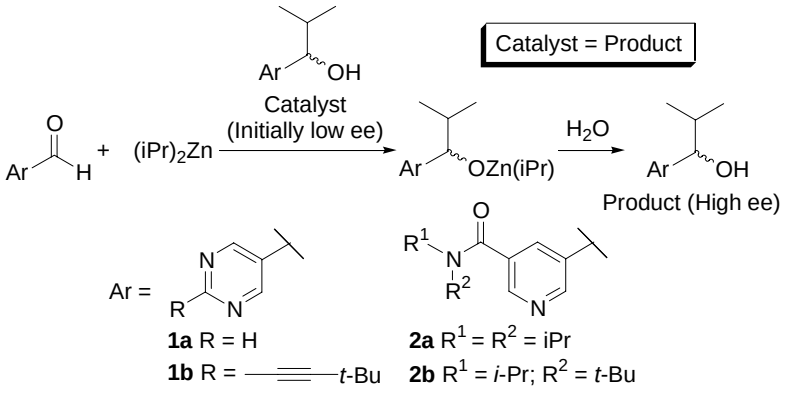
ASYMMETRIC NONLINEAR EFFECTS IN THE SOAI REACTION: A POSSIBLE MODEL FOR SPONTANEOUS GENERATION OF ASYMMETRY

Reported by Eric M. Todd September 25, 2003

INTRODUCTION

In 1953 Frank proposed that if an asymmetric system existed in which a chiral product was able to catalyze the formation of itself and inhibit the formation of its enantiomer, then a very small enantiomeric excess could be amplified to produce a highly enantioenriched product.[1] This model incorporates both the concepts of asymmetric nonlinear effects and autocatalysis. Frank challenged experimental chemists to find and characterize such a system. In 1995 Soai and coworkers reported a system which exhibits this behavior in the alkylation of pyrimidine-5-carboxaldehyde, **1a**, by diisopropylzinc (Scheme 1).[2a] Since then, the reaction has become known as the Soai reaction and they have developed several variations of their asymmetric autocatalytic reaction and have demonstrated a wide range of experimental conditions to generate a small, initial enantiomeric excess in the products which then undergo amplification.[3]

Scheme 1. Asymmetric Autocatalysis in the Soai Reaction



Recently, there has been considerable interest in the Soai reaction. Kinetic studies which clarify the complex picture of catalyst equilibria and differential reactivity behind the observed asymmetric nonlinear effects have been reported.[4] Particularly interesting are recent results which demonstrate enantiomeric excess in the products of the Soai reaction without the intentional addition of any chiral substances.[5] This abstract provides a perspective on the Soai reaction in the context of asymmetric nonlinear effects, and the spontaneous generation of asymmetry.

AUTOCATALYSIS AND NONLINEAR EFFECTS IN ASYMMETRIC SYNTHESIS

Autocatalysis is a process in which the product of a reaction interacts with the reactants to catalyze the formation of itself. A simple example is the acid catalyzed hydrolysis of an ester, in which, autocatalysis occurs whenever the product carboxylic acid participates in the acid catalysis. More sophisticated systems involve synthetically designed reactants that generate products capable of interacting with the reactants in specific ways to facilitate catalysis.[6] The Soai reaction is an example of the most advanced class of autocatalytic reactions, those that are capable of transferring regiochemical and

stereochemical information. These self-replicating systems include many biological processes such as the replication of DNA and the synthesis of proteins.[6] The Soai reaction, which is less complicated then its biological counterparts, is amenable to detailed analysis and applicable to synthetic organic chemistry.

Asymmetric nonlinear effects refer to a nonlinear relationship between the enantiomeric purity of the catalyst (ee_{aux}) and the enantiomeric purity of the product (ee_{prod}). These non-linear effects can be either positive or negative leading to a product that is of higher or lower than expected enantiomeric purity expected for a linear relationship of the ee_{prod} with the ee_{aux} of the catalyst.

