Japan Academy Prize to:

Kenso SOAI
Professor Emeritus, Tokyo University of Science

for “The Discovery of Asymmetric Autocatalysis and
Insights into the Origins of Homochirality”

Outline of the work:

Homochirality is the overwhelming predominance of a single enantiomer. Typical examples are biomolecules in living systems; proteins are composed of L-amino acids, and nucleic acids are composed of D-sugars. How and when homochirality emerged on Earth in relation to the origin of life are interesting, unsolved questions. Various hypotheses, such as chirality being triggered by circularly polarized light or quartz, have been proposed over time. However, experiments related to this subject have yielded unconvincing results because products were formed with very low enantiomeric excess (ee), often below the detection limit. No method of correlating the effect of a certain chiral trigger to chiral products with a very high ee has yet been reported.

Dr. Kenso Soai made a seminal contribution to this field by discovering an asymmetric autocatalytic reaction, now known as the Soai reaction, that resulted in an extraordinary increase in ee. This discovery led to several hypotheses about the mechanism by which homochirality emerged.

In 1995, Dr. Soai discovered an asymmetric autocatalytic reaction that resulted in an increase in ee. Although autocatalytic reactions, in which the product serves as a catalyst for its own generation, are known, no asymmetric version of this type of reaction, resulting in the self-replication of a chiral molecule with an increase in ee, has been reported. In 1953, Frank proposed the possibility of such a reaction but did not mention any specific chemical structures. Over 40 years elapsed before the first example of this type of reaction was reported by Dr. Soai.

The Soai reaction has three key features:

(1) Autocatalysis: During the reaction of diisopropylzinc with pyrimidine-5-carbaldehyde, the addition product serves as an asymmetric autocatalyst, significantly accelerating the reaction.

(2) Fidelity of chirality: The chirality of the autocatalyst is faithfully transmitted to the product, 5-pyrimidyl alkanol. For example, when the asymmetric autocatalyst has an ee greater than 99.5%, the ee of the product is also greater than 99.5%.

(3) Dramatically increased enantiomeric purity: Even when the reaction starts with an

autocatalyst with an extremely low ee (e.g., 0.00005%), the ee is increased to more than 99.5% after three consecutive cycles of asymmetric autocatalysis. Clearly, the Soai reaction exponentially amplifies the initial chirality bias to form a highly enantioenriched product.

Inspired by these extraordinary features, Soai began investigating the origins of homochirality. It was found that the Soai reaction could overcome the limitations of the abovementioned unfruitful attempts to induce chirality by chiral triggers. By using various chiral initiators, Soai established a correlation between the chirality of the initiators and the absolute configuration of the highly enantioenriched product. The chiral initiators included (1) right- and left-handed quartz, (2) irradiation with right- and left-circularly polarized light, (3) chiral crystals formed from achiral organic compounds, and (4) chiral compounds with isotopically substituted carbon, oxygen, etc. In each case, a small chirality bias was amplified via asymmetric autocatalysis, resulting in a product with a very high ee. Thus, the chirality of the initiators was correlated with the absolute configuration of the highly enantioenriched product for the first time.

Surprisingly, spontaneous absolute asymmetric synthesis was observed. When a prochiral substrate reacts in the absence of a chiral factor, a racemate, i.e., an equimolar mixture of both enantiomers, is expected to form. However, counterintuitively, the Soai reaction afforded enantioenriched products via asymmetric autocatalysis without the intervention of any chiral factor. This surprising result was attributed to stochastic fluctuations of the chirality of the initial products, which was greatly amplified to generate a stochastic distribution of left- and right-handed products. This was the first example of a spontaneous absolute asymmetric synthesis resulting in a high ee.

In summary, the discovery by Dr. Kenso Soai of asymmetric autocatalysis resulting in an increased ee has had a profound impact on multiple scientific disciplines. The ability of the Soai reaction to increase very low ee values to achieve enantiopurity may help explain the origin of homochirality. The Soai reaction has thus attracted widespread interest not only in chemistry but also in other fields.

List of Main Publications

Original Articles

(1) Catalytic Asymmetric Induction. Highly Enantioselective Addition of Dialkylzincs to Aldehydes Using Chiral Pyrrolidinylmethanols and Their Metal Salts. K. Soai, A. Ookawa, T. Kaba, and K. Ogawa, *J. Am. Chem. Soc.*, **1987**, *109*, 7111–7115.

(2) Asymmetric Self-catalytic Reaction. Self-production of Chiral 1-(3-Pyridyl)alkanols as Chiral Self-catalysts in the Enantioselective Addition of Dialkylzinc Reagents to Pyridine-3-carbaldehyde. K. Soai, S. Niwa, and H. Hori, *J. Chem. Soc., Chem. Commun.*, **1990**, 982–983.

