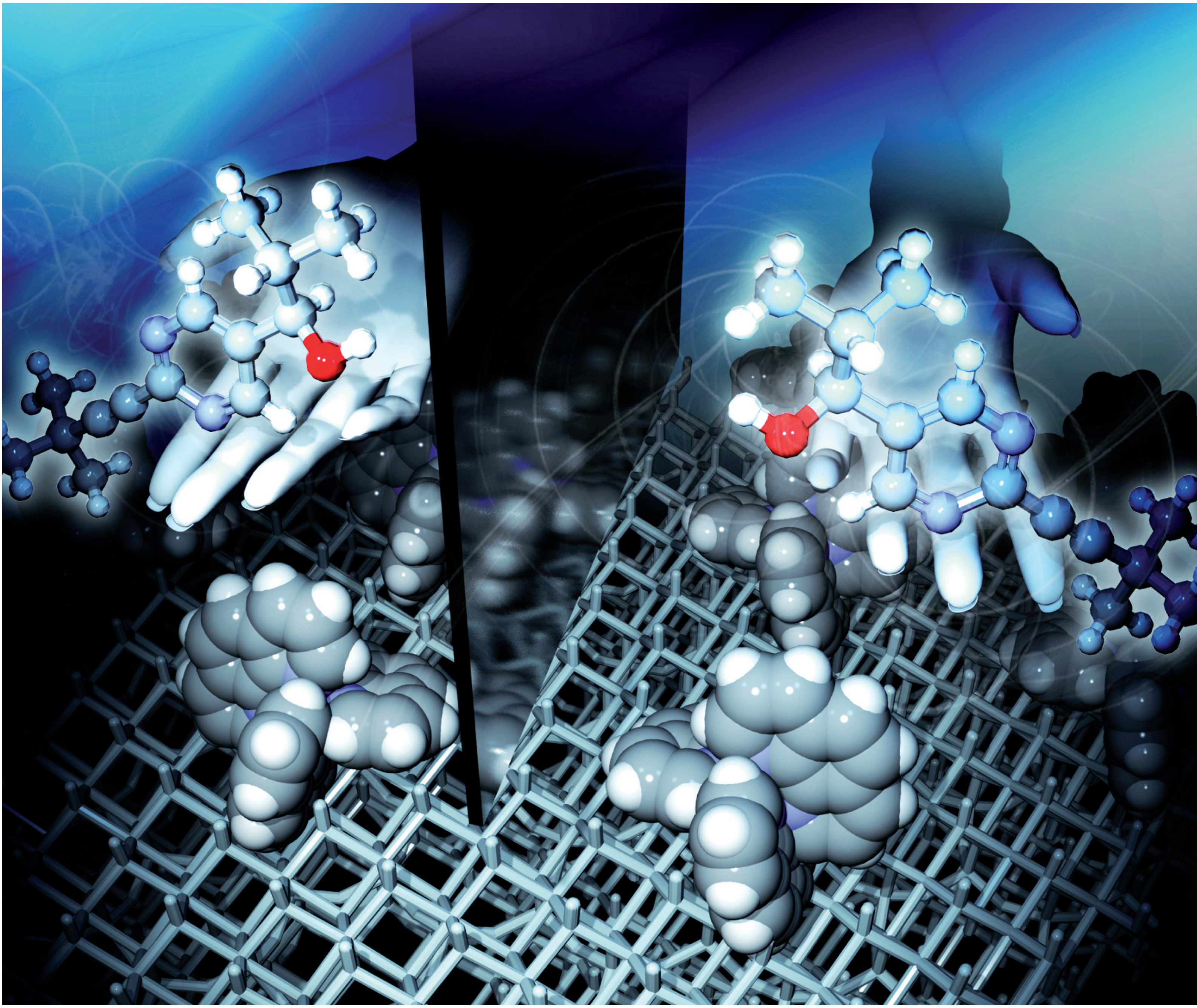
Organic & Biomolecular Chemistry

www.rsc.org/obc

Volume 7 | Number 6 | 21 March 2009 | Pages 1029-1232

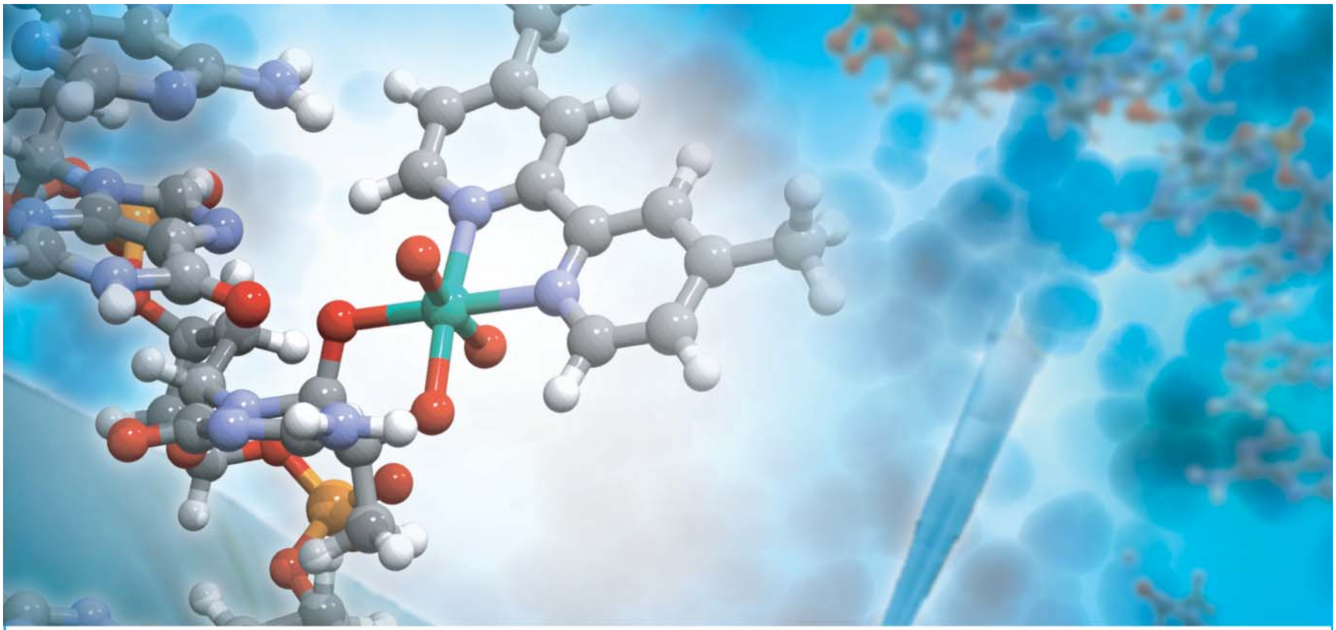


ISSN 1477-0520

RSC Publishing

COMMUNICATION
Tsuneomi Kawasaki *et al.*
Highly enantioselective asymmetric autocatalysis using chiral ruthenium complex-ion-exchanged synthetic hectorite as a chiral initiator

1477-0520(2009)7:6;1-9



Introducing Tsuneomi Kawasaki

OBC poster prize winner

Dr Tsuneomi Kawasaki from Tokyo University of Science, Japan, was awarded the *OBC* poster prize at Chirality at the Nanoscale held in Sitges, Spain on 17th-21st September 2007. His prize-winning work was entitled 'Discrimination of carbon isotope chirality by asymmetric autocatalysis with amplification of enantiomeric excess.' In his poster, Tsuneomi showed that asymmetric autocatalysis is a powerful method for discriminating chirality due only to carbon isotope substitution in organic molecules.

In this communication, Kenso Soai, Tsuneomi Kawasaki and colleagues continue their work on asymmetric autocatalysis and investigate enantioselective synthesis using chiral clays.

