

Nonlinear Effects in Asymmetric Autocatalysis

In the 1950s, no autocatalytic reactions were known. F. C. Frank was the first to suggest that a process, in which a desired reaction is assisted or an undesired reaction is suppressed, is necessary for asymmetric amplification in an autocatalytic reaction.¹ His postulate, *If it is possible to suppress one reaction pathway relative to the other, then the ee can grow rapidly as the autocatalytic reaction iterates*, has tantalized many experimentalists who have tried to prove it. A few decades later, Soai demonstrated that the addition of dialkylzincs to pyridine-3-carbaldehyde was autocatalyzed by the product of the reaction, and the product obtained was enriched in the same enantiomer as the catalyst.²

Evidence will be provided that asymmetric amplification in many asymmetric syntheses can be understood by Kagan's empirical models³, and asymmetric amplifications as positive nonlinear effects (NLEs) are manifested in asymmetrical autocatalysis as discovered by Soai. Finally, it is shown that asymmetrical autocatalysis could be an origin of homochirality of organic compounds, a prediction absent in Frank's postulate.

Nonlinear Effects in Asymmetrical Stereoselective Reactions

In many asymmetrical stereoselective syntheses, enantiomeric excess of the product (ee_{prod}) is not always proportional to enantiomeric excess of the auxiliary (ee_{aux}) employed in the reaction. If ee_{prod} is higher than ee_{aux} , (+)-NLE is obtained with amplified enantioselectivity.³ Conversely, if ee_{prod} is lower than ee_{aux} , (-)-NLE is obtained with depleted enantioselectivity (Figure 1).

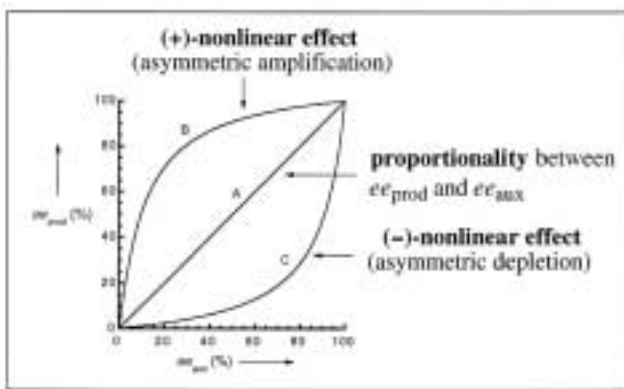


Figure 1. Nonlinear effects with partially resolved chiral auxiliaries

What are the major advantages of NLE investigations with partially resolved chiral auxiliaries? The first advantage is that NLEs which arise from auto association of the chiral auxiliaries in solution can be used to understand subtle diastereomeric interactions between enantiomers. Secondly, NLEs can be useful in understanding the species involved in the catalytic cycle and their behaviors in solution. Thirdly, NLEs can be used to generate products with ee's from enantiomerically impure chiral auxiliaries. Fourth, NLEs can be used as a probe to obtain information on the subtle mechanism by which enantioselectivity is generated.

One of the initial NLE reports pertained to the search for the mechanism of the proline-catalyzed enantioselective aldol reaction (Hajos-Parrish-Wiechert reaction).⁴ Agami suggested two prolines were involved in the enantio-differentiation step, with the first proline undergoing a chiral enamine formation on the side chain, promoting an incipient C-C bond formation which led to an enantioselective aldol product. However, he realized that in the optimized enamine intermediate, lone pair electrons on the nitrogen are deactivated by hydrogen bonding to one of the ketone groups in the ring, resulting in inhibition of subsequent C-C bond formation. Therefore, addition of one more proline in the intermediate is proposed not only to stabilize the hydrogen bonding, but also to increase the activity of the lone pair on the nitrogen (Figure 2).

