



Scientific Background to the Nobel Prize in Chemistry 2026

NON-LINEAR EFFECTS AND AUTO CATALYSIS
IN ASYMMETRIC ORGANIC SYNTHESIS

The Nobel Committee for Chemistry

Non-linear effects and autocatalysis in asymmetric organic synthesis

*The Royal Swedish Academy of Sciences has decided to award **Henri B. Kagan** and **Kenso Soai** the Nobel Prize in Chemistry 2026, for discovering non-linear effects in asymmetric catalysis and asymmetric autocatalysis.*

Introduction

The discovery and theoretical explanation by **Henri B. Kagan** of non-linear effects (NLE) in asymmetric catalysis, one of the most important classes of transformations in organic synthesis, has shown that the enantiomeric excess (*ee*)¹ of the product can exceed that of the auxiliary used in the process, a situation that was previously unthinkable. The most powerful manifestation to date of NLE in asymmetric catalysis was discovered by **Kenso Soai**, and the reaction now bears his name: the Soai reaction. In this autocatalytic reaction, a dialkylzinc reagent is added to an aldehyde, and the product acts as the catalyst in the process. When starting from achiral reagents and in the absence of added catalysts, the product is formed in considerable *ee* in an absolute asymmetric transformation.

These discoveries have deepened our understanding of chirality and how it is generated and transmitted, with significance far beyond chemistry. As an example, the central molecules of life – amino acids and sugars – are homochiral.² They are used to build proteins and enzymes, which underpin structure and catalysis of a cell, and DNA and RNA, which are essential for containing and transferring genetic information. The uniform chirality of these building blocks is crucial for their function; without it, our current life forms could not exist.³

For this homochirality to evolve requires a pool of amino acids and sugars that is enantiomerically pure or at least has an *ee*. However, abiotic synthesis of amino acids without the influence of an external chiral force invariably results in the formation of a racemate, i.e. an equal amount of the two enantiomers,⁴ and similar arguments apply for the synthesis of sugars. Thus, understanding how biological homochirality came about starting from racemic or achiral precursors is one of the most fundamental questions in chemistry, as well as in other areas, and central to understanding prebiotic chemistry that eventually resulted in the evolution of life on Earth.

The origin of homochirality in biological systems is a conundrum that has received considerable attention. Today, the prevailing argument is that homochirality came about through a progressive process, perhaps coupled to abiotic chemical evolution, that ultimately favoured D-sugars and L-amino acids.⁵⁻¹³ Such a scenario requires an initial imbalance between enantiomers, and assuming

this scenario, the question is: what chemical processes could have been responsible for such an initial imbalance?¹⁴

The discussion thus leads to a fundamental question that is of general relevance to all of chemistry: are there any chemical mechanisms that could lead to an increase of *ee* or even to homochirality when starting from a pool of substrate that is achiral or has only a small *ee*? This fundamental question is the topic of this year's Nobel Prize in Chemistry.

In 1953, *Sir Frederick Charles Frank*, a theoretical physicist at the University of Bristol with broad research interests, proposed a mathematical model describing how homochirality can be generated from an initial minuscule imbalance between *R* and *S* enantiomers.^{15,16} The aim was to provide a model for the creation of homochirality in biological systems, but the results can be applied to all closed systems. From the introductory part of Frank's paper, it is clear that he judged the problem to be trivial, at least from a theoretical aspect.

The presumption in the Frank model "is a chemical substance which is a catalyst for its own production and an anti-catalyst for the production of its optical antimer", which boils down to three discrete criteria for such processes: (i) autocatalysis, (ii) enantioselective catalysis, and (iii) inhibition ("mutual antagonism"). Frank concluded his report by laconically noting that "A laboratory demonstration may not be impossible."

The first of the three requirements, namely autocatalysis, is a well-known phenomenon in organic chemistry.¹⁷ For example, acetic acid catalyses the hydrolysis of ethyl acetate into acetic acid and ethanol; in other words, acetic acid catalyses its own formation from ethyl acetate. In more advanced settings, it has been shown that oligonucleotides¹⁸ and peptides¹⁹ can catalyse their own formation.

The second requirement, enantioselective or asymmetric catalysis, is also well documented, and aspects of it were awarded the Nobel Prize in Chemistry in 2001 (asymmetric catalysis) and 2021 (asymmetric organocatalysis). However, neither the third requirement, mutual antagonism, nor the combination of autocatalysis and asymmetric catalysis, asymmetric autocatalysis, had been described prior to the discoveries of **Kagan** and **Soai**.

Mutual inhibition, or NLE in asymmetric catalysis, was described in 1986 by **Kagan**, who showed that the product from an asymmetric epoxidation had higher enantiomeric excess (*ee*_{prod}) than that of the catalyst (*ee*_{cat}) used for the transformation.²⁰⁻²² A mechanistic rationale for the phenomenon was also provided. Since then, NLE has become an important tool for understanding asymmetric catalysis and has been used for designing new effective asymmetric catalytic processes. Today it is a fundamental concept in organic chemistry that has expanded our appreciation of chirality.

In 1990, **Soai** showed that the addition of dialkylzinc reagents to pyridine-3-carbaldehyde in the presence of a chiral catalyst, the product, is both autocatalytic and enantioselective, but the product is obtained in lower *ee* compared to that of the catalyst (ee_{prod} 35%, ee_{cat} 86%).²³ In this experiment, two of the three criteria in the Frank model were fulfilled.

Five years later, **Soai** and colleagues reported an asymmetric autocatalytic reaction in which the product had a higher *ee* than the catalyst;^{24, 25} i.e. all three criteria in the Frank model were fulfilled. A successful experiment had demonstrated how homochirality can be created in a chemical laboratory.

