

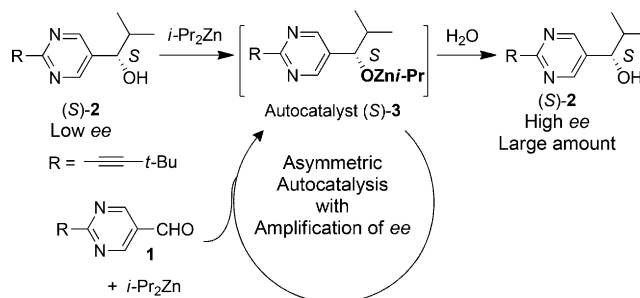
Crystal Structure of the Isopropylzinc Alkoxide of Pyrimidyl Alkanol: Mechanistic Insights for Asymmetric Autocatalysis with Amplification of Enantiomeric Excess

Arimasa Matsumoto,* Takaaki Abe, Atsushi Hara, Takayuki Tobita, Taisuke Sasagawa, Tsuneomi Kawasaki,* and Kenso Soai*

Abstract: Asymmetric amplification during self-replication is a key feature that is used to explain the origin of homochirality. Asymmetric autocatalysis of pyrimidyl alkanol in the asymmetric addition of diisopropylzinc to pyrimidine-5-carbaldehyde is a unique example of this phenomenon. Crystallization of zinc alkoxides of this 5-pyrimidyl alkanol and single-crystal X-ray diffraction analysis of the alkoxide crystals reveal the existence of tetramer or higher oligomer structures in this asymmetric autocatalytic system.

The origin of biological homochirality, such as that found in L-amino acids, is a fundamental question that has attracted the interest of scientists from a wide range of research areas.^[1] Although there are several possible origins of homochirality, propagation and amplification of chirality generated from the initial breaking of symmetry are also key topics for the evolution of homochirality. Asymmetric autocatalysis with amplification of chirality has been suggested as a mechanistic model for the evolution of homochirality. In this reaction, a chiral product serves as an asymmetric catalyst to produce more of itself; the process is thus an automultiplication of the chiral compound.

We found asymmetric autocatalysis with amplification of the enantiomeric excess (*ee*) in a real chemical reaction (Scheme 1).^[2–4] When diisopropylzinc (*i*Pr₂Zn) is added to pyrimidine-5-carbaldehyde **1** in the presence of a catalytic



Scheme 1. Asymmetric autocatalytic reaction of pyrimidyl alkanol.

amount of (*S*)-pyrimidyl alkanol **2** with a low *ee*, asymmetric autocatalytic amplification of the *ee* produces (*S*)-**2** with high *ee* as the final product. Early autocatalytic work with pyrimidine-5-carbaldehyde^[2a] and 2-methylpyrimidine-5-carbaldehyde was succeeded by the use of superior 2-alkynyl analogues^[2b] and the amplification efficiency was dramatically increased to obtain product **2** with more than 99.5 % *ee* after consecutive asymmetric autocatalytic amplification, even when the initial catalyst has only ca. 5×10^{-5} % *ee*. This unique property means that, in addition to chiral molecules, a trace imbalance of chirality induced by chiral triggers such as circularly polarized light,^[5] crystal chirality,^[6] various chiral materials,^[7] or isotope chirality^[8] can also be amplified to afford enantioenriched alkanol **2** with corresponding absolute configurations. Furthermore, spontaneous absolute asymmetric synthesis can be achieved by using this reaction.^[9]

Although the theory of asymmetric amplification during self-replication was first proposed in 1953,^[10] the above reaction remains the only practical example of a chemical reaction involving asymmetric autocatalysis that leads to high levels of amplification of *ee*. Several studies have been undertaken to understand the mechanism of this reaction. The large amplification of *ee* observed in this autocatalytic reaction is often explained by the formation of aggregates, which has been proposed to account for the positive nonlinear effect observed during asymmetric catalysis.^[11] Mechanistic studies based on kinetic experiments,^[12] reaction modeling,^[13] NMR,^[14] and DFT calculations^[15] have been examined by several research groups. Early analysis of autocatalysis kinetics showed this to be incompatible with the reactive monomer model from non-autocatalytic asymmetric zinc alkylation,^[11c] and indicated that a homochiral dimer was the active entity, with heterochiral dimers being inactive.^[12b] Dimeric catalysis with a tetramic transition-state cycle was