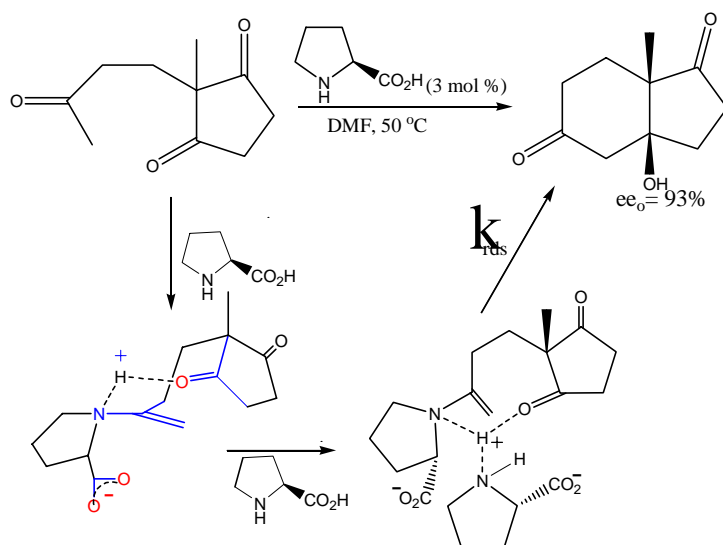


Figure 2. Two proline-mediated highly enantioselective aldol reaction

The two proline mediated intermediate mechanism was supported by both a kinetic experiment in which overall reaction rate is second order in proline concentration, and NLE investigation with partially resolved proline revealing (-)-NLE. Using the enantiomerically mixed prolines, it can be expected that two diastereomeric complexes, homochiral complexes having (*S,S*) or (*R,R*) proline combinations and heterochiral complexes having (*R,S*) or (*S,R*) proline combinations, would be formed in the two proline-mediated intermediate, with each diastereomeric complex contributing different reaction rates to the formation of the enantiomeric aldol products. In order to observe (-)-NLE, the product formation rate in heterochiral complexes (k_{hetero}) should be faster than the homochiral case (k_{homo}), which is consistent with the kinetic experiment that k_{hetero} was twice as large as k_{homo} .⁴

Kagan formulated empirical models for NLEs focused on diastereomeric interactions between metal and chiral ligands.³ He observed that the monomeric chiral ligand - metal interaction would display a linear autoinduction. However, if two chiral enantiomeric ligands are associated on a metallic center, three different catalytic species form, which would not guarantee a linear autoinduction. He proposed four basic models: ML_2 including bimetallic dimerization of (M-L), reservoir effect model which is the most generalized model, ML_3 , and ML_4 model. For simplicity, only ML_2 and the reservoir effect model are covered.

Fast ligand exchanges among two enantiomers in ML_2 systems occur on a metallic center, giving rise to three different complexes: X, Y, and Z in their steady states. Each steady state complex undergoes an irreversible rate determining step to generate a product in which the enantiomeric complexes, X and Y, produce their enantiomeric products, and the meso complex, Z, produces racemic products (Figure 3).

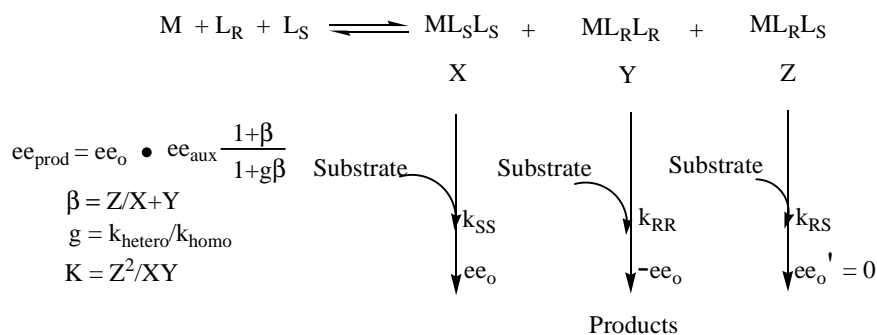


Figure 3. General catalytic cycle in ML_2 model

For example, in the Sharpless asymmetric epoxidation reaction of geraniol, (+)-NLE was observed with partially resolved diethyl tartrate (DET).⁵ The obtained data points could be best fitted by $K = 1000$, $g = 1/3$ (Figure 4). This shows that the meso titanium complex predominantly exists once the equilibrium is reached, and its activity is one-third that of the homochiral one.