It is important to stress that the Frank model is not an answer to the origin of biological homochirality. It provides one possible solution, of which there are several, to an event that occurred about 3.5–4 billion years ago and to which we will probably never have a definitive answer. Instead, the experimental validation provided by **Kagan** and **Soai** to the Frank model has deepened our fundamental understanding of how chirality is generated, transmitted and amplified in asymmetric catalysis and thus of intrinsic molecular properties that are central to organic chemistry and related disciplines.

Non-linear effects in asymmetric catalysis

For NLE, the output of a system is not directly proportional to a specific variable. Interactions between enantiomers have long been known to result in homochiral (*R*–*R* and *S*–*S* for dimers) and heterochiral (*R*–*S*, for dimers) aggregates, usually with different physical properties.

Milan Uskokovic showed that at a high concentration, the ¹H NMR spectra of racemic and enantiomerically pure dihydroquinine are not identical; he and colleagues observed doubling of some lines in the spectra when analysing non-racemic mixtures, and they ascribed the effect to diastereomeric solute-solute interactions.²⁶ Similarly, when studying the optical rotation, $[\alpha]_{\text{D}}$, of 2-ethyl-2-methylsuccinic acid, *Alain Horeau* found a deviation from the expected linear correlation between *ee* of the measured solution and the optical rotation,²⁷ and several related examples have been described in the literature.^{28, 29} The non-linearity observed in these examples relates to aggregate formations, both homochiral and heterochiral, that have different physical properties. However, it had not been shown that such interactions could affect chemical reactivity.

Hans Wynberg and *Ben Feringa* discussed the situation where an *R*-isomer reacts with a reagent to form a product compared to that of a racemate reacting with the same reagent (Fig. 1a).^{30, 31} In the first case, the *R*-isomer is surrounded by and has non-bonding interactions with other *R*-isomers, while in the second, it interacts with both *R*- and *S*-isomers. They argued that different intermolecular

non-bonding interactions are involved that could affect the activation energies for the two reactions, and thus the reaction rates, and affect the product ratios for the two cases; this was referred to as the antipodal interaction.

The antipodal effect was clearly manifested in the oxidative dimerization of tetrahydronaphthalene derivative **1** into dimer **2** (Fig. 1b). When dimerizing a racemic sample, a clear preference was evident for coupling of monomers with the same configuration compared to coupling of monomers with different configurations (73.9% *RR*, *SS* and 26.1% *RS*); this is a consequence of the enantiomeric recognition effect, which refers to what extent an isomer recognises an identical or antipodal isomer.³²

In addition, the coupling of the *S*-monomer was stereospecific, affording only the (*S,S*)-*trans* product, while in the coupling of the racemate, the (*RR,SS*)-*cis* isomer was also obtained in 7.9%. The presence of the (*RR,SS*)-*cis* isomer in the latter reaction was inferred to be the influence of the *R*-monomer on the coupling reaction of the *S*-monomer, and an example of the antipodal interaction. From this study, it was clear that diastereomeric interactions not only can affect physical properties of a system, but also can affect chemical reactivity. The same authors also noted that antipodal effects can be of significance in asymmetric synthesis for cases when (reactant)_n-metal complexes are formed.³⁰

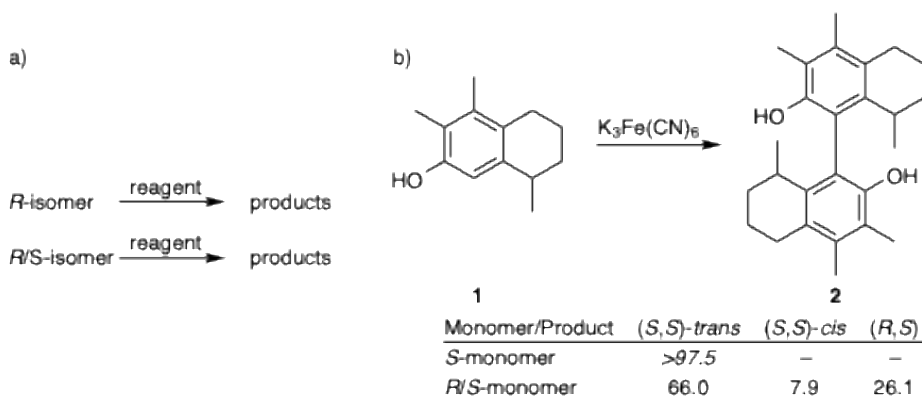


Figure 1. a) Reaction of *R*- and *R/S*-isomers with a reagent. b) Oxidative dimerization of tetrahydronaphthalene derivative **1** into dimer **2**.

Prior to 1986, it was an accepted fact that the enantiomeric excess of the product (ee_{prod}) in asymmetric catalytic reactions should correlate linearly with the ee of the ligand (ee_{ligand}), according to Eq. 1:

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

where ee_{max} is the enantiomeric excess of the product when using an enantiomerically pure reagent ($ee_{\text{ligand}} = 100\%$, Fig. 2a, line a). That year, the field was transformed by a study by **Kagan** and co-workers that redefined chemists' perception of chirality and catalysis.²⁰

They noted that the above relationship should hold true for catalysts of the type ML^* , where M is a metal and L^* a chiral ligand. To break the linear relationship between ee_{prod} and ee_{ligand} , Kagan and colleagues realised that higher order species must be involved, e.g. ML^*_2 . For such systems, the situation is more complex; it is interesting to note that **Kagan** had already contemplated this possibility in the late 1960s.²¹

The groundbreaking work described in 1986 analysed the ML^*_2 system in detail. For the case when the ligand is not enantiomerically pure ($ee_{\text{ligand}} < 100\%$), in addition to the homochiral complexes $ML_R L_R$ and $ML_S L_S$, a diastereomeric heterochiral complex $ML_R L_S$ may form. If the reactivity of the heterochiral catalyst $ML_R L_S$ is larger than that of the homochiral species, then the enantiomeric excess of the product (ee_{prod}) from such reactions will be lower than expected from a linear relationship (Eq. 1), i.e. a negative NLE³³ (–NLE, Fig. 2a, line b). Conversely, if the reactivity of the homochiral catalyst complexes is higher than that of $ML_R L_S$, then the ee_{prod} is expected to be higher than that predicted from Eq. 1 (+NLE, Fig. 2a, curve c). Thus, by invoking higher order catalyst species, a conceptual mechanism is established by which stereochemical purity of the product is higher than that of the auxiliary used to create it; i.e. the stereochemistry can be amplified.

