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## Asymmetric induction by retgersite, nickel sulfate hexahydrate, in conjunction with asymmetric autocatalysis

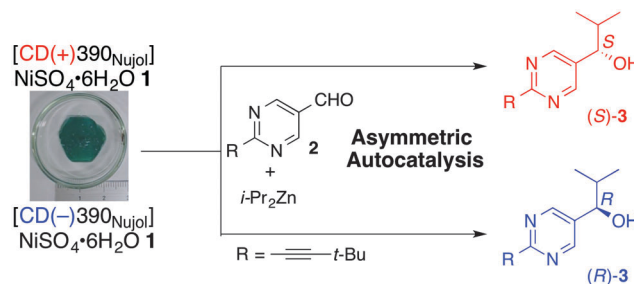
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**Retgersite, nickel sulfate hexahydrate, forms a chiral crystal with space group  $P4_12_12$  or  $P4_32_12$ . A chiral crystal of nickel sulfate hexahydrate was found to act as a chiral initiator of asymmetric autocatalysis, affording highly enantiomerically enriched pyrimidyl alkanols with the corresponding absolute configurations.**

The origin of biological homochirality is of great interest to the scientific community and several possible origins of homochirality have been proposed.<sup>1</sup> Chiral inorganic crystals are considered to be one possible origin of homochirality because the inorganic minerals are considered to have existed widely on Earth before the emergence of life.<sup>2,3</sup> Metal sulfates are one of the most abundant minerals on Earth, and the sulfate and metal ions are symmetric achiral ions.

Retgersite, nickel sulfate hexahydrate, is a naturally occurring mineral and exhibits enantiomorphism. Nickel sulfate forms various hydrate salts such as hexahydrate and heptahydrate depending on the crystallization conditions. The relatively stable  $\alpha$ -form of hexahydrate has a chiral structure. The hexahydrate crystal **1**, crystallized at 31.5–53.3 °C,<sup>4</sup> has a bright blue-green colour and has absorption bands in the visible light region; the optical properties of the crystal have been studied, including the chiral optical properties such as ORD and CD.<sup>5</sup> The absolute structure, analyzed by X-ray and ORD spectra, of **1** was first reported in 1987 and the detailed chiral optical properties of the crystal were studied recently by Asahi *et al.*<sup>6</sup> The chiral optical properties of the chiral crystal of achiral nickel sulfate have thus attracted broad interest. However, to the best of our knowledge, usage of the chirality of  $\text{NiSO}_4 \cdot 6\text{H}_2\text{O}$  in chemical reactions has not been realized. In this paper, we report asymmetric induction using chiral crystals of nickel sulfate hexahydrate in conjunction with asymmetric autocatalysis (Scheme 1).

Asymmetric autocatalysis is the reaction in which the product acts as an asymmetric catalyst for the reaction to form a



**Scheme 1** Asymmetric induction by chiral nickel sulfate hexahydrate and asymmetric autocatalysis.

product with the same structure and absolute configuration. We have been studying the asymmetric autocatalytic reaction of the pyrimidyl alkanols with amplification of enantiomeric excess.<sup>7–9</sup> By using asymmetric autocatalysts, we have reported that various inorganic<sup>10</sup> and organic<sup>11</sup> crystals act as chiral triggers for the asymmetric autocatalysis. Herein, we report that the chiral nickel sulfate hexahydrate crystal triggers asymmetric autocatalysis.

The chiral single crystal of nickel sulfate hexahydrate was obtained by recrystallization.  $\text{NiSO}_4 \cdot 6\text{H}_2\text{O}$  (**1**) (25 g) was dissolved in distilled water (33 mL) at 70 °C and was kept for 12 h and water was allowed to evaporate for 2–3 d at above 31.5 °C in a Petri dish to give a crystal of  $\text{NiSO}_4 \cdot 6\text{H}_2\text{O}$  **1** of ca. 2 cm size (Fig. 1). The solid state CD spectrum was measured with the powdered crystal of **1** in Nujol. Although the base line of the obtained CD spectrum was not flat due to the anisotropy of the crystal powders, a distinguishable signal was observed around the 390 nm region (Fig. 2b). The chirality of the crystal was determined by the CD spectrum in the 390 nm region and confirmed by the X-ray single crystal diffraction analysis using the Flack parameter (Fig. 2a).<sup>12,13</sup> The  $P4_12_12$  crystal exhibits the negative Cotton effect at 390 nm, and the  $P4_32_12$  crystal exhibits the opposite positive Cotton effect at 390 nm.<sup>5,6</sup>