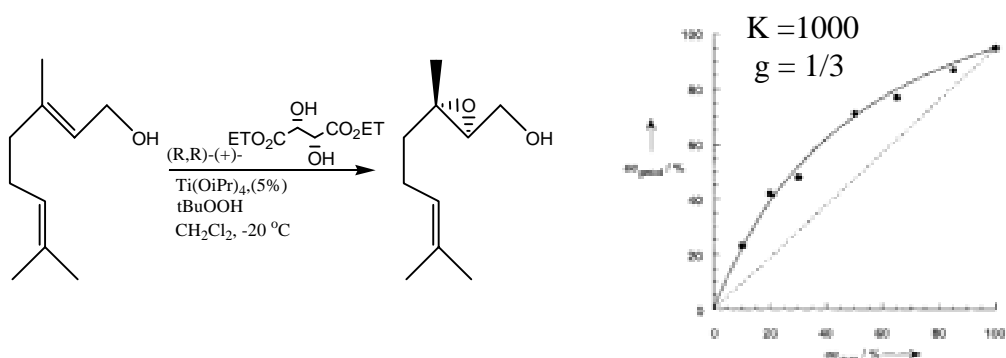


Figure 4. (+)-NLE in the Sharpless asymmetric epoxidation of geraniol

Kagan's reservoir effect model, the most generalized model, is based on generation of two different catalytic species when two enantiomers are mixed in solution: inactive reservoir catalysts and active catalysts.³ The inactive reservoir catalyst with ee of reservoir (ee_{res}), consists of aggregated ligand-metal complexes in which heterochiral complexes are predominantly existent due to their thermodynamic stabilities. Meanwhile, the active catalyst with ee_{eff} consisting of a monomeric metal - ligand complex, undergoes its catalytic cycles. Assuming that two catalytic species are in equilibrium each other, ee_{eff} would be amplified due to the disposition of monomeric catalyst to form heterochiral complexes (Figure 5).

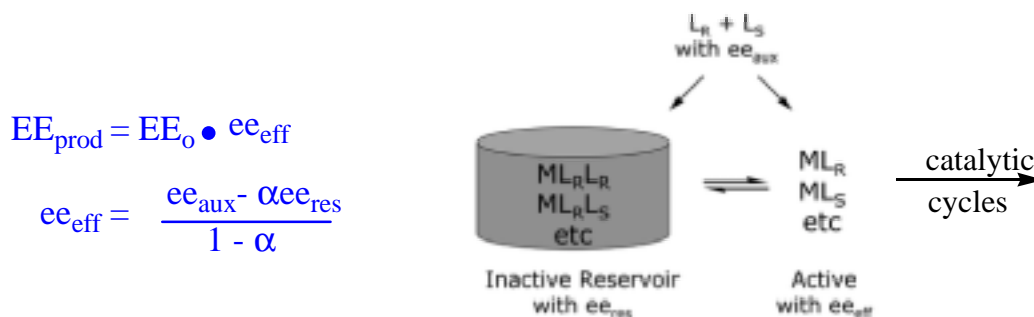


Figure 5. Reservoir effect model by which ee_{eff} of the active catalyst is amplified

Noyori successfully applied the reservoir active model to (+)-NLE upon asymmetric alkylation of benzaldehyde in the presence of partially resolved 3-exo-(dimethyl amino) isoborneol (DAIB), where the presence of 15% ee of (-) DAIB in the ethylation of benzaldehyde resulted in asymmetrically amplified ethylation products with 95% ee.⁶ In his catalytic cycles, ee_{eff} of the monomeric active catalyst is amplified in equilibrium with the dimeric species, in which the monomeric catalyst is preferentially disposed towards heterochiral complexes.