(3) Asymmetric Autocatalysis and Amplification of Enantiomeric Excess of a Chiral Molecule. K. Soai, T. Shibata, H. Morioka and K. Choji, *Nature*, **1995**, *378*, 767–768.

(4) Highly Enantioselective Catalytic Asymmetric Automultiplication of Chiral Pyrimidylalcohol. T. Shibata, H. Morioka, T. Hayase, K. Choji and K. Soai, *J. Am. Chem. Soc.*, **1996**, *118*, 471–472.

(5) Highly Enantioselective Synthesis of a Chiral 3-Quinolylalkanol by an Asymmetric Autocatalytic Reaction. T. Shibata, K. Choji, H. Morioka, T. Hayase and K. Soai, *Chem. Commun.*, **1996**, 751–752.

(6) Amplification of a Slight Enantiomeric Imbalance in Molecules based on Asymmetric Autocatalysis: The First Correlation between High Enantiomeric Enrichment in a Chiral Molecule and Circularly Polarized Light. T. Shibata, J. Yamamoto, N. Matsumoto, S. Yonekubo, S. Osanai and K. Soai, *J. Am. Chem. Soc.*, **1998**, *120*, 12157–12158.

(7) Practically Perfect Asymmetric Autocatalysis using 2-Alkynyl-5-pyrimidylalkanol. T. Shibata, S. Yonekubo and K. Soai, *Angew. Chem. Int. Ed.*, **1999**, *38*, 659–661.

(8) *d*- and *l*-Quartz-Promoted Highly Enantioselective Synthesis of a Chiral Organic Compound. K. Soai, S. Osanai, K. Kadowaki, S. Yonekubo, T. Shibata and I. Sato, *J. Am. Chem. Soc.*, **1999**, *121*, 11235–11236.

(9) Asymmetric Synthesis of an Organic Compound with High Enantiomeric Excess Induced by Inorganic Ionic Sodium Chlorate. I. Sato, K. Kadowaki and K. Soai, *Angew. Chem. Int. Ed.*, **2000**, *39*, 1510–1512.

(10) Highly Enantioselective Synthesis Induced by Chiral Primary Alcohols Due to Deuterium Substitution. I. Sato, D. Omiya, T. Saito and K. Soai, *J. Am. Chem. Soc.*, **2000**, *122*, 11739–11740.

(11) Asymmetric Induction by Helical Hydrocarbons: [6]- and [5] Helicenes. I. Sato, R. Yamashima, K. Kadowaki, J. Yamamoto, T. Shibata and K. Soai, *Angew. Chem. Int. Ed.*, **2001**, *40*, 1096–1098.

(12) Amplification of Chirality from Extremely Low to Greater than 99.5% ee by Asymmetric Autocatalysis. I. Sato, H. Urabe, S. Ishiguro, T. Shibata and K. Soai, *Angew. Chem. Int. Ed.*, **2003**, *42*, 315–317.

(13) Asymmetric Synthesis of Pyrimidyl Alkanol without Adding Chiral Substances by The Addition of Diisopropylzinc to Pyrimidine-5-carbaldehyde in Conjunction with Asymmetric Autocatalysis. K. Soai, I. Sato, T. Shibata, S. Komiya, M. Hayashi, Y. Matsueda, H. Imamura, T. Hayase, H. Morioka, H. Tabira, J. Yamamoto and Y. Kowata, *Tetrahedron Asymmetry*, **2003**, *14*, 185–188.

(14) Asymmetric Synthesis Utilizing Circularly Polarized Light Mediated by the Photoequilibrium of Chiral Olefins in Conjunction with Asymmetric Autocatalysis. I. Sato, R. Sugie, Y. Matsueda, Y. Furumura and K. Soai, *Angew. Chem. Int. Ed.*, **2004**, *43*, 4490–4492.

(15) Enantioselective Synthesis of Near Enantiopure Compound by Asymmetric Autocatalysis Triggered by Asymmetric Photolysis with Circularly Polarized Light. T. Kawasaki, M. Sato, S. Ishiguro, T. Saito, Y. Morishita, I. Sato, H. Nishino, Y. Inoue

and K. Soai, *J. Am. Chem. Soc.*, **2005**, *127*, 3274–3275.

(16) Asymmetric Amplification Using Chiral Co-crystal Formed from Achiral Organic Molecules by Asymmetric Autocatalysis. T. Kawasaki, K. Jo, H. Igarashi, I. Sato, M. Nagano, H. Koshima and K. Soai, *Angew. Chem. Int. Ed.*, **2005**, *44*, 2774–2777.