Using these chiral crystals of  $\text{NiSO}_4 \cdot 6\text{H}_2\text{O}$  **1** as chiral initiators, asymmetric autocatalysis of diisopropylzinc (*i*-Pr<sub>2</sub>Zn) and

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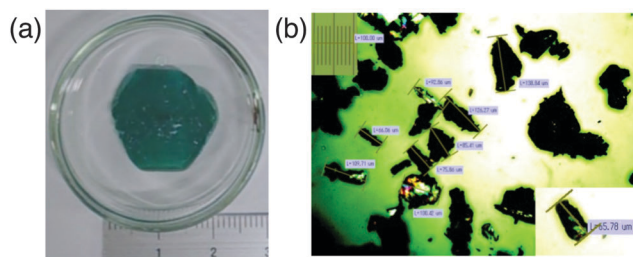


Fig. 1 (a) Single crystal of  $\text{NiSO}_4 \cdot 6\text{H}_2\text{O}$  1; (b) ground powder-like crystal of  $\text{NiSO}_4 \cdot 6\text{H}_2\text{O}$  1.

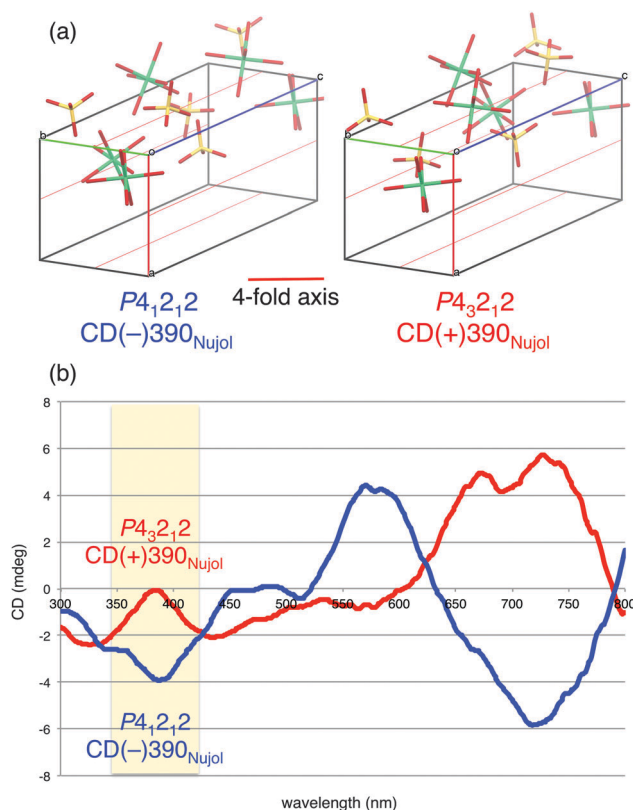
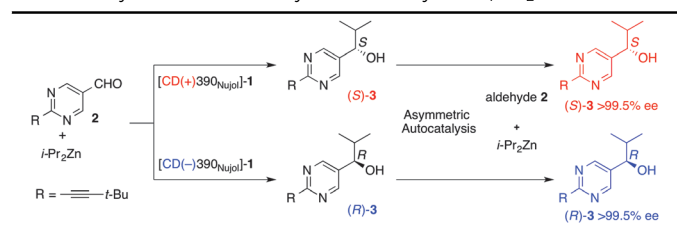


Fig. 2 (a) Crystal structure of  $\text{NiSO}_4 \cdot 6\text{H}_2\text{O}$ ; (b) CD spectrum of the  $\text{NiSO}_4 \cdot 6\text{H}_2\text{O}$  (powder, Nujol mull).

pyrimidine-5-carbaldehyde 2 was performed.<sup>14</sup> Thus, the chiral crystal of  $\text{NiSO}_4 \cdot 6\text{H}_2\text{O}$  1 was ground with agate and mortar, then it was mixed immediately with pyrimidine-5-carbaldehyde 2 and used in the reaction before the progress of the dehydration of the crystal. By adding  $i\text{-Pr}_2\text{Zn}$  slowly, addition reaction was performed in combination with asymmetric autocatalysis with amplification of enantiomeric excess (ee). After purification, the enantiomeric excess of the formed pyrimidyl alkanol 3 was determined by HPLC using a chiral column.

