, whereas *n*-butyl gave lower amplification. Interestingly the use of the very bulky triisopropylsilyl (*i.e.* R = iPr$_3$Si) group gave virtually no amplification. That changes in this R group, so distant from the site of reaction (the carbonyl group), affected the enantioselectivity to such a degree, must be important clues to the reaction mechanism. The reaction with **37** (R = *tert*-butyl) was then further optimised by varying the reaction conditions. It was found that with cumene as solvent, with 1.7 equivalents of diisopropylzinc, with 99.5% e.e. of the catalyst, that the reaction could be iterated ten times with no decrease in the e.e. of the catalyst/product, and that the *tert*-butyl product could thus be replicated in this enantiopure form by a factor of 10^7.

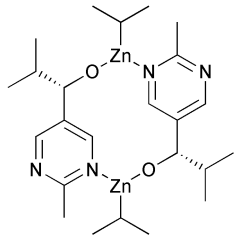
The central question, however, remains: what is the mechanism of this reaction? *How is the product influencing the reaction such that Frank's antagonistic principle operates in this autocatalytic reaction?*

Blackmond and Brown have recently provided the first answers.[39] One of the reactions reported by Soai (Scheme 13, but with methyl analogue **36**) was examined with reaction calorimetry to elucidate the reaction rate as a function of time. The rates were measured for the cases where the initial seed of catalyst is enantiopure, racemic and at 43% e.e. As expected for an autocatalytic reaction, in all cases the reaction rate rapidly increases to a maximum as the catalyst population increases, and then the rate falls off as aldehyde is consumed. Also, the reaction is fastest with enantiopure catalyst, and slowest with racemic, which is consistent with Frank's notion of antagonism suppressing the catalytic contribution of the minor enantiomer due to the presence of a nonlinear effect.

What is extraordinary about the data, however, is that the rate for the racemic catalyst is almost exactly half that of the

enantiopure case throughout the reaction. In the case of the Noyori reaction described above (Fig. 4), which was shown to follow Kagan's reservoir model, it was noted that a positive nonlinear effect would be observed when $K_{hetero} > 2K_{homo}$. The rate ratio observed by Blackmond *et al*. in the kinetic measurements of the Soai reaction, however, implies that $K_{hetero} = 2K_{homo}$ (*i.e.* that there is no preferential formation of hetero- over homochiral dimers). Yet this is the condition that implies amplification of e.e. is not possible!

Clearly, then, the reservoir model cannot be operating in this case. Blackmond *et al*. have shown that Kagan's ML_2 model, modified to account for the reaction being autocatalytic, fits the observed data for reaction e.e. as a function of conversion.[40] There are several key points that arise from this model. Firstly, the ML_2 model applies in cases where the *catalyst is a dimer*. Secondly, the data obtained for this reaction suggest that the dimer distribution is statistical, and thirdly that the heterochiral dimer is unreactive. This led the authors to propose the dimeric catalyst structure shown (**38**, (*S*,*S*)-diastereomer shown), where



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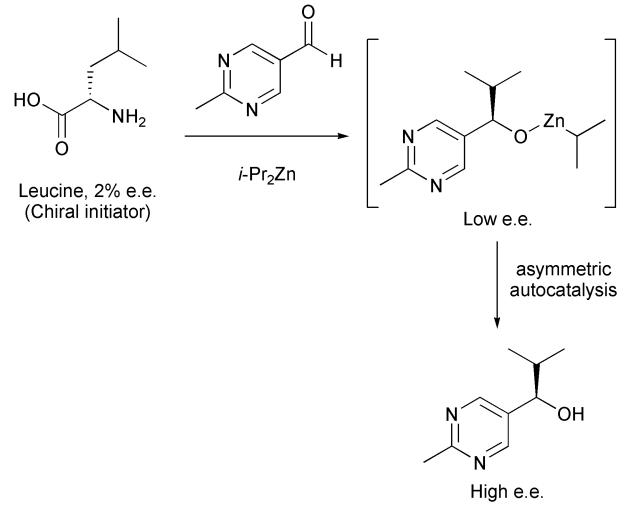
the catalyst molecules are linked head-to-tail in a bimetallic chelate. This proposed structure is also supported by preliminary NMR studies. This fascinating conclusion then leads to the question of how such a catalyst participates in the reaction. How is the substrate involved in the transition state such that (a) the enantioselectivity is high, and (b) the heterochiral dimer ((*R*,*S*)-**38**) is unreactive? The answer to this final piece of the puzzle will be of great interest to the organic chemical community.