Three asymmetric transformations, for which it was believed that more than one unit of the chiral ligand would be involved in the enantiodetermining step, were initially investigated in detail: asymmetric oxidation of a sulfide into the corresponding sulfoxide ($Ti(O\text{-}i\text{-}Pr)_4/(+)\text{-DET}/H_2O$, *t*-BuOOH, both stoichiometric and catalytic amounts of the catalyst), Sharpless epoxidation of geraniol (Fig. 2b), and the L-proline–catalysed Hajos-Parrish reaction. In none of these reactions was a linearity observed between ee_{ligand} and ee_{prod} . Instead, for the first and last reactions, a –NLE was observed, while for the Sharpless epoxidation, a +NLE was obtained; i.e. the ee_{prod} was higher than expected when using scalemic³⁴ (+)-DET (Fig. 2b).

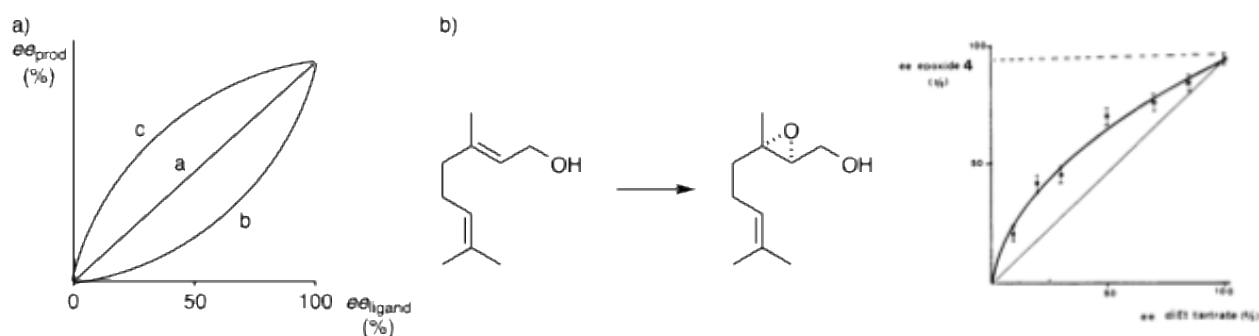


Figure 2. a) ee_{prod} as a function of ee_{ligand} . a: linear relation, b: –NLE, c: +NLE. b) Sharpless epoxidation of geraniol showing +NLE (diagram taken from ref. 20). x-axis: ee_{ligand} , y-axis: ee_{product} .

Kagan and his colleagues used a simplified reaction scheme to discuss the possible reaction outcomes (Fig. 3). When a chiral reagent is used in stoichiometric amounts and is completely consumed, there will be a linear relationship between ee_{prod} and ee_{ligand} , as in Eq. 1. For catalytic asymmetric reactions,

the reactivity of the various species must also be considered, and calculations showed that the results could be correlated with:

$$ee_{\text{prod}} = ee_{\text{max}} \times ee_{\text{ligand}} \times f \quad (2)$$

where f is a correction factor defined as:

$$f = (1 + \beta) / (1 + g\beta) \quad (3)$$

where β is the ratio between the *meso* and homochiral catalysts and g is the relative reactivity of the diastereomeric catalysts. Using Eq. 2, curves similar to those in Fig. 2a were obtained, showing, depending on the values of β and g , positive or negative NLE.

An interesting corollary was noted by the researchers for the case when the unreactive *meso*-type catalyst is formed irreversibly. For such cases, the ee_{prod} will always be equal to ee_{max} , irrespective of the value of ee_{ligand} . This work made it clear that NLE provide a simple tool to obtain insight into reaction mechanisms.

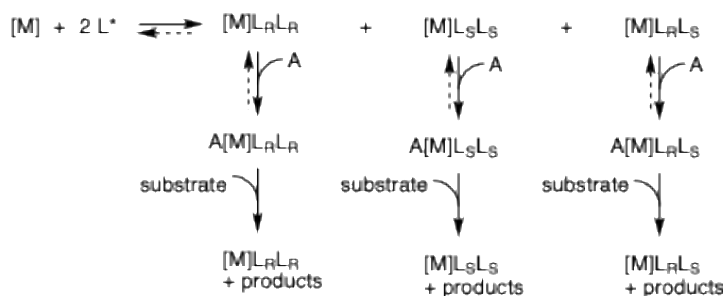


Figure 3. A simplified reaction scheme for discussing NLE. L_R , L_S = chiral ligand or chiral reagent, A = reactant, M = metallic complex.

In a subsequent study, Kagan and colleagues expanded the ML^*_2 catalyst system to include ML^*_3 and ML^*_4 complexes, as well as the reservoir effect.³⁵ The latter describes the situation where catalytically inactive ML_RL_S complexes are formed, which would alter the ratio between the remaining L_R and L_S ligands that are available for catalysis.^{36,37}

Such a reservoir system has been described in detail in work led by *Ryoji Noyori*.^{38,28,39} *Nobuki Oguni* and colleagues had shown previously that there is a strong +NLE in the asymmetric addition of diethylzinc to benzaldehyde catalysed by sterically constrained chiral tertiary β -aminoalcohols, and this stimulated research.⁴⁰ In a subsequent study, *Noyori* and co-authors found that (–)-DAIB ((–)-3-exo-(dimethylamino)isoborneol) is an excellent ligand for the reaction, showing a considerable +NLE: when ee_{ligand} is 15%, the product is obtained in ee_{prod} 98% (Fig. 4a).³⁸ Investigations of the reaction mechanism revealed that DAIB react with diethylzinc to form DAIB-ZnEt complexes, which dimerize to form three different dinuclear zinc complexes, two homochiral (**1** and **2**, Fig. 4b) and one heterochiral (**3**). However, it is the monomeric metal-ligand species (–)-**4** and (+)-**4** that are the active catalysts in the addition reaction; the dimers are reservoirs for the monomers. The NLE is then due

to the greater thermodynamic stability of dimer **3** compared to that of complexes **1** and **2**, with the result that the minor enantiomer of the scalemic DAIB ligand is not available for catalysis.