[*] Dr. A. Matsumoto, T. Abe, A. Hara, T. Tobita, T. Sasagawa, Prof. Dr. K. Soai
Department of Applied Chemistry, Tokyo University of Science
Kagurazaka, Shinjuku-ku, Tokyo 162-8601 (Japan)
E-mail: soai@rs.kagu.tus.ac.jp

Dr. A. Matsumoto, Prof. Dr. T. Kawasaki, Prof. Dr. K. Soai
Research Institute for Science and Technology
Tokyo University of Science
Kagurazaka, Shinjuku-ku, Tokyo 162-8601 (Japan)

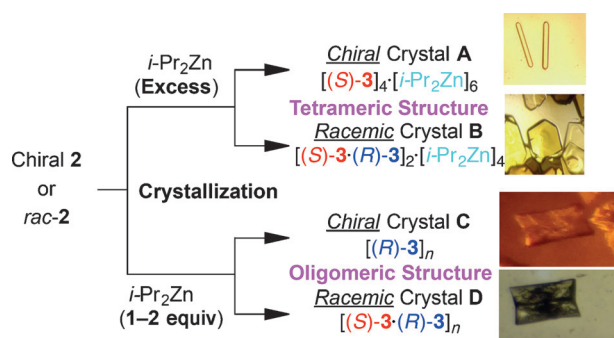
Prof. Dr. T. Kawasaki
Department of Materials Science and Engineering
Faculty of Engineering, University of Fukui
Bunkyo, Fukui 910-8507 (Japan)

Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/anie.201508036>.

© 2015 The Authors. Published by Wiley-VCH Verlag GmbH & Co. KGaA. This is an open access article under the terms of the Creative Commons Attribution Non-Commercial NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

then suggested based on the nearly second-order kinetics with respect to the aldehyde.^[12d] NMR spectroscopy also supported the existence of dimer species^[14b] and DFT calculations based on this mechanism suggested a difference in catalytic activity between enantiopure and racemic dimers.^[15d] However, the observed significant amplification efficiency^[12a,c] cannot be fully explained by these models. The inclusion of tetramers or higher oligomers in the reaction system was proposed.^[15c,e] Recently, NMR studies revealed the existence of tetramers or higher species and kinetics studies showed an inverse temperature dependence of the reaction, which also support the involvement of tetramers or higher oligomers.^[14c,d] Furthermore, various possible conformations of oligomers were calculated by DFT method.^[15b] Irrespective of whether the active catalyst or resting state is a dimer or higher oligomer(s), the formation of an aggregate seems to be a key feature of this reaction. However, no detailed structural study of the asymmetric autocatalyst has been undertaken by X-ray diffraction analysis.^[16]

Herein, we report the single-crystal X-ray analysis of the asymmetric autocatalyst **3**, that is, the isopropylzinc alkoxide of **2**, and reveal that, depending on the conditions, enantiopure and racemic alkoxides can have completely different structures (Scheme 2).



Scheme 2. Crystallization of the zinc alkoxide of 5-pyrimidyl alkanol.

Single crystals of enantiopure zinc alkoxide were generated by reacting enantiopure (*S*)-5-pyrimidyl alkanol **2** with excess neat *i*Pr₂Zn (8.4 equiv) at room temperature; the alkanol was dissolved by heating at 80 °C and single crystals were obtained after allowing the solution to stand at room temperature for 1–2 weeks. Racemic zinc alkoxide was obtained similarly by reacting racemic alkanol **2** with an excess of neat *i*Pr₂Zn (8.4 equiv).