(17) Small Amounts of Achiral β-Amino Alcohols Reverse the Enantioselectivity of Chiral Catalysts in Cooperative Asymmetric Autocatalysis. F. Lutz, T. Igarashi, T. Kawasaki and K. Soai, *J. Am. Chem. Soc.*, **2005**, *127*, 12206–12207.

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(19) Achiral Nucleobase Cytosine Acts as an Origin of Homochirality of Biomolecules in Conjunction with Asymmetric Autocatalysis. T. Kawasaki, K. Suzuki, Y. Hakoda and K. Soai, *Angew. Chem. Int. Ed.*, **2008**, *47*, 496–499.

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(21) Asymmetric Autocatalysis Triggered by Carbon Isotope ($^{13}C/^{12}C$) Chirality. T. Kawasaki, Y. Matsumura, T. Tsutsumi, K. Suzuki, M. Ito and K. Soai, *Science,* **2009**, *324*, 492–495.

(22) Generation of Absolute Controlled Crystal Chirality by the Removal of Crystal Water from Achiral Crystal of Nucleobase Cytosine. T. Kawasaki, Y. Hakoda, H. Mineki, K. Suzuki and K. Soai, *J. Am. Chem. Soc.*, **2010**, *132*, 2874–2875.

(23) Enantioselective C-C Bond Formation as a Result of the Oriented Prochirality of an Achiral Aldehyde at the Single-Crystal Face upon Treatment with a Dialkyl Zinc Vapor. T. Kawasaki, S. Kamimura, A. Amihara, K. Suzuki and K. Soai, *Angew. Chem. Int. Ed.*, **2011**, *50*, 6796–6798.

(24) Asymmetric Autocatalysis: Triggered by Chiral Isotopomer Arising from Oxygen Isotope Substitution. T. Kawasaki, Y. Okano, E. Suzuki, S. Takano, S. Oji and K. Soai, *Angew. Chem. Int. Ed.*, **2011**, *50*, 8131–8133.

(25) Asymmetric Autocatalysis Induced by Cinnabar: Observation of the Enantioselective Adsorption of a 5-Pyrimidyl Alkanol on the Crystal Surface. H. Shindo, Y. Shirota, K. Niki, T. Kawasaki, K. Suzuki, Y. Araki, A. Matsumoto and K. Soai, *Angew. Chem. Int. Ed.*, **2013**, *52*, 9135–9138.

(26) Self-replication and Amplification of Enantiomeric Excess of Chiral Multi-functionalized Large Molecule by Asymmetric Autocatalysis. T. Kawasaki, M. Nakaoda, Y. Takahashi, Y. Kanto, N. Kuruhara, K. Hosoi, I. Sato, A. Matsumoto and K. Soai, *Angew. Chem. Int. Ed.*, **2014**, *53*, 11199–11202.

(27) Crystal Structure of Isopropylzinc Alkoxide of Pyrimidyl Alkanol: Mechanistic Insights for Asymmetric Autocatalysis with Amplification of Enantiomeric Excess. A.

Matsumoto, T. Abe, A. Hara, T. Tobita, T. Sasagawa, T. Kawasaki and K. Soai, *Angew. Chem. Int. Ed.*, **2015**, *54*, 15218–15221.

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(29) Achiral Inorganic Gypsum Acts as an Origin of Chirality through Its Enaniotopic Surface in Conjunction with Asymmetric Autocatalysis. A. Matsumoto, Y. Kaimori, M. Uchida, H. Omori, T. Kawasaki and K. Soai, *Angew. Chem. Int. Ed.*, **2017**, *56*, 545–548.

(30) Formation of Enantioenriched Alkanol with Stochastic Distribution of Enantiomers in the Absolute Asymmetric Synthesis Under Heterogeneous Solid-Vapor Phase Conditions. Y. Kaimori, Y. Hiyoshi, T. Kawasaki, A. Matsumoto and K. Soai, *Chem. Commun.*, **2019**, *55*, 5223–5226.

Review and Books

(1) Asymmetric Autocatalysis. Chiral Symmetry Breaking and the Origins of Homochirality of Organic Molecules. K. Soai, *Proc. Jpn. Acad., Ser. B*, **2019**, *95*, 89–109.

(2) “*Amplification of Chirality*,” Ed. K. Soai, Topics in Current Chemistry, Vol. 284, Springer, **2008**, Heidelberg.

(3) “*Asymmetric Autocatalysis. The Soai Reaction*,” Ed. K. Soai, T. Kawasaki and A. Matsumoto, Catalysis Series No. 43, The Royal Society of Chemistry, **2022**, London.