Dr Kawasaki (left) receiving his award from *OBC* assistant editor Joanne Thomson

RSC Publishing

www.rsc.org/obc

Registered Charity Number 207890

Highly enantioselective asymmetric autocatalysis using chiral ruthenium complex-ion-exchanged synthetic hectorite as a chiral initiator†

Tsuneomi Kawasaki,[a,b] Toshiki Omine,[a] Kenta Suzuki,[a] Hisako Sato,[c,d] Akihiko Yamagishi[e] and Kenso Soai*[a,b]

Received 5th January 2009, Accepted 15th January 2009
First published as an Advance Article on the web 23rd January 2009
DOI: 10.1039/b823282b

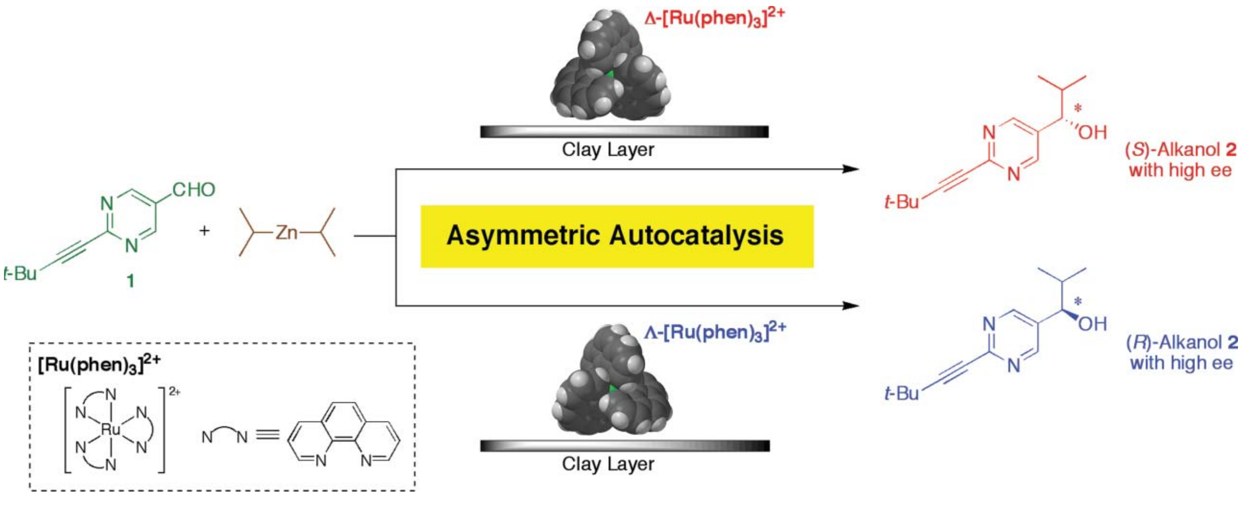
The synthetic hectorite containing intercalated chiral Δ- and Λ-tris(1,10-phenanthroline)ruthenium(II) ions acts as a heterogeneous chiral catalyst in the enantioselective addition of diisopropylzinc to pyrimidine-5-carbaldehyde to afford, in combination with asymmetric autocatalytic amplification of enantiomeric excess, 5-pyrimidyl alkanol with high enantiomeric excess.

In the field of asymmetric catalysis, the development of efficient heterogeneous chiral catalysts to control enantioselective organic reactions is a major focus of research interest.[1] One of the main advantages of a heterogeneous catalyst over a homogeneous catalyst is easy separation of the catalyst from the reaction mixture, which can be recovered and reused in the next reaction. Although heterogeneous chiral catalysts have been developed for enantioselective reactions, most of them are polystyrene-bound and organic polymer-based chiral catalysts.[2] However, inorganic materials such as silicas, zeolites and clay minerals have significant advantages over organic polymers, because of the large surface area and remarkable stability against chemical and physical destruction.[3–6]

Among these inorganic materials, synthetic sodium hectorite (Laponite XLG, Rockwood Additives, Ltd.) has been used in a wide range of scientific research[7] because of its unique properties, such as an expanded interlayer space, cation exchange ability and great stability. However, immobilization of chiral organic cations and metal complexes onto the surface of synthetic hectorite has been reported,[8] to the best of our knowledge, for only a limited number of applications of this type of material to enantioselective synthesis. Thus, highly enantioselective synthesis using a chiral metal complex immobilized on synthetic hectoride is an emerging challenge.