Single-crystal X-ray diffraction analysis, which was performed at 100 K, revealed that the enantiopure alkoxides form a tetramer structure in the orthorhombic space group *P*2₁2₁2₁ (Crystal **A**, Figure 1a), and that racemic alkoxides form a tetramer structure in the monoclinic space group *C*2/*c* (Crystal **B**, Figure 1b). In both structures, two alkoxides form Zn₂O₂ square dimers and two dimers coordinate to each other to form a 12-membered macrocycle through nitrogen coordination to the zinc atom in a Zn₂O₂ square; both structures contain coordinatively unsaturated zinc. In the racemic tetramer **B**, (*R*)- and (*S*)-alkoxides form Zn₂O₂ square dimers, and macrocycle were also constructed with (*R*)- and

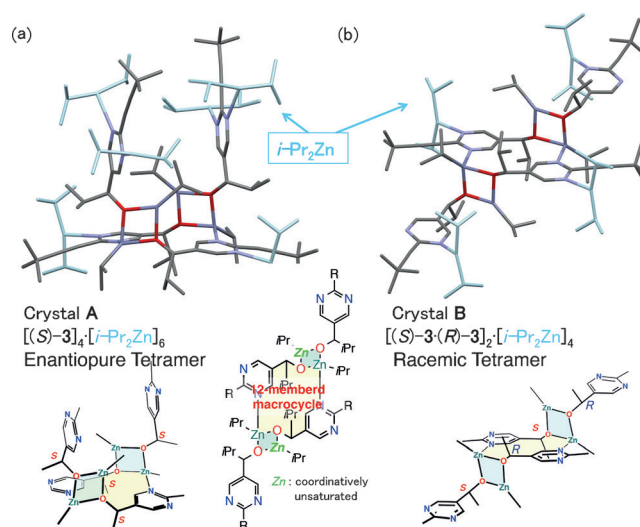


Figure 1. Single-crystal X-ray structures and simplified schematic drawing of alkoxide tetramer crystallized with excess *i*Pr₂Zn. a) Enantiopure alkoxide tetramer crystal **A**. b) Racemic alkoxide tetramer crystal **B**.

(*S*)-alkoxides. This Zn₂O₂ square and macrocycle tetramer structure has good accordance with the proposed stable tetramer structure by DFT calculations including steric hindrance of isopropyl group.^[16c] In the chiral tetramer **A**, six *i*Pr₂Zn moieties coordinate to the nitrogen atoms that do not coordinate to the Zn₂O₂ square. These coordinated *i*Pr₂Zn are activated by nitrogen coordination, with C–Zn–C angles of 156–164°, and with a C–Zn bond length of 1.99–2.01 Å.^[16–18] In the racemic alkoxide crystal **B**, four *i*Pr₂Zn moieties coordinate.

The most remarkable difference between enantiopure and racemic alkoxide is the direction of the outer alkoxide groups. In the racemic tetramer **B**, two Zn₂O₂ rings are located on the side opposite to the 12-membered macrocycle and the pyrimidyl alkoxide is also located on the opposite side. In contrast, in the chiral tetramer **A**, the Zn₂O₂ rings are located on the same face as the 12-membered macrocycle and the pyrimidyl alkoxides form a face-to-face structure. The Zn–N distance in the 12-membered macrocycle is slightly extended because of this face-to-face structure (Zn–N distance of 2.20 and 2.26 Å for racemic **B** and enantiopure **A** crystal structures, respectively). Thus, the enantiopure tetramer seems to be less stable than the racemic tetramer.^[19]

Zinc alkoxide with oligomeric structures^[16c] was also observed upon changing the crystallization conditions. Mixing 1–2 equivalents of *i*Pr₂Zn with either enantiopure or racemic alkanol afforded Crystals **C** and **D**, respectively, with different structures (Figure 2). Similar to the tetramer structure, Zn₂O₂ dimer structures were bridged through coordination of the zinc atoms to the pyrimidine nitrogen atoms. In these structures, Zn–N coordination led to a one-dimensional (1D) oligomer structure. Although the crystal packing and parameters are different for the enantiopure and racemic oligomer crystals, in contrast to the tetramer structures, the 1D oligomer structures of the alkoxides (for example, the angle of the Zn₂O₂ square) are quite similar in the enantiopure (**C**) and racemic (**D**) versions. These results suggest that