The addition of alkylzinc reagents to aldehydes in the presence of chiral amino alcohols is a catalytic asymmetric system, related to the Soai reaction, which shows positive nonlinear effects. Through detailed mechanistic studies, Noyori and coworkers developed a model to explain the positive nonlinear effects observed (Figure 1).[7] This model consists of catalytically active enantiomeric monomers in equilibrium with non-active hetero and homodimers of the catalyst. In the case where $K_{Hetero} > 2K_{Homo}$ positive nonlinear effects are observed due to the heterodimeric complex altering the relative concentrations of the *R* and *S* monomers. When enantiopure catalyst is used the model simplifies to a catalytic monomer in equilibrium with its homochiral dimer and a linear relationship between ee_{prod} and ee_{aux} is observed. With a mixture of *R* and *S* enantiomers of a catalyst, the Noyori model predicts a decrease in the concentrations of both the *R* and *S* enantiomers due to formation of the stable heterochiral dimer. Assuming there is an excess of one enantiomer over the other, the concentration of the major monomeric enantiomer will increase in relation to the concentration of the minor monomeric enantiomer. This increase in the fraction of major to minor catalytically active monomer is responsible for the observed nonlinear effect.

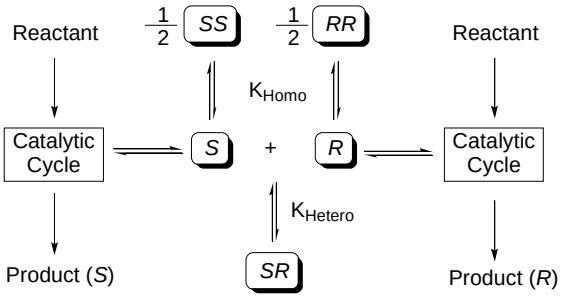
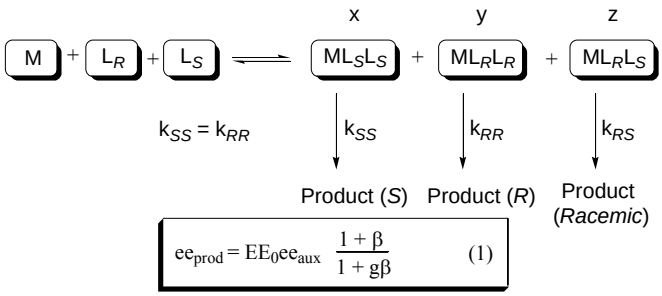


Figure 1. Noyori's Model for Asymmetric Nonlinear Effects

Kagan and coworkers have presented an alternate description of nonlinear effects.[8] In deriving the ML_2 model (Figure 2), Kagan considered a theoretical system consisting of a catalytic metal with two chiral ligands. However, this model is also



$$ee_{prod} = EE_0 ee_{aux} \frac{1+\beta}{1+g\beta} \quad (1)$$

where EE_0 = ee of product when enantiopure catalyst is used

$g = \frac{k_{RS}}{k_{RR}}$ = relative activities of hetero and homo complexes

$\beta = \frac{z}{(x+y)}$ = relative amounts of hetero and homo complexes

Figure 2. Kagan's Model for Aymmetric Nonlinear Effects

valid when no metals are present and the ligands, themselves, are the catalysts. This model leads to an expression of the relationship between the enantiopurity of the catalyst and the observed enantiopurity of the product (equation 1). The term containing g and β accounts for the nonlinear effects by considering the equilibrium distribution and relative catalytic reactivity of the catalyst dimers. If there is no heterodimer formed, then β = 0, and there is a linear relationship between ee_{prod} and ee_{aux}. Likewise, if the different dimers have equal reactivity, then g = 1, and a linear relationship is observed. An important difference between the Kagan and the Noyori models is that in the Noyori model the monomeric species are catalytically active and nonlinear effects arise from the difference in stability of homo and heterochiral dimeric complexes. In Kagan's ML_2 model, it is the dimers that facilitate catalysis and account for the nonlinear effects in terms of the stability and the reactivity of the dimeric complexes.