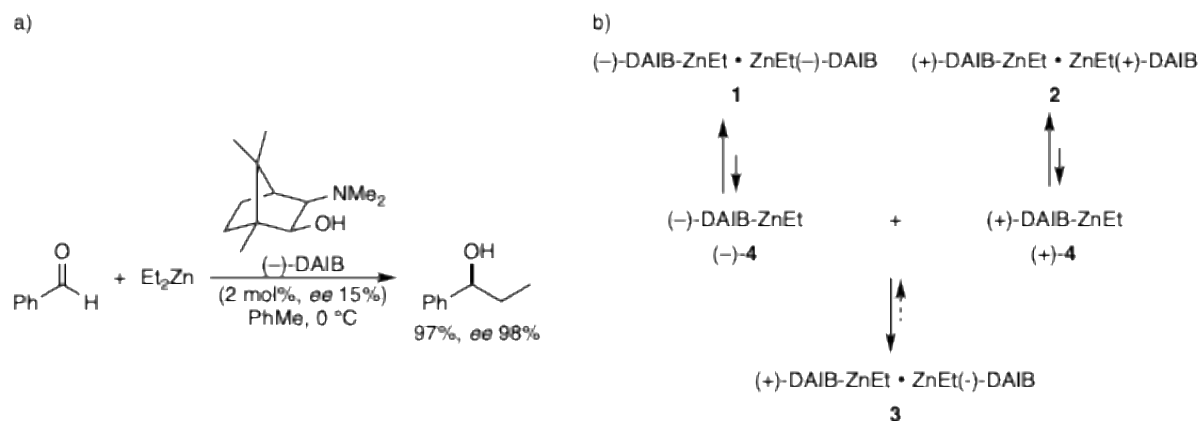


Figure 4. a) The catalytic asymmetric addition of diethylzinc to benzaldehyde in the presence of scalemic DAIB. b) Mechanistic rationale for the +NLE observed in the reaction.

Another early example of the importance of NLE for elucidating the intricate details of catalytic reaction mechanisms was provided by *Eric N. Jacobsen* and co-workers in their studies of the (salen)Cr(III)-catalysed nucleophilic ring-opening of *meso* epoxides.⁴¹ In this reaction, a significant NLE was observed, and the stereochemical outcome could not be accommodated with a monomeric catalyst species. Instead, detailed mechanistic investigations revealed a dual activation of the electrophile and nucleophile by two different metal centres in the enantio-determining step. This work established key concepts, such as cooperative catalysis, and assisted in incorporating NLE as an integrated part of mechanistic investigations.

A common denominator in the ML^*_2 system discussed by **Kagan** is that the heterochiral dimer is less reactive than the homochiral, in order to provide a +NLE or, as in the addition of diethylzinc to benzaldehyde, a non-reactive reservoir. In both cases, ee_{prod} cannot exceed ee_{max} , which follows from Eq. 2 and is also intuitively appreciated. A detailed analysis by **Kagan** of the ML^*_3 system revealed that if the heterochiral metal ligand complex ($ML_R L_R L_S$) is much more reactive than the homochiral (large g values, see Eq. 2), then the ee_{prod} can indeed exceed ee_{max} , but only at relatively high values of ee_{ligand} ; the phenomenon was referred to as a hyperpositive NLE.³⁵

Stéphane Bellemin-Laponnaz and colleagues reported the first, and as yet only, example of hyperpositive NLE in the asymmetric addition of dimethylzinc to benzaldehyde using (–)-NBE ((1*R*,2*S*)-*N*-Benzylephedrine) as a chiral ligand and affording 1-phenylethanol (Fig. 5a).^{42, 43} For this case, however, ee_{prod} reached a maximum (53%) at a low ee of the ligand (ee_{ligand} 5%) and then tapered off to reach ee_{prod} 16% when ee_{ligand} was 100%, clearly indicating a different mechanism compared to the ML^*_3 system. When using a scalemic ligand in the reaction, a precipitate was formed, which, upon hydrolysis, returned the racemic ligand. Based on a detailed mechanistic investigation, it was

proposed that both monomeric (ML^*) and dimeric catalysts ($ML^* \cdot ML^*$) are active in this reaction. At low ee_{ligand} , when a dimeric heterochiral (*meso*, $ML_R \cdot ML_S$) complex precipitates out from the reaction mixture, the concentration of the ligand will be low, and the reaction will be catalysed by a monomeric catalyst. Conversely, as the ee_{ligand} increases, the concentration of the available ligand will increase, and the reaction will be catalysed by both monomeric and dimeric catalysts. In this reaction, the monomeric catalyst is more enantioselective than the dimeric one.

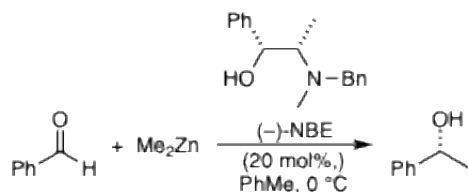


Figure 5. Asymmetric catalytic addition of dimethylzinc to benzaldehyde using (–)-NBE as chiral ligand.