The results are summarized in Table 1. As shown in entry 1, (*S*)-pyrimidyl alkanol 3 was obtained in the presence of a chiral crystal of  $\text{NiSO}_4 \cdot 6\text{H}_2\text{O}$  with the positive Cotton effect at 390 nm [ $\text{CD}(+)390_{\text{Nujol}}$ ]. On the other hand, (*R*)-3 was obtained in the presence of a chiral crystal of  $\text{NiSO}_4 \cdot 6\text{H}_2\text{O}$  with the negative Cotton effect [ $\text{CD}(-)390_{\text{Nujol}}$ ] (entry 2). Although the yields and

Table 1 Asymmetric autocatalysis initiated by  $\text{NiSO}_4 \cdot 6\text{H}_2\text{O}$  1



Entry	Crystal 1		Pyrimidyl alkanol 3		Amplification of ee by asymmetric autocatalysis <sup>c</sup>		Configuration
	$\text{CD}390$	$\text{nm}_{\text{Nujol}}$	Yield (%)	ee <sup>d</sup> (%)	Yield (%)	ee <sup>d</sup> (%)	
1 <sup>a</sup>	(+)	27	3	77	50 (>99.5) <sup>e</sup>	<i>S</i>	
2 <sup>a</sup>	(-)	28	3	72	37 (>99.5) <sup>e</sup>	<i>R</i>	
3 <sup>a</sup>	(+)	81	9	72	28	<i>S</i>	
4 <sup>a</sup>	(+)	27	2	78	76	<i>S</i>	
5 <sup>a</sup>	(+)	27	5	74	95	<i>S</i>	
6 <sup>a</sup>	(-)	37	6	80	91	<i>R</i>	
7 <sup>b</sup>	(+)	14	4	85	53	<i>S</i>	
8 <sup>b</sup>	(-)	30	4	73	68	<i>R</i>	

<sup>a</sup> Reaction conditions: molar ratio, 1:2:  $i\text{-Pr}_2\text{Zn}$  = 16:1:3 in toluene at 0 °C, and additional 2:  $i\text{-Pr}_2\text{Zn}$  = 2:4 and 8:16 were added stepwise.

<sup>b</sup> Reaction conditions: molar ratio, 1:2:  $i\text{-Pr}_2\text{Zn}$  = 32:1:9 in toluene at 0 °C, and additional 2:  $i\text{-Pr}_2\text{Zn}$  = 2:12 and 8:48 were added stepwise.

<sup>c</sup> Asymmetric autocatalytic reaction with the obtained alkanol after removing  $\text{NiSO}_4 \cdot 6\text{H}_2\text{O}$ . <sup>d</sup> The ee value was determined using HPLC on a chiral stationary phase. HPLC conditions: CHIRALPAK IB (4.6 mm  $\varnothing$   $\times$  250 mm), 5% 2-propanol in hexane, 1.0 mL  $\text{min}^{-1}$ , 254 nm, r.t., retention time (min) 10.3 for (*S*)-3, 13.9 for (*R*)-3. <sup>e</sup> After additional 2 to 5 rounds of asymmetric autocatalytic reaction.

ees were not so high probably due to the heterogeneous conditions with the existence of crystallization water, the sense of enantioselectivity exhibits good reproducibility for the several different crystal samples. It should be noted that the ee of the formed alkanol 3 was amplified to be nearly enantiomerically pure (>99.5% ee) during the subsequent asymmetric autocatalysis (entries 1 and 2).

We have demonstrated, by using asymmetric autocatalysis of pyrimidyl alkanols, that the chiral natural mineral of retergsite  $\text{NiSO}_4 \cdot 6\text{H}_2\text{O}$  induces the chirality of the chiral organic compound with high ee. These results suggest that common inorganic sulfate minerals on Earth may be considered to be the origin of chirality of the chiral organic compounds.