THE SOAI REACTION

Over the past eight years, Soai and coworkers have published several autocatalytic alkylations of heterocyclic aldehydes with diisopropylzinc which show amplification of enantiomeric excesses (Scheme 1).[3] In a typical experiment they start with catalyst/alcohol of low enantiopurity and then perform the alkylzinc addition iteratively, using a portion of the product of one reaction as the catalyst for the next reaction. This is repeated until a high enantiopurity is achieved. Experimental data from the reactions of heteroaromatic aldehydes in Scheme 1 is presented in Table 1. All the data reported in Table 1 represents single experiments and although the general trends are convincing, the error in these values were not reported.

Table 1. Representative Soai Reaction Data

Aldehyde	Initial Catalyst Enantiopurity % ee	Final Enantiopurity % ee[c]	Number of Iterations to Final Enantiopurity	Reference
1b	$5(10)^{-5}$ *S* [a]	> 99.5 *S*	3	2b
1b	$5(10)^{-5}$ *R* [a]	> 99.5 *R*	3	2b
1a	5 *S*	89 *S*	5	2a
2a	4 *S*	87 *S*	8	2c
2a	4 *R*	86 *R*	8	2c
2b	4 *S*	78 S	9	2c

[a]Enantiomeric excess is approximate from prepared solutions. [c]Final enantiopurity represents a combination of formed product and initially added catalyst.

The most impressive system developed by Soai and coworkers is the autocatalytic reaction involving 2-alkynyl-5-pyrimidyl aldehyde, **1b**.[2b, 9] Starting with a catalytic amount of either enantiomer of the catalyst/product alcohol **1b** with an ee of approximately 0.00005%, they were able to generate the

corresponding enantiomer of the catalyst/product alcohol **1b** in greater then 99.5% ee in three iterations.[2b] They speculated that the steric nature of the *t*-butyl alkyne and its mild electron withdrawing effect were primarily responsible for the outstanding asymmetric amplification seen in this system, although no model was proposed to rationalize these speculations.[9]

In an earlier study on the affects of structure on the observed asymmetric amplification, Soai and coworkers examined the autocatalysis of the 5-carbamoyl-3-pyridyl alcohols **2**.[2c] The results of iterative experiments involving **2** show a positive nonlinear effect. The alcohol (*S*)-**2b** took nine iterations to amplify the enantiomeric excess from 4% to 78%, whereas both enantiomers of alcohol **2a**, starting with 4% ee catalyst/product provided > 85% ee in eight iterations.

SPONTANEOUS GENERATION OF ASYMMETRY

The Soai reaction may be viewed as relevant to the origin of biological homochirality. Most of the proposed theories on the origin of homochirality begin with a symmetry-breaking event, which is then amplified.[10, 11] The Soai reaction provides a model for the mechanism of amplification. To demonstrate the possible applicability of their model, Soai and coworkers have shown that a wide range of chiral substances can initiate the generation of asymmetric amplification.[3]

It also has been proposed that no outside symmetry-breaking event would necessarily be required for the generation of homochirality. These proposals have been recently collected in a commentary by Mislow,[10] in which he presents the argument that even with completely achiral reagents, it is statistically inevitable that a slight excess of one enantiomer will be generated. For example, consider a reaction in which achiral precursors are used to generate 10^{20} molecules of a chiral product. If this reaction is repeated for a statistically large number of trials, half of these trials could produce an enantiomeric excess of either *R* or *S* of more then $6.7(10)^{9}$ molecules ($6.7(10)^{-9}$ % ee).[12, 13]