In a series of studies, *Donna G. Blackmond* has expanded the mathematical models developed by **Kagan** and co-workers, showing that the reaction rate can be expressed as a function of ee_{cat} in asymmetric catalytic reactions,³⁷ and that the reaction rate and ee_{prod} may vary with conversion.^{44, 45} Her work has clearly demonstrated that the analysis of NLE can be a powerful diagnostic tool for gaining mechanistic insight and information about the active catalytic species.⁴⁴

Blackmond and colleagues also showed that asymmetric amplification can operate in asymmetric reactions without invoking ML^*_n systems. They observed an NLE in an aldol reaction catalysed by L-proline in a mixed phase system.⁴⁶ They showed that when scalemic proline is used at concentrations above the solubility limit, a racemic compound will precipitate, and the resulting eutectic composition will correspond to an ee of about 50% of the proline remaining in solution. As a consequence, in the proline-catalysed aldol reaction investigated, a +NLE was observed at $ee_{\text{proline}} < 50\%$ and a (–)-NLE at higher ee . Similar observations were also reported independently by Yujiro Hayashi.⁴⁷ In a later investigation of an organocatalytic cascade reaction, *Blackmond* and *Jordi Burés* suggested that the observed NLE could be explained by a disruption of pre-equilibria in reversible steps occurring before an irreversible product forming step, and they stressed that understanding the origin of NLE can be of importance when designing new such reactions.^{48, 49}

A fundamental aspect of the ML^*_2 -system when adding scalemic chiral ligands is that the stereoisomer in excess is used to deactivate the minor stereoisomer by forming the less reactive heterochiral dimers. An alternative strategy, referred to as chiral poisoning, is to use a readily available chiral additive to selectively deactivate one of the stereoisomers of a racemic or scalemic catalyst; such a strategy is particularly attractive when the enantiomerically pure catalyst is difficult to obtain. The concept was developed by *John W. Faller*, who applied it to a Rh-catalysed asymmetric hydrogenation reaction with racemic chiraphos⁵⁰ as a chiral ligand, and using readily available (*S*)-

methophos⁵¹ as the chiral poison, and to a Ti-racemic BINOL-catalysed asymmetric allylation reaction, in which diisopropyl D-tartrate was used as the chiral poison.^{52, 53} Instead of deactivating a specific stereoisomer of a catalyst, it can be activated by an additive, and this approach was demonstrated by *Koichi Mikami* in the Ti-racemic BINOL-catalysed glyoxalate ene reaction.⁵⁴ Similar strategies have also been used with great success by *Oliver Trapp* to enrich one stereoisomer of configurationally flexible biphenyl catalysts.⁵⁵

A striking example of the power of +NLE was provided by researchers at Merck in the synthesis of L-699,392, a leukotriene antagonist.⁵⁶⁻⁵⁸ A key step in this process is a reduction of a prochiral ketone to the corresponding secondary alcohol using stoichiometric amounts of β -chlorodiisopinocampheylborane. The reducing agent is prepared from α -pinene and chloroborane-methylsulfide complex, and when using α -pinene of 70% optical purity, the product was obtained in 95% *ee*.

Since the discovery of the NLE in asymmetric catalysis, several additional examples have been documented, indicating the generality of the phenomenon.³⁶

Asymmetric autocatalysis – the Soai reaction

In an asymmetric autocatalytic process, the chiral product serves as a catalyst for its own formation. For example, in a reaction in which an (*R*) catalyst is used, the (*R*) catalyst will be preferentially formed (Fig. 6a), and such reactions have been considered important for the formation of biological homochirality on Earth.³⁶

However, such processes are not sufficient for attaining amplification of the (*R*) isomer.^{59, 60} If the *ee* of the catalyst (*ee*_{ligand}) is 100% and it generates a product with an *ee* of 90% (*ee*_{max}), then *ee*_{prod} will be 90%. When this product is used as a catalyst, the product will be *ee*_{prod} = 81%, and this erosion of the *ee* will continue in subsequent reactions. To reach an increased ratio of the (*R*) stereoisomer, the catalyst must not only promote the formation of itself but also be "an anti-catalyst for the production of its optical antimer".¹⁵

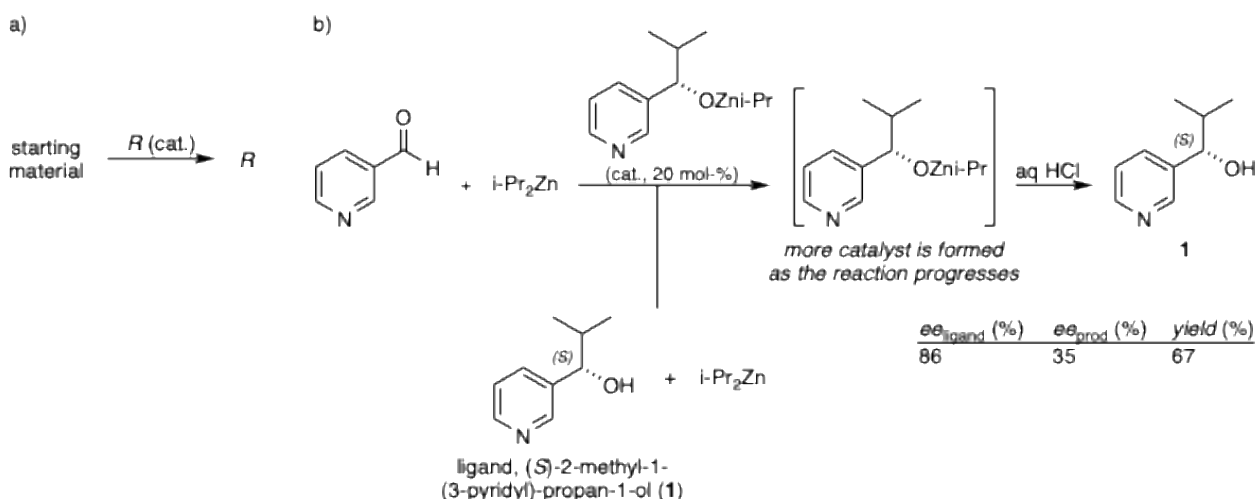


Figure 6. a) Asymmetric autocatalysis. In this example, a catalyst with (*R*) configuration produces more of itself, with a preference for the (*R*) configuration. b) Asymmetric autocatalytic addition of $i\text{-Pr}_2\text{Zn}$ to pyridine-3-carbaldehyde.