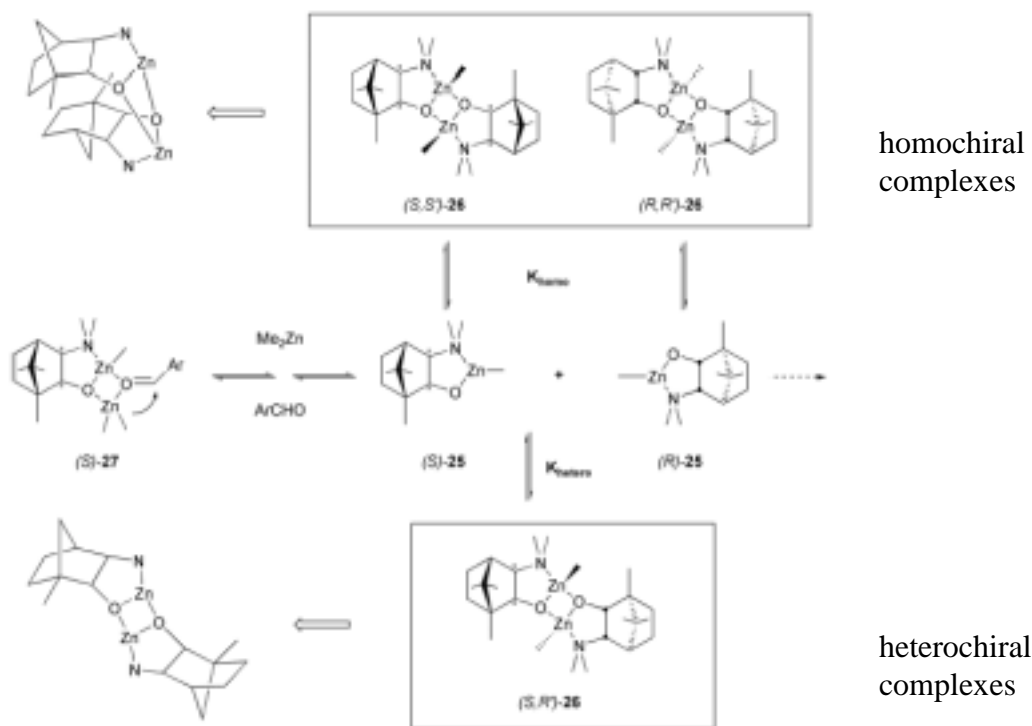


Figure 6. Mechanism of NLEs in the Noyori reaction

Noyori found that the crucial boundary condition for NLEs between two dimeric equilibrium constants, in which $K_{hetero} > 2K_{homo}$, is mandatory for (+)-NLE. It implies that if two chiral ligands are statistically distributed between two dimeric catalysts such as $K_{hetero} = 2K_{homo}$, amplification effects of the product ee are not expected. His kinetic model was further elaborated by Blackmond who discovered via a calorimetric kinetic study that a product-binding zinc complex inhibits fast recovery of active monomeric catalyst.⁷

NLEs have been investigated for other asymmetric stereoselective reactions such as 1,4-addition of cuprates, glyoxylate-ene reaction, aldol condensation, asymmetric sulfoxidation and nucleophilic ring-opening of epoxides.^{3,8,9} The most common feature in these NLEs is that the reservoir active model could be applied to describe the catalytic behaviors of aggregated bidentate ligands.

Asymmetric Autocatalysis

As an application of asymmetric amplification via (+)-NLE, enantioselectivity of the product in asymmetric autocatalysis is amplified by the reaction product itself as a catalyst. Soai discovered that isopropylation of pyrimidine-5-aldehyde in the presence of a catalytic amount of the reaction product with 5% ee resulted in 42% yield with 55% ee, which is far greater than that of the initial catalyst.¹⁰ When the reaction was repeated successively, it was found after three rounds that not only had ee of the product exponentially increased to 85%, but also, the amounts of the major alcohol increased by a factor of 94, while the minor alcohol only increased by a factor of less than 10, (Figure 7).