Singleton and coworkers have tested the Soai reaction in an effort to determine if amplification of a statistically generated enantiomeric excess can reach an observable level (Figure 3).[5a] Starting with the Soai reaction for **3** without the use of any chiral additives, enantiomeric excesses were detected in 48 of 48 trials. Enantiomeric excesses were detected from the second to the eighth generation and ranged from 3% to 86% ee depending on the generation and experimental conditions. However, the configuration of the enantiomer in excess was found to be dependent on the origins of the solvent used in the

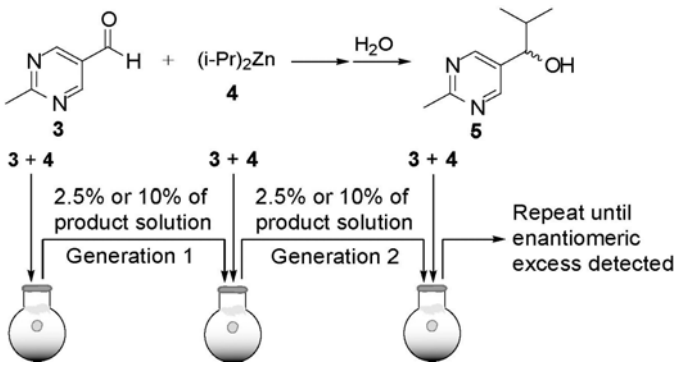


Figure 3. Singleton's Experimental Setup[5a]
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reaction. Using solvent from the same bottle gave the same configuration in enantiomeric excess. Singleton and coworkers speculated that these reactions were not examples of an amplification of statistical asymmetry due to this variation. They performed several controls, including rigorously purifying their solvent and reagents, conducting the reaction with and without the presence of ambient light, and using glass and Teflon reaction vessels. In all cases, they observed enantiomeric excesses that depended on the solvent. They suggested that the enantioselectivity was arising from chiral, undetectable, homogeneous impurities in the solvent.

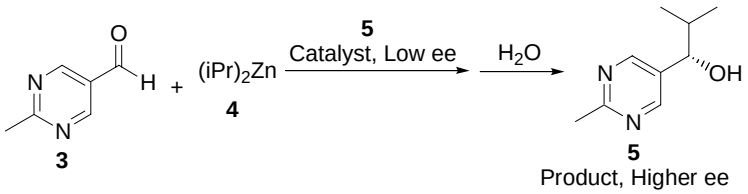
Soai and coworkers subsequently performed a similar experiment using **1b** and a toluene/ether solvent mixture.[5b] Under these conditions they observed a stochastic distribution in the formation of the two enantiomers for the 37 trials they conducted. They speculated that the ether, being better able to coordinate with the zinc, lessened the effect of any possible chiral impurities.

Singleton and coworkers also experimentally demonstrated the ability of enantiomers to compete with one another by allowing two systems showing opposite enantiomer amplifications to diffuse into each other.[5a] They placed a small amount of each enantiomerically pure FMOC protected alanine on each end of a tube filled with glass beads to direct the configuration of the Soai reaction product/catalyst at that respective end of the tube. The Soai reaction for **3** was then conducted by placing the reagents in the center of the tube. This was done iteratively, leaving 10% of the reaction mixture in the tube to catalyze the next reaction. They found that the portion of the tube showing *S* enantiomer amplification in the Soai reaction was able to diffuse into the space occupied by the system showing *R* amplification. After six generations, the *S* enantiomer was dominant over the entire length of the tube. Statistically, there should be an equal chance for either enantiomer to overcome the other. Singleton and coworkers only report one trial of this experiment and do not comment on other factors that could contribute to the successful competition of one enantiomer over the other.

KINETIC MODELS OF THE SOAI REACTION

The best current mechanistic understanding of the Soai reaction is built on the kinetic studies provided by Blackmond and coworkers.[4b, c, d] They used reaction microcalorimetry to monitor the Soai reaction of **3** autocatalyzed by (*S*)-**5** (Scheme 2) in real time (Figure 4).[4b] Their experiments measure reaction heat flow, which is directly proportional to the rate of the reaction. Figure 4 shows a heat flow that is characteristic of an autocatalytic reaction. Autocatalytic reactions typically begin slowly due to a relatively small

Scheme 2. Reaction Studied by Blackmond and Coworkers



amount of product/catalyst. As the reaction proceeds, more product/catalyst is generated and the rate of the reaction increases until the starting material concentration becomes rate limiting. After this point a rate decrease is observed until the starting materials are completely depleted.