In 1989, *Albert Alberts* and *Wynberg* showed that the addition of diethylzinc to benzaldehyde, catalysed by an orthotitanate prepared from TiCl_4 and scalemic (*R*)-1-phenyl-1-propanol- d_1 (ee_{ligand} 70%), yielded (*R*)-1-phenyl-1-propanol with ee_{prod} 32%, a process that was referred to as enantioselective autoinduction.⁶¹ In this process, the chiral non-deuterated ligand is obtained as the product, but not the chiral catalyst, which is a criterion for autocatalysis. A year earlier, *Oguni* and colleagues had reported a significant +NLE in the addition of diethylzinc to benzaldehyde catalysed by scalemic sterically constrained, chiral tertiary aminoalcohols (*vide supra*),⁴⁰ and *Wynberg* speculated that this reaction, if a suitable substrate can be identified, might be a strong candidate for developing an asymmetric autocatalytic process.⁶²

Indeed, in 1990, **Soai**, who had been investigating the asymmetric addition of dialkylzinc to aromatic and aliphatic aldehydes in the presence of chiral aminoalcohols,^{63, 64} discovered that the addition of diisopropylzinc to pyridine-3-carbaldehyde, using a catalyst prepared from alcohol **1** (ee_{ligand} 86%) and $i\text{-Pr}_2\text{Zn}$, afforded alcohol **1** (ee_{prod} 35%) with the same absolute configuration as that used for preparing the catalyst (Fig. 6b).²³ A similar autocatalytic behaviour was also observed when using ferrocenyl aldehyde and an aromatic dialdehyde, together with their corresponding alcohols, as coupling partners.^{65, 66} An asymmetric autocatalytic process had indeed been discovered, and the next step was to investigate if it was possible to attain amplification of the stereochemistry, a +NLE.

Five years later, **Soai** showed that alcohol (*S*)-**4**, of only a small ee , catalyses the addition of diisopropylzinc to pyrimidine-5-carbaldehyde to promote the formation of (*S*)-**4** with an impressive +NLE (Fig. 7).²⁴ For example, when a catalyst was prepared from (*S*)-**4** with ee_{ligand} 5% and used in the addition of diisopropylzinc to pyrimidine-5-carbaldehyde (**2**), alcohol (*S*)-**4** was obtained in ee_{prod} 55% – a considerable amplification compared to the stereochemical purity of that of the original catalyst (Entry 1).²⁴ When the product from this reaction, the newly formed alcohol (*S*)-**4**, as well as

the ligand used for preparing the catalyst, was used as a catalyst for the addition of $i\text{-Pr}_2\text{Zn}$ to aldehyde **2**, the product was again obtained with an increased enantiomeric excess (ee_{prod} 87%, Entry 2). This sequence was then repeated until a plateau was reached at ee_{prod} 90% (Entries 3–5). Thus, through a series of five consecutive runs, the ee of alcohol (*S*)-**4** could be amplified from 5% to 90%.

The autocatalytic asymmetric addition of dialkylzinc to pyrimidine-5-carbaldehyde and similar derivatives with amplification of the stereochemical information is now referred to as the Soai reaction.⁶⁷⁻⁷⁰ An even more spectacular example was identified when it was shown that addition of $i\text{-Pr}_2\text{Zn}$ to aldehyde **3** using alkynyl derivate **5** of extremely low enantiomeric excess (ee_{ligand} 0.00005%) provided alcohol **5** with $ee_{\text{prod}} > 99.5\%$ after three consecutive runs (Entries 6–8), which corresponds to an amplification of the stereoisomeric ratio by a factor of 630,000.⁷¹ In addition to the pyrimidyl derivatives shown in Fig. 7, similar amplifying asymmetric autocatalysis has been shown in only a few other systems.⁷²⁻⁷⁵

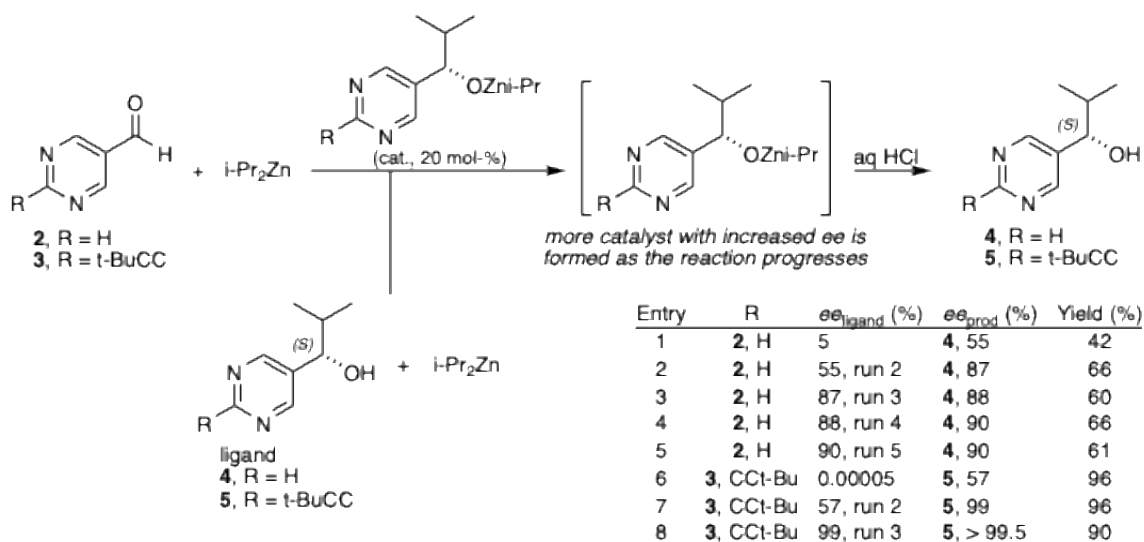


Figure 7. The Soai reaction. The amplifying asymmetric autocatalysis in the addition of $i\text{-Pr}_2\text{Zn}$ to pyrimidyl carbaldehydes.

