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Enantioselective Synthesis Induced by Chiral Crystal Composed of DL-Serine in Conjunction with Asymmetric Autocatalysis

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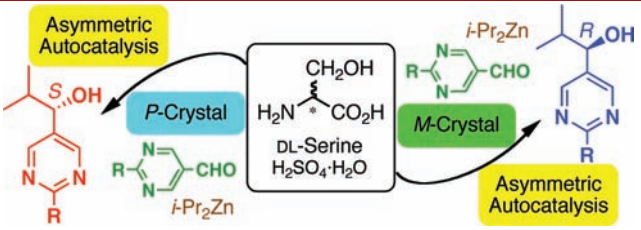
ABSTRACT



Asymmetric autocatalysis initiated by chiral crystals containing racemic DL-serine was achieved. *P*- and *M*-crystals of DL-serine acted as the source of chirality of asymmetric autocatalysis to afford highly enantioenriched (>99.5% ee) (*S*)- and (*R*)-pyrimidylalkanols after the amplification of ee. This is the first example of the usage of the crystal, which contains the same number of D- and L-enantiomers as an origin of chirality in enantioselective synthesis.

The origin of biological homochirality,[1] such as is seen in l-amino acids,[2,3] has attracted much attention since the discovery of molecular chirality by Pasteur.[4] Circularly polarized light,[5] chiral inorganic crystals[6] (such as quartz[6d,e]), chiral organic crystals formed from achiral organic compounds,[7] spontaneous absolute asymmetric synthesis,[1b] and sublimation[8] have all been theorized as being origins of chirality.[9]

Pasteur first reported that racemic sodium ammonium tartrate crystallizes as a conglomerate, and he separated the same enantiomorphs.[4] However, in general, the crystallization as a conglomerate is less common compared with

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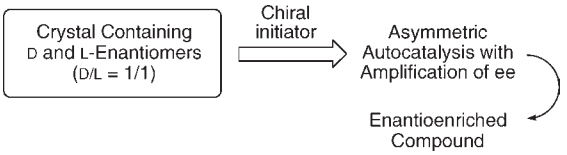
crystallization as a racemic compound consisting of crystals in which the (+) and (−)-enantiomers are present in a 1:1 ratio down to the unit cell level.

In very rare cases, the crystal of racemic compounds belongs to the chiral space group to possess the crystalline chirality.[1i] Using these enantiomorphs as reaction substrates, stereospecific solid-state reactions have been reported, that is, the X-ray irradiation of cobalt complex by Ohashi[10] and the photochemical reaction of dienes by Lahav[11] to afford enantioenriched compounds, respectively. However, any substance that contains equal amounts of both enantiomers has not been used as chiral catalyst or initiator for the enantioselective synthesis.

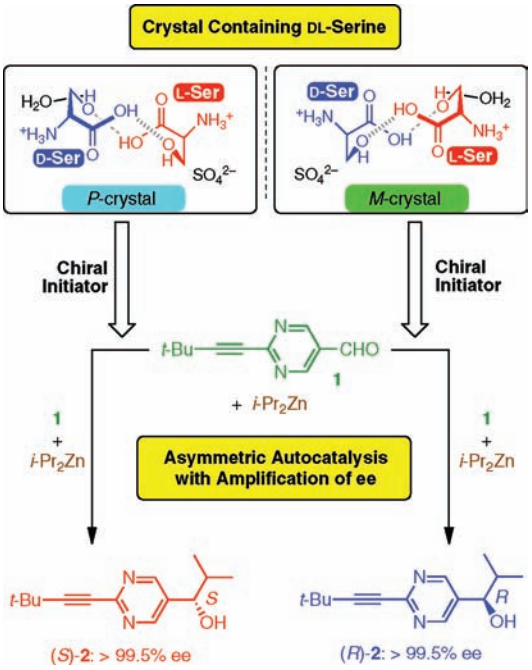
We have previously reported on asymmetric autocatalysis with amplification of ee in the diisopropylzinc (i-Pr_2Zn) addition to pyrimidine-5-carbaldehyde using pyrimidylalkanol as an asymmetric autocatalysis.[12−15] Starting from pyrimidylalkanol with an extremely low ee (ca. 0.00005%), three consecutive asymmetric autocatalysis steps afforded almost an enantiopure pyrimidyl alkanol with >99.5% ee.[14b] In addition, various chiral compounds and crystals can act as chiral initiators of asymmetric autocatalysis.[16]

Scheme 1. Concept of This Work



Here, we report on an unprecedented phenomenon where a crystal composed of DL-serine acts as a chiral initiator of asymmetric autocatalysis affording an enantioenriched compound (Scheme 1). To the best of our knowledge, we believe that this is the first example of DL-amino acids acting as chiral initiators of asymmetric synthesis (Scheme 2). The absolute configuration of product **2** was controlled well by the crystal chirality of the DL-serine[17] (DL-diserinium sulfate hydrate,[18] space group: $P2_12_12_1$) that contained an equimolar amount of D- and L-serine. The enantiomorphs were indicated corresponding to the *P*- or *M*-helicity in the molecular arrangement (Figures S1 and S2, Supporting Information). In the unit cell, DL-serine forms a cyclic aggregate by the hydrogen bonds between hydroxyl and carboxyl groups. In the *P*-crystal, a hydrogen bond between H_2O and D-serine (not L-serine) was observed. In an opposite manner, H_2O was bonded to L-serine in the *M*-crystal.