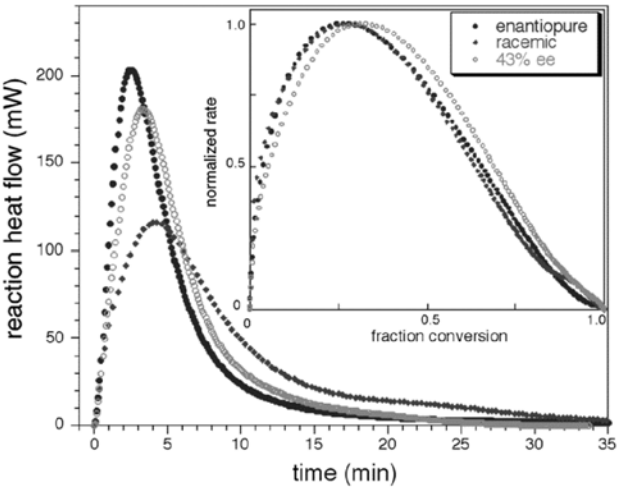


Figure 4. Reaction Microcalorimetry Data[4d]
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Interestingly, the rate of the reaction with racemic catalyst is approximately half that of the reaction with enantiopure catalyst. This implies that the Noyori model (Figure 1) cannot be applicable to the Soai reaction. There would have to be no preference ($K_{Hetero} = 2K_{Homo}$) between the dimeric complexes in the Noyori model for the rate of the reaction with racemic catalyst to be half that of the reaction with enantiopure catalyst. However, the Noyori model requires that the heterochiral complex be more stable then the homochiral complexes ($K_{Hetero} > 2K_{Homo}$) for asymmetric amplification to occur.

With the Noyori model excluded, Blackmond and coworkers developed their own model (Figure 5) based on Kagan's ML_2 system (Figure 2).[4b] This model explains the asymmetric amplification as arising from an increased reactivity of the homochiral dimers versus the heterochiral dimer. Blackmond and coworkers propose that all the dimeric species are equally stable and nonlinear effects can only arise when there is an excess of one enantiomer in the catalyst. Using this model, they arrive at the rate law given by equation 2, where the term $[\mathbf{5}]_{active}$ represents the sum of the homodimer concentrations and is a function of the concentration of **5** and the terms g and β. Blackmond and coworkers proposed **6** as the catalytically active dimer of **5** (Figure 6) based on several x-ray crystal structures of related zinc complexes,[4b] however they provide no explanation of how this complex could catalyze its own formation with asymmetric amplification.