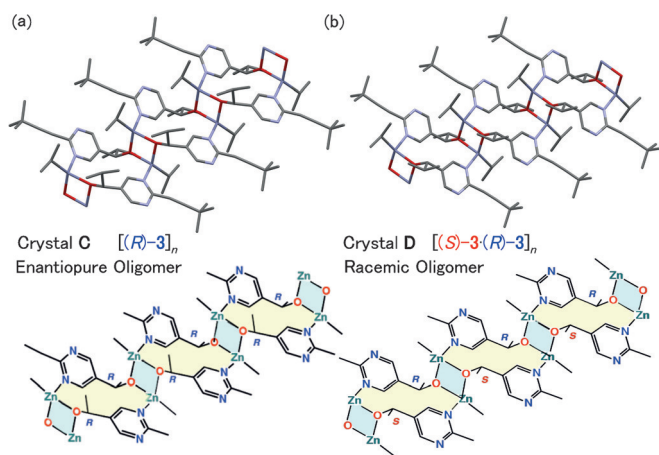


Figure 2. Single-crystal X-ray structures and simplified schematic drawing of alkoxide oligomer crystallized with 1–2 equiv $i\text{Pr}_2\text{Zn}$. a) Enantiopure alkoxide oligomer crystal **C**. b) Racemic alkoxide oligomer crystal **D**.

higher oligomeric structures of both enantiopure and racemic alkoxides exist in the reaction mixture as an equilibrium that depends on the concentration of the alkoxide and $i\text{Pr}_2\text{Zn}$.

In the tetramer crystal **A**, the coordinatively unsaturated zinc is considered to play an important role in the coordination and activation of the aldehyde. When enantiopure catalyst is crystallized in the presence of THF, a highly coordinating solvent, THF occupies the coordination site of the tricoordinating zinc atom to form a crystal **E** of a different structure from crystal **A** (Figure 3). This result is thus consistent with the fact that the asymmetric autocatalytic reaction of pyrimidyl alkanol is suppressed in the presence of THF.^[15b]

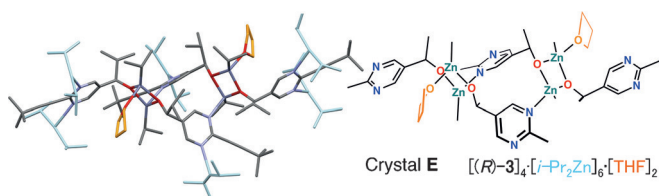


Figure 3. THF-coordinated structure of enantiopure tetramer Crystal **E**.

In conclusion, we have obtained single crystals of the zinc alkoxide of pyrimidyl alkanol. The X-ray structure analysis of these crystals constitutes the first direct observation of the aggregate structure of an asymmetric autocatalyst. Both enantiopure and racemic alkoxides form either tetramer or higher oligomeric structures, the form of which changes dramatically depending on the enantiopurity, amount of $i\text{Pr}_2\text{Zn}$, and solvent. We believe that these coordinative tetramer structures may be key for delivering the high enantiomeric amplification and spontaneous symmetry breaking in the asymmetric autocatalytic reaction of pyrimidyl alkanol.

Experimental Section

Experimental Details for the preparation of Crystals **A–E** and X-ray diffraction analysis were described in supporting information.

CCDC 1420664 (crystal **A**), 1420666 (crystal **B**), 1420663 (crystal **C**), 1420665 (crystal **D**), and 1420667 (crystal **E**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

Acknowledgements

This work has been financially supported by Grant-in-Aid for Scientific Research from Japan Society for the Promotion of Science (JSPS KAKENHI Grant Numbers 23685012, 26810026 & 15H03781) and MEXT-Supported Program for the Strategic Research Foundation at Private Universities, 2012–2016.

Keywords: asymmetric amplification · autocatalysis · enantioselectivity · X-ray diffraction · zinc alkoxide

How to cite: *Angew. Chem. Int. Ed.* **2015**, *54*, 15218–15221
Angew. Chem. **2015**, *127*, 15433–15436