Scheme 2. Asymmetric Autocatalysis Using the Crystal Containing DL-Serine as a Source of Chirality



Asymmetric autocatalysis induced by a DL-serine racemic compound was performed, as shown in Table 1. When the addition of i-Pr_2Zn to pyrimidine-5-carbaldehyde **1** was conducted in the presence of a *M*-crystal as a chiral source, then (*R*)-5-pyrimidylalkanol **2** with a 95% ee was obtained in an 83% yield after the amplification of ee by asymmetric autocatalysis (Table 1, series I, entry 1). On the other hand, when an *P*-crystal was employed as the chiral source of the asymmetric autocatalysis, then (*S*)-alkanol **2** with a 94% ee was synthesized in a high yield (entry 2). The stereochemical correlation between the crystalline chirality of racemic serine and the resulting pyrimidyl alkanol **2**, i.e., a *M*-crystal induced the formation of (*R*)-**2** and an

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Table 1. Enantioselective Synthesis of Pyrimidylalkanol **2** Induced by Chiral Crystal of Racemic Serine

	crystal of *rac*-serine		5-pyrimidylalkanol **2**		
entry[a]	sample no.	config[b]	yield (%)	ee[c] (%)	config
−series I−[d]					
1	1	*M*	83	95	*R*
2	2	*P*	86	94	*S*
3	3	*M*	84	91	*R*
4	4	*P*	89	94	*S*
5	5	*M*	89	92	*R*
6	6	*P*	86	88	*S*
7	7	*M*	88	88	*R*
8	8	*P*	87	84	*S*
−series II−[e]					
9	9	*M*	88	92	*R*
10	10	*P*	87	85	*S*
11	11	*M*	87	90	*R*
12	12	*P*	89	92	*S*
13[f]	11	*M*	92	>99.5	*R*
14[f]	12	*P*	92	>99.5	*S*

[a] Asymmetric autocatalysis was performed as follows: The crystals of DL-serine were ground using agate pestle and mortar together with **1** before use. To a mixture of finely powdered *rac*-serine (32.6 mg, 0.1 mmol) and **1** (4.7 mg, 0.025 mmol) was added *i*-Pr_2Zn (0.1 mmol, 0.1 mL, 1.0 M in toluene) dropwise over a period of 1.5 h at 0 °C. After the mixture was stirred for 12 h, toluene (0.75 mL) and *i*-Pr_2Zn (0.3 mmol, 0.3 mL, 1.0 M in toluene) were added at 0 °C. A solution of **1** (18.8 mg, 0.1 mmol) in toluene (0.75 mL) was added over a period of 30 min at 0 °C and the reaction mixture stirred at 0 °C for 1.5 h. Once again, after toluene (5.0 mL) and *i*-Pr_2Zn (0.8 mmol, 0.8 mL, 1.0 M in toluene) were added, a solution of **1** (75.3 mg, 0.4 mmol) in toluene (2.0 mL) was added dropwise over a period of 30 min at 0 °C. After the mixture was stirred for 30 min, the reaction was quenched. After the extraction and concentration, purification by column chromatography (SiO_2) gave the product **2**. [b] The absolute configuration was determined by the X-ray single-crystal structure analysis (see also the Supporting Information). [c] The ee value was determined by HPLC using a chiral stationary phase. [d] A small piece of a single crystal indicated here was used as seed crystal of stirred crystallization. The produced powder-like crystal was subjected to asymmetric autocatalysis. [e] The finely powdered single crystal was used as chiral initiator of asymmetric autocatalysis. [f] An additional three rounds of asymmetric autocatalysis were performed (see also ref 14b).

P-crystal promoted the production of (*S*)-**2**, reproduced well, as shown in entries 3−8.

When a single crystal-based chiral inducer was used as the chiral source for asymmetric autocatalysis, then the same relationship between the chirality of the racemic serine and the absolute configuration of **2** was observed (entries 9−12). It should be noted that the enantiomeric purity could be enhanced significantly to >99.5% ee by applying a further asymmetric autocatalytic amplification of ee (entries 13 and 14). Thus, the crystal chirality of the racemic compound, serine, is responsible for the enantioselective addition of *i*-Pr_2Zn to aldehyde **1** to give an enantioenriched compound in conjunction with asymmetric autocatalysis.

In this enantioselective reaction, chiral crystals of DL-serine acted as the chiral trigger for asymmetric autocatalysis. The initial enantioselective addition of *i*-Pr_2Zn to aldehyde **1** should proceed under the influence of the chiral surface of the serine racemic compound. Thus, an initial asymmetric induction may occur and may afford an enantioimbalanced asymmetric autocatalyst (i.e., the isopropylzinc alkoxide of **2**). Subsequent asymmetric autocatalysis would enhance the small chirality to afford the highly enantioenriched alkanol **2** with an absolute configuration corresponding to the chirality of the serine racemic compound used.

As described above, a highly enantioselective synthesis was achieved by utilizing the crystalline chirality of a DL-serine. This is the first realization of the synthesis of an enantioenriched compound using a racemic compound as the origin of chirality, in conjunction with asymmetric autocatalysis.[15]

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Supporting Information Available. The preparation of chiral crystal of DL-serine and the determination of *P*/*M*-chirality. This material is available free of charge via the Internet at http://pubs.acs.org.