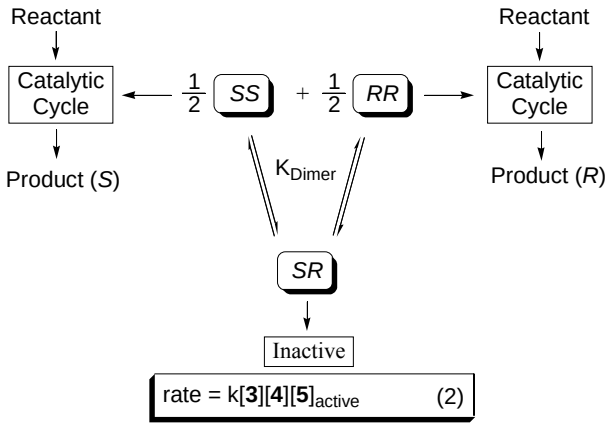

Figure 5. Kinetic Model Developed by Blackmond

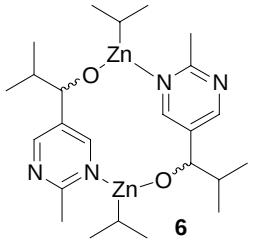

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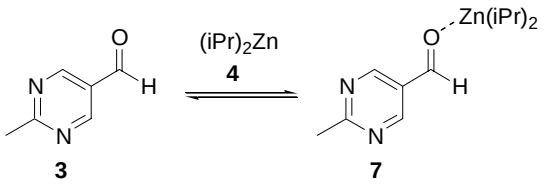
Figure 6. Speculated Structure for $[5]_{active}$

Blackmond and coworkers did revise their model after further experimentation showed that the rate law given by equation 2 was only valid if the aldehyde and diisopropylzinc were used in stoichiometric amounts.[4d] The rate law in equa-

tion 3 (Scheme 3) was proposed as the simplest model that was applicable to all the experimental results. They interpreted this as the previously postulated dimeric species, $[\mathbf{5}]_{active}$, proposed to be structure **6**, interacting with two equivalents of the aldehyde coordinated to diisopropylzinc, **7**. This chemical interpretation gives the rate law in equation 4. Assuming that the formation of the aldehyde-zinc complex is very favorable, the concentration of **7** would be equal to the concentration of aldehyde, **3**, initially added ([**3**] = [**7**]). Substituting this into equation 4 gives the rate law in equation 3. Furthermore, in the case where diisopropylzinc and **3** are used in a 1:1 stoichiometry ([**3**] = [**4**]) the rate law in equation 3 equals the originally proposed rate law in equation 2. This model reproduces both kinetic and enantiomeric excess data as a function of time at various stoichiometries.

Scheme 3. Aldehyde-Zinc Complex and Blackmond's Revised Model



$$\text{rate} = k[\mathbf{3}][\mathbf{3}][\mathbf{5}]_{active} \quad (3)$$

$$\text{rate} = k[\mathbf{7}][\mathbf{7}][\mathbf{5}]_{active} \quad (4)$$

The model of Blackmond and coworkers does not yet provide a model for the interactions that promote the transmission of chiral information in their suggested catalytic species. The previously mentioned examples of the Soai reaction do suggest the possibility of steric limitations particularly in the autocatalysis of **3b**, which is consistent with the more congested tetrameric transition state in the revised Blackmond model. However a model is needed to rationalize the observations of Soai and coworkers on the *t*-butyl alkyne being important for the observed asymmetric amplification. It is likely that electronic effects of substituents on the pyrimidyl ring could affect the stability of dimeric autocatalytic species, which could have an impact on the equilibrium constants in the Blackmond model.

APPLICATIONS

The recent attention the Soai reaction has received has caught the eye of industry.[14] The advantages of an autocatalytic process with amplification of enantiopurity has definite benefits for industrial applications in terms of efficiency and product purification. Furthermore, the reaction microcalorimetry methods developed by Blackmond are also becoming valuable tools for industry in the optimization of chemical processes.[15]

CONCLUSION

Asymmetric autocatalysis with amplification of enantiomeric excess in the Soai reaction is an area under study and development. The kinetic studies of Blackmond and coworkers have provided insight into the mechanism of the Soai reaction. However, a complete mechanism for the Soai reaction is

going to require a description of how the chiral information passes through the autocatalytic cycle. The full elucidation of the mechanism of the Soai reaction should pose a very interesting area of future research for organic chemists and allow extension and rational development of this very promising area.

REFERENCES

(1) Frank, F. C. *Biochim. Biophys. Acta* **1953**, *11*, 459-463.

(2) (a) Soai, K.; Shibata, T.; Morioka, H.; Choji, K. *Nature (London)* **1995**, *378*, 767-768. (b) Sato, I.; Urabe, H.; Ishiguro, S.; Shibata, T.; Soai, K. *Angew. Chem., Int. Ed. Engl.* **2003**, *42*, 315-317. (c) Tanji, S.; Kodaka, Y.; Ohno, A.; Shibata, T.; Sato, I.; Soai, K. *Tetrahedron: Asymmetry* **2000**, *11*, 4249-4253.