It has also been shown that racemates of organic molecules, when treated with circular polarised light, can induce high ee_{prod} in the Soai reaction.⁷⁶ Other instances include the chirality of minerals, organic crystals and surfaces,⁷⁷ as well as isotope chirality^{78, 69}

The Soai reaction is a good platform for testing the possibility of symmetry breaking: i.e. if there can be a preferential formation of one stereoisomer without any stereochemical informational input, a process referred to as absolute asymmetric synthesis.⁷⁹ Such model systems are of considerable significance when discussing the origin of biological homochirality.⁸⁰ Such symmetry breaking had previously only been documented in spontaneous deracemization processes.⁸¹

Both **Soai** and *Daniel Singleton*, independently of each other, showed that this is indeed possible with the Soai reaction (Fig. 8, R = t-BuCC in **Soai**'s experiment,⁸² and R = Me in Singleton's^{83, 84}).⁸⁵ When diisopropylzinc is added to aldehyde **3**, the zinc alkoxide **6** is formed as a racemate. In such a molecular aggregate that is macroscopically characterised as an equal mixture of the two stereoisomers, however, there will be a statistical fluctuation over time that might favour a stochastic miniscule preference for either of the two stereoisomers, a phenomenon referred to by *Kurt Mislow* as *cryptochirality*.⁸⁶ The discriminating power, the +NLE, of the Soai reaction is then powerful enough to sense the imbalance between the stereoisomers of **6**, which will be manifested in the stereochemical outcome from the reaction. Indeed, during a series of 37 experiments, 18 resulted in a preferential formation of (*R*)-**6**, and 19 gave (*S*)-**6**, the ee_{prod} varying from 15% to 91%.⁸²

The discovery of the Soai reaction was also the first successful laboratory experiment to verify the Frank model for generation of biological homochirality in the absence of external chiral influence. It is indeed a significant accomplishment, showing that enantiomerically enriched or homochiral products can be generated from non-chiral starting materials. The Soai reaction is an important proof of concept, though it is not relevant for the emergence of biological homochirality in aqueous systems. Contemporary efforts to resolve this issue instead focus on network processes and kinetic resolution.^{7, 87}

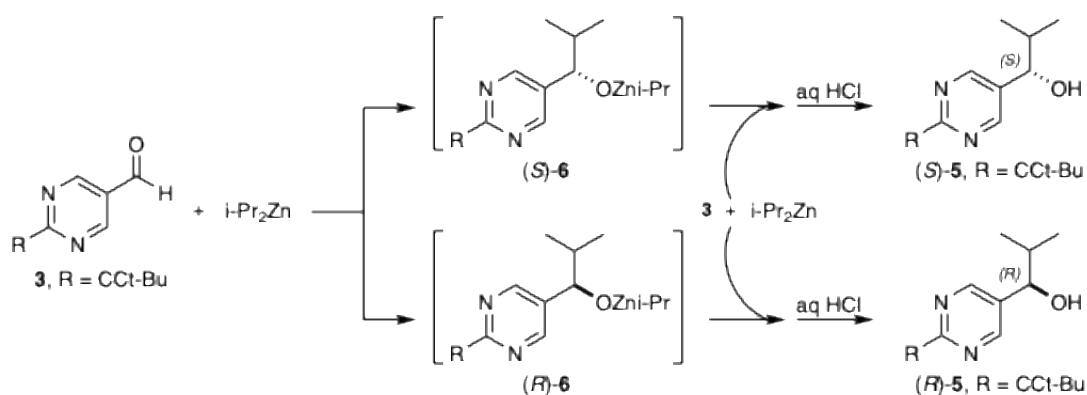


Figure 8. Absolute asymmetric synthesis in the Soai reaction. The outlined reaction mechanism and intermediates are schematic.

Developing an understanding of reaction mechanisms is a fundamental part of organic chemistry, and the rationale that emerges from such activities is used for prediction, control and, perhaps most intellectually rewarding, design of new and as-yet untested reactions that can address currently unattainable problems. The Soai reaction is the only example so far of an asymmetric autocatalytic reaction with amplification of stereochemistry and that is also applicable to absolute asymmetric synthesis.

Erick Carreira and colleagues have developed an asymmetric autocatalytic process for the efficient synthesis of a key intermediate used for the preparation of Efavirenz, an antiretroviral drug used for the treatment of HIV-infection.⁸⁸ For this case, however, no details of NLE were reported.

For the past three decades, the elucidation of a detailed reaction mechanism for NLE has been a challenging quest that has received considerable interest and has involved several research groups. These efforts have been summarised in an excellent review.⁶⁷ Here, only a brief summary is outlined of the timeline leading up to our current understanding of the reaction mechanism of the Soai reaction.

In the original work led by **Soai** from 1990, which included discussion of autocatalysis with erosion of the stereochemical information, the reaction was proposed to involve a catalytically active zinc monoalkoxide.²³ Five years later, the asymmetric autocatalysis with amplification of the stereochemistry was described; however, it was concluded that detailed understanding of the mechanism remained to be clarified, particularly the underlying reason for the +NLE.²⁴

After half a decade, *Blackmond*, *John Brown* and collaborators investigated the reaction heat in the Soai reaction and concluded that the data were most consistent with a dimeric catalyst; i.e. the mechanism previously proposed by *Noyori* for the addition of dialkylzinc to aldehydes is not applicable in that case.⁸⁹ In a kinetic modelling of the reaction, *Blackmond* provided evidence for a tetrameric transition state and reported that the reaction rate and +NLE could be accurately predicted over a wide range of reaction conditions.⁹⁰