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## Notes and references

- (a) I. Weissbuch, L. Addadi, Z. Berkovitch-Yellin, E. Gati, M. Lahav and L. Leiserowitz, *Nature*, 1984, **310**, 161; (b) M. Bolli, R. Micura and A. Eschenmoser, *Chem. Biol.*, 1997, **4**, 309; (c) B. L. Feringa and R. A. van Delden,



- Angew. Chem., Int. Ed.*, 1999, **38**, 3418; (d) M. M. Green, J.-W. Park, T. Sato, A. Teramoto, S. Lifson, R. L. B. Selinger and J. V. Selinger, *Angew. Chem., Int. Ed.*, 1999, **38**, 3139; (e) J. M. Ribó, J. Crusats, F. Sagués, J. Claret and R. Rubires, *Science*, 2001, **292**, 2063; (f) D. K. Kondepudi and K. Asakura, *Acc. Chem. Res.*, 2001, **34**, 946; (g) K. Mislow, *Collect. Czech. Chem. Commun.*, 2003, **68**, 849; (h) 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; (i) S. Pizzarello and A. L. Weber, *Science*, 2004, **303**, 1151; (j) C. Viedma, *Phys. Rev. Lett.*, 2005, **94**, 65504; (k) Y. Hayashi, M. Matsuzawa, J. Yamaguchi, S. Yonehara, Y. Matsumoto, M. Shoji, D. Hashizume and H. Koshino, *Angew. Chem., Int. Ed.*, 2006, **45**, 4593; (l) M. Klussmann, H. Iwamura, S. P. Mathew, D. H. Wells, U. Pandya, A. Armstrong and D. G. Blackmond, *Nature*, 2006, **441**, 621; (m) V. A. Soloshonok, H. Ueki, M. Yasumoto, S. Mekala, J. S. Hirschi and D. A. Singleton, *J. Am. Chem. Soc.*, 2007, **129**, 12112; (n) T. Satyanarayana, S. Abraham and H. B. Kagan, *Angew. Chem., Int. Ed.*, 2009, **48**, 456; (o) R. Breslow and Z.-L. Cheng, *Proc. Natl. Acad. Sci. U. S. A.*, 2010, **107**, 5723; (p) I. Weissbuch and M. Lahav, *Chem. Rev.*, 2011, **111**, 3236; (q) F. E. Held, A. Fingerhut and S. B. Tsogoeva, *Tetrahedron: Asymmetry*, 2012, **23**, 1663; (r) Y. Saito and H. Hyuga, *Rev. Mod. Phys.*, 2013, **85**, 603; (s) G. Valero, J. M. Ribó and A. Moyano, *Chem. – Eur. J.*, 2014, **20**, 17395; (t) S. Olsson, P. M. Björemark, T. Kokoli, J. Sundberg, A. Lennartson, C. J. McKenzie and M. Håkansson, *Chem. – Eur. J.*, 2015, **21**, 5211.
- 2 (a) D. K. Kondepudi, R. J. Kaufman and N. Singh, *Science*, 1990, **250**, 975; (b) J. M. McBride and R. L. Carter, *Angew. Chem., Int. Ed.*, 1991, **30**, 293.
- 3 (a) R. M. Hazen, T. R. Filley and G. A. Goodfriend, *Proc. Natl. Acad. Sci. U. S. A.*, 2001, **98**, 5487; (b) R. M. Hazen, in *Progress in Biological Chirality*, ed. G. Pályi, C. Zicchi and L. Caglioti, Elsevier, Oxford, 2004, pp. 137–151; (c) R. M. Hazen and D. A. Sverjensky, *Cold Spring Harbor Perspect. Biol.*, 2010, **2**, a002162.
- 4 V. L. Manomenova, E. B. Rudneva, A. É. Voloshin, L. V. Soboleva, A. B. Vasil and B. V. Mchedlishvili, *Crystallogr. Rep.*, 2005, **50**, 877.
- 5 (a) L. R. Ingersoll, P. Rudnick, F. G. Slack and N. Underwood, *Phys. Rev.*, 1940, **57**, 114; (b) K. Stadnicka, A. M. Glazer and M. Koralewski, *Acta Crystallogr., Sect. B: Struct. Sci.*, 1987, **43**, 319; (c) T. Harada, T. Sato and R. Kuroda, *Chem. Phys. Lett.*, 2008, **456**, 268.
- 6 Symposium abstract: T. Taniguchi, K. Ishikawa, M. Tanaka, T. Asahi, *Chirality* 2013, P-016, Shanghai, July 7–10, 2013.
- 7 (a) K. Soai, T. Shibata, H. Morioka and K. Choji, *Nature*, 1995, **378**, 767; (b) I. Sato, H. Urabe, S. Ishiguro, T. Shibata and K. Soai, *Angew. Chem., Int. Ed.*, 2003, **42**, 315; (c) T. Kawasaki, Y. Matsumura, T. Tsutsumi, K. Suzuki, M. Ito and K. Soai, *Science*, 2009, **324**, 492; (d) A. Matsumoto, S. Oji, S. Takano, K. Tada, T. Kawasaki and K. Soai, *Org. Biomol. Chem.*, 2013, **11**, 2928; (e) 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.