- [1] a) I. Weissbuch, L. Addadi, Z. Berkovitch-Yellin, E. Gati, M. Lahav, L. Leiserowitz, *Nature* **1984**, *310*, 161–164; b) D. K. Kondepudi, R. J. Kaufman, N. Singh, *Science* **1990**, *250*, 975–976; c) M. Bolli, R. Micura, A. Eschenmoser, *Chem. Biol.* **1997**, *4*, 309–320; d) J. S. Siegel, *Chirality* **1998**, *10*, 24–27; e) B. L. Feringa, R. A. van Delden, *Angew. Chem. Int. Ed.* **1999**, *38*, 3418–3438; *Angew. Chem.* **1999**, *111*, 3624–3645; f) M. M. Green, J.-W. Park, T. Sato, A. Teramoto, S. Lifson, R. L. B. Selinger, J. V. Selinger, *Angew. Chem. Int. Ed.* **1999**, *38*, 3138–3154; *Angew. Chem.* **1999**, *111*, 3328–3345; g) J. M. Ribó, J. Crusats, F. Sagués, J. Claret, R. Rubires, *Science* **2001**, *292*, 2063–2066; h) H. Zepik, E. Shavit, M. Tang, T. R. Jensen, K. Kjaer, G. Bolbach, L. Leiserowitz, I. Weissbuch, M. Lahav, *Science* **2002**, *295*, 1266–1269; i) K. Mislow, *Collect. Czech. Chem. Commun.* **2003**, *68*, 849–864; j) S. Pizzarello, A. L. Weber, *Science* **2004**, *303*, 1151; k) C. Viedma, *Phys. Rev. Lett.* **2005**, *94*, 065504; l) V. A. Soloshonok, H. Ueki, M. Yasumoto, S. Mekala, J. S. Hirschi, D. A. Singleton, *J. Am. Chem. Soc.* **2007**, *129*, 12112–12113; m) R. Breslow, Z.-L. Cheng, *Proc. Natl. Acad. Sci. USA* **2010**, *107*, 5723–5725; n) I. Weissbuch, M. Lahav, *Chem. Rev.* **2011**, *111*, 3236–3267; o) K.-H. Ernst, *Phys. Status Solidi B* **2012**, *249*, 2057–2088; p) Y. Saito, H. Hyuga, *Rev. Mod. Phys.* **2013**, *85*, 603–621; q) J. M. Ribó, C. Blanco, J. Crusats, Z. El-Hachemi, D. Hochberg, A. Moyano, *Chem. Eur. J.* **2014**, *20*, 17250–17271; r) S. Olsson, P. M. Björemark, T. Kokoli, J. Sundberg, A. Lennartson, C. J. McKenzie, M. Håkansson, *Chem. Eur. J.* **2015**, *21*, 5211–5219.
- [2] a) K. Soai, T. Shibata, H. Morioka, K. Choji, *Nature* **1995**, *378*, 767; b) T. Shibata, S. Yonekubo, K. Soai, *Angew. Chem. Int. Ed.* **1999**, *38*, 659–661; *Angew. Chem.* **1999**, *111*, 746–748; c) I. Sato, H. Urabe, S. Ishiguro, T. Shibata, K. Soai, *Angew. Chem. Int. Ed.* **2003**, *42*, 315–317; *Angew. Chem.* **2003**, *115*, 329–331.
- [3] a) K. Soai, T. Kawasaki, *Top. Curr. Chem.* **2007**, *284*, 1–31; b) T. Kawasaki, K. Soai, *Bull. Chem. Soc. Jpn.* **2011**, *84*, 879–892; c) K. Soai, T. Kawasaki, *Asymmetric Autocatalysis - Discovery and State of The Art. In The Soai Reaction and Related Topic* (Eds.: G. Pályi, C. Zicchi, L. Caglioti), Academia Nazionale di Scienze Lettere e Arti Modena, Modena, Edizioni Artestampa, **2012**, pp. 9–34; d) T. Kawasaki, K. Soai, *Isr. J. Chem.* **2012**, *52*, 582–590; e) T. Kawasaki, I. Sato, H. Mineki, A. Matsumoto, K. Soai, *Yuki Gosei Kagaku Kyokaiishi* **2013**, *71*, 109–123; f) K. Soai, T. Kawasaki, *Top. Organomet. Chem.* **2013**, *44*, 261–279; g) K. Soai, T. Kawasaki, A. Matsumoto, *Chem. Rec.* **2014**, *14*,