Part IV. Concluding remarks—relevance to the origin of biochemical homochirality

This review has focused on asymmetric autocatalytic reactions. Molecular self-replication is necessarily a feature of such systems, but we have limited our discussion to asymmetric processes. There is a fascinating and rapidly growing field concerned with the study of more complex self-replicating systems, which is outside the scope of this review.[41] For example, Ghadiri has reported examples of peptide self-replication in which the product peptide catalyses the ligation of its constituent fragments,[42] and von Kiedrowski has reported the autocatalysis and cross-catalysis of hexadeoxynucleotide analogues.[43] The distinguishing feature of much of the chemistry involved with these other systems is that whilst they display autocatalysis, they do not display asymmetric autocatalysis, in the sense that no asymmetric centre is created as part of the reaction, and so the reactions do not display a growth or decline of enantiomeric excess. These reactions are crucial in understanding the processes of the self-replication of more complex life-like systems, but here we are concerned with those reactions that gave rise to pronounced asymmetry in the first place.

One of the last great questions in science is that of how life began. In the context of this review, then, I take life's origin to mean the emergence of a selfishly self-replicating chiral organic molecule, rather than an achiral or inorganic one, or a system whereby such a molecule necessarily has to oligomerise. There is a great deal of interest in how an initial stereochemical bias might have been introduced to a racemic Earth.[44,45] That meteorites such as the Murchison meteorite contain slight enantiomeric enhancements of amino acids apparently of extraterrestrial origin[46] is an interesting finding, but one that simply pushes the issue one step back, and the question of the origin of this imbalance remains.

Soai has made the connection between the asymmetric autocatalytic reactions he has reported and more biologically realistic reactions and processes. Circularly polarised light has been found to be capable of generating a small e.e. in amino acids exposed to such radiation by selective destruction of one enantiomer rather than the other.[47] This is a most interesting finding. Soai has shown that amino acids are capable of initiating his asymmetric autocatalytic reaction (in which they then take no further part) which then amplifies the e.e. of the pyrimidyl alcohol (Scheme 14).[48] Clearly this organometallic



Scheme 14 Soai's report of amino acids in low e.e. initiating an asymmetric autocatalytic reaction with amplification of chirality.

reaction is unlikely to have played a part in a very aqueous world! The demonstration acts as a proof of principle, however, in that a small chiral seed is enough to kick-start the asymmetric amplification. Interestingly, circularly polarised light has been observed to occur naturally in regions of star formation.[49] Similarly, Soai has demonstrated that these reactions can be kick-started by other chiral sources, such as quartz crystals[50] and paracyclophanes.[51]

The significance of asymmetric autocatalysis with regards a mechanism for the origin of life lies in the demonstration that an initial, small chiral imbalance (from whatever origin) is able to be amplified by a simple reaction through a nonlinear effect, and that since the reaction also happens to be autocatalytic, that a molecule can indeed replicate itself rapidly at the expense of its enantiomer. We are therefore able to verify a simple reaction that exhibits all the characteristics of an organic reaction that might have played a part in the establishment of a large chiral imbalance from an initial seeding. Indeed the pyrimidyl compounds studied by Soai have an obvious similarity to the heterocyclic rings associated with nucleic acids.

The missing piece of the puzzle is of course the identification of a realistic organic reaction exhibiting the same characteristics of asymmetric amplification. We now know a great deal about the pre-requisites for this amplification. Crucially Blackmond *et al.* have identified the dimeric catalyst at the heart of the Soai reaction. Can we observe these characteristics in a reaction producing something more biochemical-like? For this, we need to identify other reactions that are capable of asymmetric autocatalysis under more realistic conditions, in particular aqueous conditions. Perhaps a likely candidate at the outset of a

search would be a Strecker version of the Soai reaction, where an imine is the substrate and a cyanide ion the nucleophile. What is clearer, however, is that a detailed understanding of the mechanism of the Soai reaction will educate this interesting search.

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