On the other hand, during our continuing study on asymmetric autocatalysis[9,10] we found that the asymmetric autocatalysis of 5-pyrimidyl alkanol in the enantioselective addition of diisopropylzinc (i-Pr_2Zn) to pyrimidine-5-carbaldehyde proceeds with an amplification of enantiomeric excess (ee).[11,12]

We report here that the synthetic sodium hectorite ($(Na_{0.70})[(Si_{8.00})(Mg_{3.50}Li_{0.30})]O_{20}(OH)_4$), in which the chiral Δ- and Λ-tris(1,10-phenanthroline)ruthenium(II) cation, $[Ru(phen)_3]^{2+}$ is intercalated,[13] acts as a heterogeneous chiral inducer in the enantioselective addition of i-Pr_2Zn to pyrimidine-5-carbaldehyde **1** to afford, in combination with asymmetric autocatalysis, 5-pyrimidyl alkanol **2** with high ee. Octahedral $[Ru(phen)_3]^{2+}$ shows chirality because of the topological coordination of its achiral bidentate phenanthroline ligands, therefore the absolute configuration of the corresponding alkanol **2** was controlled efficiently by the chirality of the ligand configuration around the metal center (Scheme 1).[14]



Scheme 1 Asymmetric autocatalysis initiated by synthetic hectorite, which was modified using the chiral intercalator Δ- and Λ-$[Ru(phen)_3]^{2+}$ cations.

---

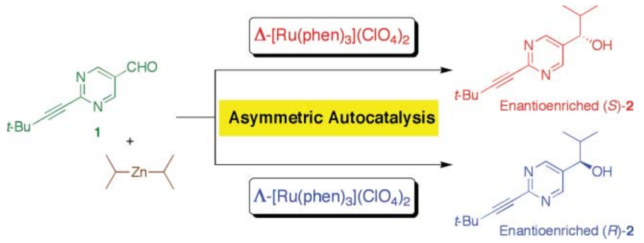
[a] Department of Applied Chemistry, Tokyo University of Science, Kagurazaka, Shinjuku-ku, Tokyo, 162-8601, Japan. E-mail: soai@rs.kagu.tus.ac.jp; Fax: +81 3 5261 4631; Tel: +81 3 5228 8261
[b] Chiral Materials Research Center, Research Institute of Science and Technology, Tokyo University of Science, Kagurazaka, Shinjuku-ku, Tokyo, 162-8601, Japan
[c] Graduate School of Science, The University of Tokyo, Hongo, Bunkyo-ku, Tokyo, 113-0033, Japan
[d] PRESTO, Japan Science and Technology Agency, Chiba
[e] Ochanomizu University, Ohtsuka, Bunkyo-ku, Tokyo, 112-8610, Japan
† This work was supported by a Grant-in-Aid from the Ministry of Education, Culture, Sports, Science and Technology.

Table 1 Heterogeneous enantioselective synthesis of chiral pyrimidyl alkanol **2** by the reaction of i-Pr$_2$Zn with aldehyde **1** in the presence of the chiral ruthenium complex modified synthetic hectorite

		Pyrimidyl alkanol **2**		
Entry[a]	Intercalator[b]	Yield[c] (%)	Ee[d] (%)	Configuration
1	Δ-$[Ru(phen)_3]^{2+}$	80	69	*S*
2	Λ-$[Ru(phen)_3]^{2+}$	91	90	*R*
3	Δ-$[Ru(phen)_3]^{2+}$	82	63	*S*
4	Λ-$[Ru(phen)_3]^{2+}$	80	69	*R*
5	Δ-$[Ru(phen)_3]^{2+}$	90	44	*S*
6	Λ-$[Ru(phen)_3]^{2+}$	85	72	*R*