- 70–83; h) K. Soai, T. Kawasaki, A. Matsumoto, *Acc. Chem. Res.* **2014**, *47*, 3643–3654.
- [4] a) M. Avalos, R. Babiano, P. Cintas, J. L. Jiménez, J. C. Palacios, *Chem. Commun.* **2000**, 887–892; b) D. G. Blackmond, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5732–5736; c) J. Podlech, T. Gehring, *Angew. Chem. Int. Ed.* **2005**, *44*, 5776–5777; *Angew. Chem.* **2005**, *117*, 5922–5924; d) “Topics in Current Chemistry” J. M. Brown, I. D. Gridnev, J. Klankermayer, *Amplification of Chirality*, Vol. 284 (Ed.: K. Soai), Springer, Berlin, **2008**, pp. 35–65; e) T. Gehring, M. Busch, M. Schlageter, D. Weingand, *Chirality* **2010**, *22*, E173–E182; f) B. Barabás, J. Tóth, G. Pályi, *J. Math. Chem.* **2010**, *48*, 457–489; g) G. Lente, *Symmetry* **2010**, *2*, 767–798; h) J.-C. Micheau, C. Coudret, T. Buhse, in *The Soai Reaction and Related Topic* (Eds: G. Pályi, C. Zucchi, L. Caglioti), Accad. Nazl. Sci. Lett. Arti, Edizioni Artestampa, Modena, **2012**, pp. 169; i) A. J. Bissette, S. P. Fletcher, *Angew. Chem. Int. Ed.* **2013**, *52*, 12800–12826; *Angew. Chem.* **2013**, *125*, 13034–13061.
- [5] a) I. Sato, R. Sugie, Y. Matsueda, Y. Furumura, K. Soai, *Angew. Chem. Int. Ed.* **2004**, *43*, 4490–4492; *Angew. Chem.* **2004**, *116*, 4590–4592; b) T. Kawasaki, M. Sato, S. Ishiguro, T. Saito, Y. Morishita, I. Sato, H. Nishino, Y. Inoue, K. Soai, *J. Am. Chem. Soc.* **2005**, *127*, 3274–3275.
- [6] a) K. Soai, S. Osanai, K. Kadowaki, S. Yonekubo, T. Shibata, I. Sato, *J. Am. Chem. Soc.* **1999**, *121*, 11235–11236; b) I. Sato, K. Kadowaki, K. Soai, *Angew. Chem. Int. Ed.* **2000**, *39*, 1510–1512; *Angew. Chem.* **2000**, *112*, 1570–1572; c) T. Kawasaki, K. Suzuki, Y. Hakoda, K. Soai, *Angew. Chem. Int. Ed.* **2008**, *47*, 496–499; *Angew. Chem.* **2008**, *120*, 506–509; d) H. Shindo, Y. Shiota, K. Niki, T. Kawasaki, K. Suzuki, Y. Araki, A. Matsumoto, K. Soai, *Angew. Chem. Int. Ed.* **2013**, *52*, 9135–9138; *Angew. Chem.* **2013**, *125*, 9305–9308; e) H. Mineki, Y. Kaimori, T. Kawasaki, A. Matsumoto, K. Soai, *Tetrahedron: Asymmetry* **2013**, *24*, 1365–1367; f) T. Kawasaki, M. Uchida, Y. Kaimori, T. Sasagawa, A. Matsumoto, K. Soai, *Chem. Lett.* **2013**, *42*, 711–713; g) A. Matsumoto, T. Ide, Y. Kaimori, S. Fujiwara, K. Soai, *Chem. Lett.* **2015**, *44*, 688–690.
- [7] a) I. Sato, K. Kadowaki, H. Urabe, J. H. Jung, Y. Ono, S. Shinkai, K. Soai, *Tetrahedron Lett.* **2003**, *44*, 721–724; b) S. Hitosugi, A. Matsumoto, Y. Kaimori, R. Iizuka, K. Soai, H. Isobe, *Org. Lett.* **2014**, *16*, 645–647; c) T. Kawasaki, Y. Araki, K. Hatase, K. Suzuki, A. Matsumoto, T. Yokoi, Y. Kubota, T. Tatsumi, K. Soai, *Chem. Commun.* **2015**, *51*, 8742–8744.