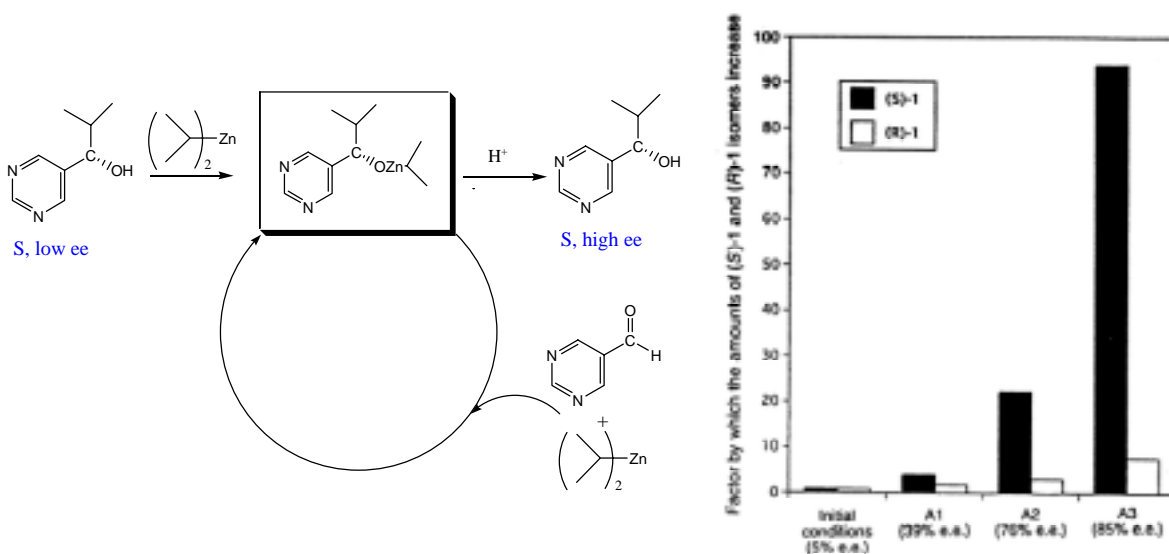


Figure 7. Asymmetric autocatalysis found by Soai

Frank's autoinduction in which asymmetric amplification of one enantiomer can be possible in the suppression of the reaction pathway toward the other was finally manifested on the Soai asymmetric autocatalysis. In 2001, the mechanism of the Soai reaction was finally proposed by Blackmond via a calorimetric kinetic study in which a

bimetallic species was proposed as the active catalytic species for Soai asymmetric autocatalysis (Figure 8).¹¹

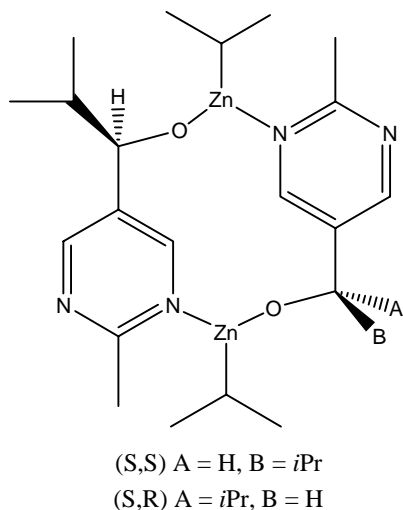


Figure 8. Proposed bimetallic active catalyst in Soai asymmetric catalysis

Origin of homochirality of organic compounds explored by asymmetric autocatalysis

Let's assume that the prebiotic Earth consisted of racemate, where some chiral perturbations such as circularly polarized light caused small chiral imbalances in Earth to produce tiny chiral seeds with a low ee. Then, the chiral seeds catalyzed a simple reaction to generate a chiral product with a low ee, and the reaction product catalyzed the next reactions successively. After repetitive catalytic cycles through (+)-NLE, the desired homochirality of the organic molecules would be achieved.^{12,13,14}

Soai successfully applied this theory to his asymmetric autocatalytic reactions. It was known that when racemic leucines are exposed to right circularly polarized light, *R*-leucine is effectively destroyed to produce *L*-leucine with 2% ee.¹⁵ When *L*-leucine with 2% ee was employed as a chiral seed to catalyze the alkylation of the pyrimidyl aldehyde, the product with 21% ee was obtained.¹⁶

Conclusion

Nonlinear effects (NLEs) between ee_{aux} and ee_{prod} are caused by subtle diastereomeric interactions between enantiomers in solution. As shown in many asymmetrical syntheses, NLEs could be employed as a probe to seek possible mechanisms by which enantioselectivity is generated. The bimetallic species was a core

active catalyst in the heart of Soai asymmetrical autocatalysis, which could be explored as a part of the origins of biochemical homochirality.