In 2007, based on density functional theory (DFT) calculations, *Jürgen Klankermayer*, *Ilya Gridnev* and *Brown* suggested a square-macrocycle-square (SMS) as a most likely end product in a mechanistic pathway, thus superseding the previous dimeric model.⁹¹ Observation of an unusual inverse temperature dependence on the reaction rate in the Soai reaction, together with kinetic studies and NMR investigation, led *Brown* and *Blackmond* to propose in 2010 that the active catalyst is derived from the SMS tetrameric species.⁹² Two years later, *Gridnev* proposed a catalytic cycle involving the SMS zinc alkoxide, based on DFT calculations.⁹³

In 2015, by mixing diisopropylzinc and 2-alkynylpyrimidylalkanols, *Arimasa Matsumoto*, *Tsuneomi Kawasaki* and **Soai** were able to isolate crystals of the alkoxides, the structures of which were determined by X-ray crystallography: when using an excess of $i\text{-Pr}_2\text{Zn}$, homochiral and heterochiral tetramers were obtained, the structures of which resemble the SMS complex. In these structures, two zinc alkoxides form Zn_2O_2 square dimers, and two of these coordinate with each other via an aromatic nitrogen atom of one dimer and a zinc atom of the other dimer, resulting in a 12-membered macrocycle. Both tetramers contain two unsaturated zinc atoms with the potential to function as

Lewis acids and activate an aldehyde, which is required for catalysis.⁹⁴ When instead using 1-2 equivalents Et_2Zn , oligomeric structures were obtained.

The discussion above is complicated by the fact that different mechanisms have been proposed for different substrates (pyridyl-, pyrimidyl-, and 2-alkynylpyrimidyl carbaldehydes) and different reagents (Et_2Zn and $i\text{-Pr}_2\text{Zn}$). Further weaknesses are that the mechanisms do not explain (i) how the SMS complex, if it is the active catalyst, functions and binds the substrate, (ii) the enantioselectivity and +NLE, (iii) the narrow substrate scope of the Soai reaction, and (iv) the cause of the inverse temperature dependence.

Responding to this challenge, *Scott Denmark* and colleagues proposed a detailed mechanism for the Soai reaction.⁹⁵⁻⁹⁷ Based on kinetic studies, including surrogate substrates, spectroscopic investigations of zinc alkoxides, and DFT calculations, they proposed a mechanism involving the Soai SMS complex in which the substrate coordinates to the homochiral tetramer catalyst through a floor-to-floor arrangement involving two coordinatively unsaturated zinc atoms. In this scenario, transfer of an alkyl moiety to the activated aldehyde then delivers the correct stereoisomeric product. Such floor-to-floor coordination of the substrate is, for geometrical reasons, disfavoured in the heterochiral tetramer, which was clearly indicated in the DFT calculation. This then accounts for the amplification of stereochemistry in the autocatalytic reaction and is in line with both the Kagan principle for asymmetric amplification and the Frank model for generation of homochirality.

At about the same time, *Oliver Trapp* and colleagues investigated the Soai reaction mechanism using *in situ* HRMS spectroscopic methods, kinetic simulations and DFT calculations, and proposed a mechanism involving transient hemiacetal zinc complexes (product-substrate dimer).⁹⁸⁻¹⁰⁰ In this mechanism, a diisopropyl zinc alkoxide monomer is in equilibrium with its homo- and heterochiral dimers, with the homochiral structure being the most favoured thermodynamically. Reaction of the monomer with the substrate aldehyde forms a zinc hemiacetal complex and is the slowest step in the catalytic cycle. Addition of the substrate and $i\text{-Pr}_2\text{Zn}$ to this intermediate, followed by intramolecular alkyl transfer and coordination of an additional substrate aldehyde, results in a complex that can now be cleaved into two identical zinc hemiacetal catalysts.

In this model, the asymmetric amplification is due to the slow and unfavourable formation of the hemiacetal, but once it is formed, the much faster autocatalytic reaction can proceed. The homo- and heterochiral dimers are not responsible for entrapment of the minor enantiomer and instead provide a kinetic barrier between the monomers and the catalytic cycle. Here, the asymmetric amplification is due to a kinetically controlled nonequilibrium stationary state, which is different from the

mechanism put forward by Kagan and Frank. The insights gained from this investigation can provide an impetus for developing new asymmetric autocatalytic processes, as argued by the authors.

It can be noted that zinc acetals had previously been detected as intermediates in the Soai reaction using ^1H NMR spectroscopy.¹⁰¹ However, they were later judged not to be involved in the catalytic cycle based on results from DFT calculations.¹⁰²

In addition to this, *Jean-Claude Micheau* and *Thomas Buhse* have used XRD data, DFT calculations and selected experimental kinetic data to build a kinetic and thermodynamic model of the Soai reaction.¹⁰³

Two detailed mechanisms have been put forward for the Soai reaction, differing among other things in the structure of the active catalyst, the rate determining steps and the cause of the asymmetric amplification. Both models have been argued to be accommodated, considering that different substrates were used in the investigations by *Denmark* and *Trapp*, respectively.¹⁰⁴

Consequences and applications

Chirality is a fundamental aspect of molecular structure. The discoveries by **Kagan** and **Soai** are groundbreaking and have reshaped our understanding of how chirality can be generated and amplified in a closed system. The concepts are now integrated with our current understanding of asymmetric catalytic processes. NLE in asymmetric catalysis offer a tool for determining reaction mechanisms but have also opened new perspectives in the search for alternative amplification mechanisms. The most illustrious example of this effect is the asymmetric autocatalysis – the Soai reaction – which results in homochirality without assistance of an external chiral factor. The discovery of the Soai reaction has vitalised the search for the origin of biological homochirality.

The discoveries awarded with the 2026 Nobel Prize in chemistry have deepened our appreciation of molecular chirality, with implications that extend well beyond the realms of organic chemistry.

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- (1) ee (enantiomeric excess) = $|R-S| / R+S \times 100$
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