[a] Typical experiment (entry 1): i-Pr$_2$Zn in toluene (0.075 mL, 0.075 mmol) was added dropwise to a toluene (0.1 mL) solution of Λ-form synthetic hectorite (87 mg) and aldehyde **1** (4.7 mg, 0.025 mmol) over a period of 2 h at 0 °C. After stirring overnight, toluene (1.1 mL) and i-Pr$_2$Zn in toluene (0.2 mL, 0.2 mmol) were added, then a toluene (1.0 mL) solution of **1** (18.8 mg, 0.1 mmol) was added. After stirring for 2 h, toluene (3.6 mL) and i-Pr$_2$Zn in toluene (0.8 mL, 0.8 mmol) were added successively, and then a toluene (2.5 mL) solution of **2** (75.3 mg, 0.4 mmol) was added and the reaction mixture was stirred for 2 h at 0 °C. Once again, toluene (7.2 mL) and i-Pr$_2$Zn in toluene (1.6 mL, 1.6 mmol) were added, and a toluene (5.0 mL) solution of **1** (150.6 mg, 0.8 mmol) was added. After the mixture was stirred for 2 h at 0 °C, the reaction was quenched with 1 M hydrochloric acid (5 mL), and neutralized with a saturated sodium hydrogen carbonate solution (15 mL). The mixture was then filtered using Celite, and the filtrate extracted using ethyl acetate three times. The combined organic layers were dried over anhydrous sodium sulfate and evaporated *in vacuo.* Purification of the residue using silica gel column chromatography (hexane:ethyl acetate = 3:1 to 2:1, v/v) gave the (*S*)-5-pyrimidyl alkanol **2** with 69% ee in 81% yield. [b] See ref. 13. [c] Isolated yield. [d] The ee value was determined by HPLC using a chiral stationary phase (Daicel Chiralpak IB column (250 × 4.6 mm ID), eluent = 5% 2-propanol in hexane, flow rate 1.0 mL min^{-1}, 254 nm UV detector, retention time 10.5 min for (*S*)-**2**, 15.2 min for (*R*)-**2**).

Table 2 Enantioselective synthesis of chiral pyrimidyl alkanol **2** by the reaction of i-Pr$_2$Zn with aldehyde **1** in the presence of the chiral ruthenium complex



		Pyrimidyl alkanol **2**		
Entry[a]	Configuration of Ru-complex	Yield[b] (%)	Ee[c] (%)	Configuration
1	Δ	89	91	*S*
2	Λ	85	88	*R*
3	Δ	85	91	*S*
4	Λ	90	84	*R*
5	Δ	91	87	*S*
6	Λ	87	85	*R*

[a] See footnote *a* in Table 1. [b] See footnote *c* in Table 1. [c] See footnote *d* in Table 1.

The results of the enantioselective addition of i-Pr$_2$Zn to pyrimidine-5-carbaldehyde **1** in the presence of chiral $[Ru(phen)_3]^{2+}$ intercalated synthetic hectorite are shown in Table 1. When the i-Pr$_2$Zn addition was performed in the presence of Δ-$[Ru(phen)_3]^{2+}$ intercalated synthetic hectorite, (*S*)-5-pyrimidyl alkanol **2** was obtained in 80% yield with an ee of 69% (Table 1, Entry 1). On the other hand, in the presence of Λ-$[Ru(phen)_3]^{2+}$ intercalated synthetic hectorite, the opposite enantiomer, (*R*)-**2** with 90% ee was formed in 91% yield (Entry 2). Asymmetric autocatalyses using Δ- and Λ-$[Ru(phen)_3]^{2+}$ immobilized synthetic hectorite support this reproducibility, that is, the Δ-form induced the formation of (*S*)-**2** and Λ-**1**, (*R*)-**2** respectively (Entries 3–6). Thus, the absolute configurations of the resulting alkanols **2** depend on those of the chiral intercalating ruthenium complexes.

Next, we examined the asymmetric autocatalytic reaction utilizing $[Ru(phen)_3](ClO_4)_2$ complex as a source of chirality to investigate the adsorption effect of the ruthenium complex toward the ability to achieve asymmetric induction. The results of the enantioselective asymmetric autocatalysis in the presence of only the ruthenium complex without intercalation are shown in Table 2. When the i-Pr$_2$Zn addition was performed in the presence of Δ-$[Ru(phen)_3](ClO_4)_2$, (*S*)-5-pyrimidyl alkanol **2** was obtained in 89% yield with an ee of 91% (Table 2, Entry 1). Conversely, when the Λ-complex was subjected to the autocatalytic i-Pr$_2$Zn addition, the formation of the opposite enantiomer, (*R*)-**2** with 88% ee was induced in 85% yield (Entry 2). The correlation between the topology of the ruthenium complex and the absolute configuration of the corresponding **2** was reproducible, that is, the Δ- and Λ-$[Ru(phen)_3](ClO_4)_2$ act as the chiral initiators of asymmetric autocatalysis to afford the enantiomerically enriched *S*- and *R*-pyrimidyl alkanol **2**, respectively (Entries 3–6).