- [8] a) I. Sato, D. Omiya, T. Saito, K. Soai, *J. Am. Chem. Soc.* **2000**, *122*, 11739–11740; b) T. Kawasaki, Y. Matsumura, T. Tsutsumi, K. Suzuki, M. Ito, K. Soai, *Science* **2009**, *324*, 492–495; c) T. Kawasaki, M. Shimizu, D. Nishiyama, M. Ito, H. Ozawa, K. Soai, *Chem. Commun.* **2009**, 4396–4398; d) T. Kawasaki, Y. Okano, E. Suzuki, S. Takano, S. Oji, K. Soai, *Angew. Chem. Int. Ed.* **2011**, *50*, 8131–8133; *Angew. Chem.* **2011**, *123*, 8281–8283; e) T. Kawasaki, H. Ozawa, M. Ito, K. Soai, *Chem. Lett.* **2011**, *40*, 320–321; f) A. Matsumoto, S. Oji, S. Takano, K. Tada, T. Kawasaki, K. Soai, *Org. Biomol. Chem.* **2013**, *11*, 2928–2931.
- [9] a) K. Soai, I. Sato, T. Shibata, S. Komiya, M. Hayashi, Y. Matsueda, H. Imamura, T. Hayase, H. Morioka, H. Tabira, J. Yamamoto, Y. Kowata, *Tetrahedron: Asymmetry* **2003**, *14*, 185–188; b) D. A. Singleton, L. K. Vo, *Org. Lett.* **2003**, *5*, 4337–4339; c) T. Kawasaki, K. Suzuki, M. Shimizu, K. Ishikawa, K. Soai, *Chirality* **2006**, *18*, 479–482; d) K. Suzuki, K. Hatase, D. Nishiyama, T. Kawasaki, K. Soai, *J. Syst. Chem.* **2010**, *1*, 5.
- [10] F. C. Frank, *Biochim. Biophys. Acta* **1953**, *11*, 459–463.
- [11] a) C. Puchot, O. Samuel, E. Dunach, S. Zhao, C. Agami, H. B. Kagan, *J. Am. Chem. Soc.* **1986**, *108*, 2353–2357; b) N. Oguni, Y. Matsuda, T. Kaneko, *J. Am. Chem. Soc.* **1988**, *110*, 7877–7878; c) M. Kitamura, S. Okada, S. Suga, R. Noyori, *J. Am. Chem. Soc.* **1989**, *111*, 4028–4036; d) T. Satyanarayana, S. Abraham, H. B. Kagan, *Angew. Chem. Int. Ed.* **2009**, *48*, 456–494; *Angew. Chem.* **2009**, *121*, 464–503.
- [12] a) I. Sato, D. Omiya, K. Tsukiyama, Y. Ogi, K. Soai, *Tetrahedron: Asymmetry* **2001**, *12*, 1965–1969; b) D. G. Blackmond, C. R. McMillan, S. Ramdeehul, A. Schorm, J. M. Brown, *J. Am. Chem. Soc.* **2001**, *123*, 10103–10104; c) I. Sato, D. Omiya, H. Igarashi, K. Kato, Y. Ogi, K. Tsukiyama, K. Soai, *Tetrahedron: Asymmetry* **2003**, *14*, 975–979; d) F. G. Buono, D. G. Blackmond, *J. Am. Chem. Soc.* **2003**, *125*, 8978–8979.
- [13] a) T. Buhse, *Tetrahedron: Asymmetry* **2003**, *14*, 1055–1061; b) J. R. Islas, D. Lavabre, J.-M. Grevy, R. H. Lamoneda, H. R. Cabrera, J.-C. Micheau, T. Buhse, *Proc. Natl. Acad. Sci. USA* **2005**, *102*, 13743–13748; c) G. Lente, *J. Phys. Chem. A* **2005**, *109*, 11058–11063; d) K. Micskei, G. Póta, L. Caglioti, G. Pályi, *J. Phys. Chem. A* **2006**, *110*, 5982–5984; e) B. Barabás, L. Caglioti, C. Zucchi, M. Maioli, E. Gal, K. K. Micskei, G. Pályi, *J. Phys. Chem. B* **2007**, *111*, 11506–11510; f) K. Micskei, G. Rábai, E. Gál, L. Caglioti, G. Pályi, *J. Phys. Chem. B* **2008**, *112*, 9196–9200; g) M. Busch, M. Schlageter, D. Weingand, T. Gehring, *Chem. Eur. J.* **2009**, *15*, 8251–8258; h) J. Crusats, D. Hochberg, A. Moyano, J. M. Ribó, *ChemPhysChem* **2009**, *10*, 2123–2131; i) É. Dóka, G. Lente, *J. Am. Chem. Soc.* **2011**, *133*, 17878–17881; j) J.-C. Micheau, C. Coudret, J.-M. Cruz, T. Buhse, *Phys. Chem. Chem. Phys.* **2012**, *14*, 13239–13248; k) G. Ercolani, *Tetrahedron: Asymmetry* **2014**, *25*, 405–410; l) B. Barabás, C. Zucchi, M. Maioli, K. Micskei, G. Pályi, *J. Mol. Model.* **2015**, *21*, 33.