(3) For reviews of the Soai reaction see: (a) Soai, K.; Sato, I. *Chirality* **2002**, *14*, 548-554. (b) Soai, K.; Shibata, T.; Sato, I. *Acc. Chem. Res.* **2000**, *33*, 382-390.

(4) Kinetic Studies: (a) Sato, I.; Omiya, D.; Tsukiyama, K.; Ogi, Y.; Soai, K. *Tetrahedron: Asymmetry* **2001**, *12*, 1965-1969. (b) Blackmond, D. G.; McMillan, C. R.; Ramdeehul, S.; Schorm, A.; Brown, J. M. *J. Am. Chem. Soc.* **2001**, *123*, 10103-10104. (c) Blackmond, D. G. *Adv. Synth. Catal.* **2002**, *344*, 156-158. (d) Buono, F. G.; Blackmond, D. G. *J. Am. Chem. Soc.* **2003**, *125*, 8978-8979. (e) Sato, I.; Omiya, D.; Igarashi, H.; Kato, K.; Ogi, Y.; Tsukiyama, K.; Soai, K. *Tetrahedron: Asymmetry* **2003**, *14*, 975-979. (f) Buhse, T. *Tetrahedron: Asymmetry* **2003**, *14*, 1055-1061.

(5) (a) Singleton, D. A.; Vo, L. K. *J. Am. Chem. Soc.* **2002**, *124*, 10010-10011. (b) Soai, K.; Sato, I.; Shibata, T.; Komiya, S.; Hayashi, M.; Matsueda, Y.; Imamura, H.; Hayase, T.; Morioka, H.; Tabira, H.; Yamamoto, J.; Kowata, Y. *Tetrahedron: Asymmetry* **2003**, *14*, 185-188.

(6) For reviews of autocatalysis and self-replication and its implications to the origin of homochirality see: (a) Pham, Son M. Organic Seminar Abstracts 1997-1998, Semester I; University of Illinois: Urbana, Il, Nov 24, 1997; p33-40. (b) Robertson, A.; Sinclair, A. J.; Philp, D. *Chem. Soc. Rev.* **2000**, *29*, 141-152.

(7) Kitamura, M.; Suga, S.; Niwa, M.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 4832-4842.

(8) Guillaneux, D.; Zhao, S. H.; Samuel, O.; Rainford, D.; Kagan, H. B. *J. Am. Chem. Soc.* **1994**, *116*, 9430-9439.

(9) Shibata, T.; Yonekubo, S.; Soai, K. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 659-661.

(10) Mislow, K. *Collect. Czech. Chem. Commun.* **2003**, *68*, 849-864.

(11) For theories regarding possible symmetry breaking events see: (a) Avalos, M.; Babiano, R.; Cintas, P.; Jimenez, J. L.; Palacios, J. C. *Chem. Commun* **2000**, 887-892. (b) Kondepudi, D. K.; Asakura, K. *Acc. Chem. Res.* **2001**, *34*, 946-954. (c) Siegel, J. S. *Nature (London)* **2002**, *419*, 346-347.

(12) (a) Statistical enantiomeric excess calculated from $k = 0.6743/\sqrt{N}$ where k is the statistical dissymmetry and N is the total number of molecules in a sample. The variable k is approximately the probability of achieving a completely equal number of enantiomers. The statistical average number of molecules in excess is given by kN. (b) Relationship derived by L. A. Pars and presented by Mills.[13]

(13) Mills, W. H. *Chem. Ind. (London)* **1932**, *51*, 750-759.

(14) Stephenson, G. R. *Chem. Ind. (London)* **2003**, 27-28.

(15) O'Driscoll, C. *Chemistry in Britain* **2002**, *38*, 34-37.