In conclusion, autocatalytic enantioselective addition of i-Pr$_2$Zn to pyrimidine-5-carbaldehyde **2** in the presence of chiral Δ- and Λ-$[Ru(phen)_3]^{2+}$ complex-ion-exchanged synthetic hectorite as the heterogeneous inducer gave (*S*)- and (*R*)-5-pyrimidyl alkanol **2** with high ee, respectively, in conjunction with amplification of ee.[15] In addition, using the ruthenium complex alone without the intercalation, the same relationship between the absolute configuration of ruthenium cation and obtained chiral product pyrimidyl alkanol **2** was observed. We believe that the results reported here enhance the possibility of the synthetic hectorite modified by chiral complex being used as a solid-state asymmetric catalyst for many organic reactions.

Notes and references

1 *Chiral Catalysts Immobilization and Recycling*, ed. D. E. De Vos, I. F. J. Vankelecom, and P. A. Jacobs, Wiley-VCH, Weinheim, 2000; J. A. Gladysz, *Chem. Rev.*, 2002, **102**, 3215–3892; H.-U. Blaser, *Tetrahedron: Asymmetry*, 1991, **2**, 843–866.
2 S. Itsuno and J. M. Fréchet, *J. Org. Chem.*, 1987, **52**, 4140–4143; K. Soai, S. Niwa and M. Watanabe, *J. Org. Chem.*, 1988, **53**, 927–928.
3 P. McMorn and G. J. Hutchings, *Chem. Soc. Rev.*, 2004, **33**, 108–122.
4 K. Soai, M. Watanabe and A. Yamamoto, *J. Org. Chem.*, 1990, **55**, 4832–4835.
5 K. C. W. Chong, J. Sivaguru, T. Shichi, Y. Yoshimi, V. Ramamurthy and J. R. Scheffer, *J. Am. Chem. Soc.*, 2002, **124**, 2858–2859.
6 S. Fujita, H. Sato, N. Kakegawa and A. Yamagishi, *J. Phys. Chem. B*, 2006, **110**, 2533–2540.
7 S. Takagi, D. A. Tryk and H. Inoue, *J. Phys. Chem. B*, 2002, **106**, 5455–5460; S. Takagi, M. Shimada, M. Eguchi, T. Yui, H. Yoshida, D. A. Tryk and H. Inoue, *Langmuir*, 2002, **18**, 2265–2272; R. Sasai, N. Iyi, T. Fujita, F. L. Arbeloa, V. M. Martinez, K. Takagi and H. Itoh, *Langmuir*, 2004, **20**, 4715–4719.

8 S. Shimazu, T. Hirano and T. Uematsu, *Applied Catalysis*, 1987, **34**, 255–261; J. M. Fraile, J. I. García, J. A. Mayoral and M. Roldán, *Org. Lett.*, 2007, **9**, 731–733.

9 K. Soai, T. Shibata and I. Sato, *Acc. Chem. Res.*, 2000, **33**, 382–390; K. Soai, in *Fundamentals of Life*, ed. G. Pályi, C. Zucchi, and L. Caglioti, Elsevier, Paris, 2002, ch. III. 7, pp. 427–435; K. Soai and T. Kawasaki, *Chirality*, 2006, **18**, 469–478; K. Soai, T. Kawasaki, in *Asymmetric Synthesis -The Essentials*, ed. C. Brase, Wiley-VCH, 2007, pp. 212–216; K. Soai, T. Kawasaki, in *Recent Developments in Physical Chemistry*, ed. E. Diaz-Herrera, and E. Juaristi, American Institute of Physics, Melville, New York, 2008, pp. 68–79; K. Soai and T. Kawasaki, *Top. Curr. Chem.*, 2008, **284**, 1–33.

10 C. Bolm, F. Bienewald and A. Seger, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 1657–1659; M. Avalos, R. Babiano, P. Cintas, J. L. Jiménez and J. C. Palacios, *Chem. Commun.*, 2000, 887–892; M. H. Todd, *Chem. Soc. Rev.*, 2002, **31**, 211–222; J. Podlech and T. Gehring, *Angew. Chem., Int. Ed.*, 2005, **44**, 5776–5777; L. Caglioti, C. Zucchi and G. Pályi, *Chemistry Today (Chimica Oggi)*, 2005, **23**, 38–39; I. D. Gridnev, *Chem. Lett.*, 2006, **35**, 148–153; J. Stankiewicz and L. H. Eckardt, *Angew. Chem., Int. Ed.*, 2006, **45**, 342–344.