- [14] a) I. D. Gridnev, J. M. Serafimov, H. Quiney, J. M. Brown, *Org. Biomol. Chem.* **2003**, *1*, 3811–3819; b) I. D. Gridnev, J. M. Serafimov, J. M. Brown, *Angew. Chem. Int. Ed.* **2004**, *43*, 4884–4887; *Angew. Chem.* **2004**, *116*, 4992–4995; c) M. Quaranta, T. Gehring, B. Odell, J. M. Brown, D. G. Blackmond, *J. Am. Chem. Soc.* **2010**, *132*, 15104–15107; d) T. Gehring, M. Quaranta, B. Odell, D. G. Blackmond, J. M. Brown, *Angew. Chem. Int. Ed.* **2012**, *51*, 9539–9542; *Angew. Chem.* **2012**, *124*, 9677–9680.
- [15] a) I. D. Gridnev, J. M. Brown, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5727–5731; b) I. D. Gridnev, *Chem. Lett.* **2006**, *35*, 148–153; c) J. J. Klankermayer, I. D. Gridnev, J. M. Brown, *Chem. Commun.* **2007**, 3151–3153; d) L. Schiaffino, G. Ercolani, *Angew. Chem. Int. Ed.* **2008**, *47*, 6832–6835; *Angew. Chem.* **2008**, *120*, 6938–6941; e) L. Schiaffino, G. Ercolani, *ChemPhysChem* **2009**, *10*, 2508–2515; f) L. Schiaffino, G. Ercolani, *Chem. Eur. J.* **2010**, *16*, 3147–3156; g) G. Ercolani, L. Schiaffino, *J. Org. Chem.* **2011**, *76*, 2619–2626; h) I. D. Gridnev, A. K. Vorobiev, *ACS Catal.* **2012**, *2*, 2137–2149.
- [16] X-ray crystal structure of another iPr_2Zn complex: A. Lennartson, A. Hedström, M. Håkansson, *Acta Crystallogr. Sect. E* **2007**, *63*, m123–m125.
- [17] M. B. Hursthouse, M. Motevalli, P. O'Brien, J. R. Walsh, A. C. Jones, *J. Mater. Chem.* **1991**, *1*, 139–140.
- [18] J. Bacsá, F. Hanke, S. Hindley, R. Odedra, G. R. Darling, A. C. Jones, A. Steiner, *Angew. Chem. Int. Ed.* **2011**, *50*, 11685–11687; *Angew. Chem.* **2011**, *123*, 11889–11891.
- [19] Although the crystal structure cannot be compared directly with the solution structure, this face-to-face conformation of the enantiopure tetramer is quite different from the suggested stable conformation from previous DFT studies (e.g. Ref. [16h]). Preliminary DFT calculations on both tetramer structures based on this crystal structure after removing the coordinating iPr_2Zn were performed at the the B3LYP/6–311 + G(d,p)//B3LYP/6–31G(d) level. The results of these calculations starting from the observed X-ray structure conformations indicate that the enantiopure alkoxide has a higher energy than the more open racemic tetramer by 4.8 kcal mol^{−1}.

Received: August 27, 2015

Revised: September 19, 2015

Published online: October 23, 2015