References

- 1) Frank, F. *Biochim. Biophys. Acta.* **1953**, *11*, 459. "Spontaneous asymmetric synthesis"
- 2) Soai, K.; Niwa, S.; Hori, H. *Chem. Commun.* **1990**, 982. "Asymmetric self-catalytic reaction"
- 3) Girard, C.; Kagan, H. *Angew. Chem. Int. Ed.* **1998**, *37*, 2922. "Nonlinear effects in asymmetrical synthesis and stereoselective reactions: ten years of investigation"
- 4) Agami, C.; *Bull. Soc. Chim. Fr.* **1988**, 499. "Mechanism of the proline-catalyzed enantioselective aldol reaction, recent advances"
- 5) Puchot, C.; Samuel, E.; Dunach, E.; Zhao, S.; Agami, H.; Kagan, H. *J. Am. Chem. Soc.* **1986**, *108*, 2353. "Nonlinear effects in asymmetric synthesis"
- 6) Kitamura, M.; Suga, S.; Oka, H.; Noyori, R. *J. Am. Chem. Soc.* **1998**, *120*, 9800. "Quantitative analysis of the chiral amplification in the amino alcohol-promoted asymmetric alkylation of aldehydes with dialkylzincs"
- 7) Rosner, T. Sears, P.; Nugent, W.; Blackmond, D. *Org. Lett.* **2000**, *2*, 2511. "Kinetic investigation of product inhibition in amino alcohol-catalyzed asymmetric alkylation of benzaldehyde with diethylzinc."
- 8) Hansen, K.; Leighton, J.; Jacobsen, E. J. *Am. Chem. Soc.* **1996**, *118*, 10924. "On the mechanism of the asymmetrical nucleophilic ring-opening of epoxides catalyzed by (Salen)Cr^{III} complexes"
- 9) Komatsu, N.; Hashizume, M.; Sugita, T.; Uemura, S. *J. Org. Chem.* **1993**, *58*, 7624. "Kinetic resolution of sulfoxides catalyzed by chiral titanium-binaphol complex"
- 10) Soai, K.; Shibata, T.; Morioka, H.; Choji, K. *Nature.* **1995**, *378*, 767. "Asymmetric autocatalysis and amplification of enantiomeric excess of a chiral molecule"
- 11) Blackmond, D.; McMilan, C.; Ramdeehul, S.; Schorm, A.; Brown, J. *J. Am. Soc. Chem.* **2001**, *123*, 10103. "Origins of asymmetric amplification in autocatalytic alkylzinc additions"

- 12) Todd, M. *Chem. Soc. Rev.* **2002**, *31*, 211. "Asymmetric autocatalysis: product recruitment for the increase in the chiral environment"
- 13) Singleton, D.; Vo, L.; *J. Am. Chem. Soc.* **2002**, *124*, 10010. "Enantioselective synthesis without discrete optically active additives"
- 14) Siegel, J. *Chirality*. **1998**, *10*, 24. "Homochiral imperative of molecular evolution"
- 15) Flores, J.; Bonner, W.; Massey, G. *J. Am. Chem. Soc.* **1977**, *99*, 3622.
"Asymmetric photolysis of (*R S*) leucine with circularly polarized ultraviolet light"
- 16) Shibata, T.; Yamamoto, J.; Matsumoto, N.; Yonekubo, S.; Osanai, S.; Soai, K. *J. Am. Chem. Soc.* **1998**, *120*, 12157. "Amplification of the small chiral imbalance in molecules based on asymmetric autocatalysis: the first correction between high enantiomeric enrichment in a chiral molecule and circularly polarized light"