11 K. Soai, T. Shibata, H. Morioka and K. Choji, *Nature*, 1995, **378**, 767–768; T. Shibata, S. Yonekubo and K. Soai, *Angew. Chem., Int. Ed.*, 1999, **38**, 659–661; I. Sato, H. Urabe, S. Ishiguro and T. Shibata, *Angew. Chem., Int. Ed.*, 2003, **42**, 315–317; F. Lutz, T. Kawasaki and K. Soai, *Tetrahedron: Asymmetry*, 2006, **17**, 486–490.

12 T. Shibata, J. Yamamoto, N. Matsumoto, S. Yonekubo, S. Osanai and K. Soai, *J. Am. Chem. Soc.*, 1998, **120**, 12157–12158; I. Sato, D. Omiya, T. Saito and K. Soai, *J. Am. Chem. Soc.*, 2000, **122**, 11739–11740; 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; 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; K. Soai, S. Osanai, K. Kadowaki, S. Yonekubo, T. Shibata and I. Sato, *J. Am. Chem. Soc.*, 1999, **121**, 11235–11236; T. Kawasaki, K. Jo, H. Igarashi, I. Sato, M. Nagano, H. Koshima and K. Soai, *Angew. Chem., Int. Ed.*, 2005, **44**, 2774–2777; T. Kawasaki, H. Tanaka, T. Tsutsumi, T. Kasahara, I. Sato and K. Soai, *J. Am. Chem. Soc.*, 2006, **128**, 6032–6033; T. Kawasaki, K. Suzuki, Y. Hakoda and K. Soai, *Angew. Chem., Int. Ed.*, 2008, **47**, 496–499.

13 N. Kakegawa and A. Yamagishi, *Chem. Mater.*, 2005, **17**, 2997–3003.

14 T. Kawasaki, T. Omine, M. Sato, Y. Morishita and K. Soai, *Chem. Lett.*, 2007, **36**, 30–31; I. Sato, K. Kadowaki, Y. Ohgo, K. Soai and H. Ogino, *Chem. Commun.*, 2001, 1022–1023.

15 F. Lutz, T. Igarashi, T. Kinoshita, M. Asahina, K. Tsukiyama, T. Kawasaki and K. Soai, K., *J. Am. Chem. Soc.*, 2008, **130**, 2956–2958; I. Sato, D. Omiya, H. Igarashi, K. Kato, Y. Ogi, K. Tsukiyama and K. Soai, *Tetrahedron: Asymmetry*, 2003, **14**, 975–979; D. G. Blackmond, C. R. McMillan, S. Ramdeehul, A. Schorm and J. M. Brown, *J. Am. Chem. Soc.*, 2001, **123**, 10103–10104; I. D. Gridnev, J. M. Serafimov and J. M. Brown, *Angew. Chem., Int. Ed.*, 2004, **43**, 4884–4887; T. Buhse, *Tetrahedron: Asymmetry*, 2003, **14**, 1055–1061; J. R. Islas, D. Lavabre, J.-M. Grevy, R. H. Lamoneda, H. R. Cabrera, J.-C. Micheau and T. Buhse, *Proc. Natl. Acad. Sci. USA*, 2005, **102**, 13743–13748; G. Lente, *J. Phys. Chem. A*, 2004, **108**, 9475–9478; Y. Saito and H. Hyuga, *J. Phys. Soc. Jpn.*, 2004, **73**, 1685–1688; K. Micskei, G. Pota, L. Caglioti and G. Pályi, *J. Phys. Chem. A*, 2006, **110**, 5982–5984; J. Klankermayer, I. D. Gridnev and J. M. Brown, *Chem. Commun.*, 2007, 3151–3153; L. Schiaffino and G. Ercolani, *Angew. Chem., Int. Ed.*, 2008, **47**, 6832–6835; G. Pályi, K. Micskei, L. Zekany, C. Zucchi and L. Caglioti, *Magyar Kem. Lapja*, 2005, **60**, 17–24.