- 8 (a) K. Soai and T. Kawasaki, *Top. Curr. Chem.*, 2008, **284**, 1; (b) T. Kawasaki and K. Soai, *Bull. Chem. Soc. Jpn.*, 2011, **84**, 879; (c) K. Soai and T. Kawasaki, *Asymmetric Autocatalysis – Discovery and State of The Art*, in *The Soai Reaction and Related Topic*, ed. G. Pályi, C. Zicchi and L. Caglioti, Academia Nazionale di Scienze Lettere e Arti Modena, Modena, Edizioni Artestampa, 2012, pp. 9–34; (d) T. Kawasaki and K. Soai, *Isr. J. Chem.*, 2012, **52**, 582; (e) T. Kawasaki, I. Sato, H. Mineki, A. Matsumoto and K. Soai, *Yuki Gosei Kagaku Kyokaishi*, 2013, **71**, 109; (f) K. Soai and T. Kawasaki, *Top. Organomet. Chem.*, 2013, **44**, 261; (g) K. Soai, T. Kawasaki and A. Matsumoto, *Chem. Rec.*, 2014, **14**, 70; (h) K. Soai, T. Kawasaki and A. Matsumoto, *Acc. Chem. Res.*, 2014, **47**, 3643.
- 9 (a) D. G. Blackmond, *Proc. Natl. Acad. Sci. U. S. A.*, 2004, **101**, 5732; (b) J. Podlech and T. Gehring, *Angew. Chem., Int. Ed.*, 2005, **44**, 5776; (c) J. M. Brown, I. Gridnev and J. Klankermayer, *Top. Curr. Chem.*, 2008, **284**, 35; (d) L. Caglioti and G. Pályi, *Chim. Oggi*, 2008, **26**, 41; (e) T. Gehring, M. Busch, M. Schlageter and D. Weingand, *Chirality*, 2010, **22**, E173; (f) B. Barabás, J. Toth and G. Pályi, *J. Math. Chem.*, 2010, **48**, 457; (g) G. Lente, *Symmetry*, 2010, **2**, 767; (h) J.-K. Micheau, C. Coudret and T. Buhse, in *The Soai Reaction and Related Topic*, ed. G. Pályi, C. Zucchi and L. Caglioti, Accad. Nazl. Sci. Lett. Arti, Edizioni Artestampa, Modena, 2012, p. 169; (i) T. Gehring, M. Quaranta, B. Odell, D. G. Blackmond and J. M. Brown, *Angew. Chem., Int. Ed.*, 2012, **51**, 9539; (j) A. J. Bissette and S. P. Fletcher, *Angew. Chem., Int. Ed.*, 2013, **52**, 12800; (k) K. Micskei, G. Rábai, E. Gál, L. Caglioti and G. Pályi, *J. Phys. Chem. B*, 2008, **112**, 9196; (l) I. D. Gridnev and A. K. Vorobiev, *ACS Catal.*, 2012, **2**, 2137; (m) G. Ercolani and L. Schiaffino, *J. Org. Chem.*, 2011, **76**, 2619; (n) B. Barabás, C. Zucchi, M. Maioli, K. Micskei and G. Pályi, *J. Mol. Model.*, 2015, **21**, 33, DOI: 10.1007/s00894-015-2576-6.
- 10 (a) K. Soai, S. Osanai, K. Kadowaki, S. Yonekubo, T. Shibata and I. Sato, *J. Am. Chem. Soc.*, 1999, **121**, 11235; (b) I. Sato, K. Kadowaki and K. Soai, *Angew. Chem., Int. Ed.*, 2000, **39**, 1510; (c) H. Shindo, Y. Shirota, K. Niki, T. Kawasaki, K. Suzuki, Y. Araki, A. Matsumoto and K. Soai, *Angew. Chem., Int. Ed.*, 2013, **52**, 9135.
- 11 (a) T. Kawasaki, K. Jo, H. Igarashi, I. Sato, M. Nagano, H. Koshima and K. Soai, *Angew. Chem., Int. Ed.*, 2005, **44**, 2774; (b) T. Kawasaki, K. Suzuki, Y. Hakoda and K. Soai, *Angew. Chem., Int. Ed.*, 2008, **47**, 496; (c) T. Kawasaki, Y. Hakoda, H. Mineki, K. Suzuki and K. Soai, *J. Am. Chem. Soc.*, 2010, **132**, 2874; (d) D. J. Carter, A. L. Rohl, A. Shtukenberg, S. D. Bian, C.-H. Hu, L. Baylon, B. Kahr, H. Mineki, K. Abe, T. Kawasaki and K. Soai, *Cryst. Growth Des.*, 2012, **12**, 2138; (e) H. Mineki, T. Hanasaki, A. Matsumoto, T. Kawasaki and K. Soai, *Chem. Commun.*, 2012, **48**, 10538; (f) T. Kawasaki, M. Uchida, Y. Kaimori, T. Sasagawa, A. Matsumoto and K. Soai, *Chem. Lett.*, 2013, **42**, 711; (g) A. Matsumoto, T. Ide, Y. Kaimori, S. Fujiwara and K. Soai, *Chem. Lett.*, 2015, **44**, 688.



- 12 S. Parsons and H. D. Flack, *Acta Crystallogr., Sect. A: Found. Crystallogr.*, 2004, **60**, s61.
- 13 The Flack  $x$  determined using the quotients  $[(I+) - (I-)] / [(I+) + (I-)]$  method is 0.025(5) for P<sub>4</sub><sub>1</sub><sub>2</sub><sub>1</sub><sub>2</sub> and 0.044(7) for P<sub>4</sub><sub>3</sub><sub>2</sub><sub>1</sub><sub>2</sub>.
- 14 Typical experimental procedure (Table 1, entries 1–6): a crystal of nickel sulfate hexahydrate **1** was ground using a pestle and mortar (particle size estimated from microscope images to be 66–140  $\mu\text{m}$ ). Toluene solution of *i*-Pr<sub>2</sub>Zn (0.15 mL, 0.15 mmol) was added dropwise at 0 °C with stirring to a mixture of powder-like crystal **1** (0.21 g, 0.80 mmol) and aldehyde **2** (9.4 mg, 0.050 mmol) in the presence of toluene (0.50 mL). After stirring overnight at 0 °C, toluene (1.0 mL) was added to the mixture. Then toluene solution of *i*-Pr<sub>2</sub>Zn (0.20 mL, 0.20 mmol) and toluene (0.5 mL) solution of

aldehyde **2** (19 mg, 0.10 mmol) were added dropwise alternately over a period of 1 h. After stirring for 4 h at 0 °C, toluene (1.5 mL) was added, then toluene solution of *i*-Pr<sub>2</sub>Zn (0.80 mL, 0.80 mmol) and toluene (1.0 mL) solution of **2** (75 mg, 0.40 mmol) were added dropwise alternately over a period of 2 h and the mixture was stirred overnight. The reaction was quenched with a mixed solution (14 mL) of saturated aq. ammonium chloride and aq. ammonia (sat. NH<sub>4</sub>Cl:30% NH<sub>4</sub>OH = 2:1 (v/v)). The resulting mixture was extracted with ethyl acetate. The combined organic layers were dried over anhydrous sodium sulfate. Purification of the residue by silica gel column chromatography gave 5-pyrimidyl alkanol **3**. Further asymmetric autocatalysis using the obtained alkanol **3** was performed to amplify the enantiomeric excess.

