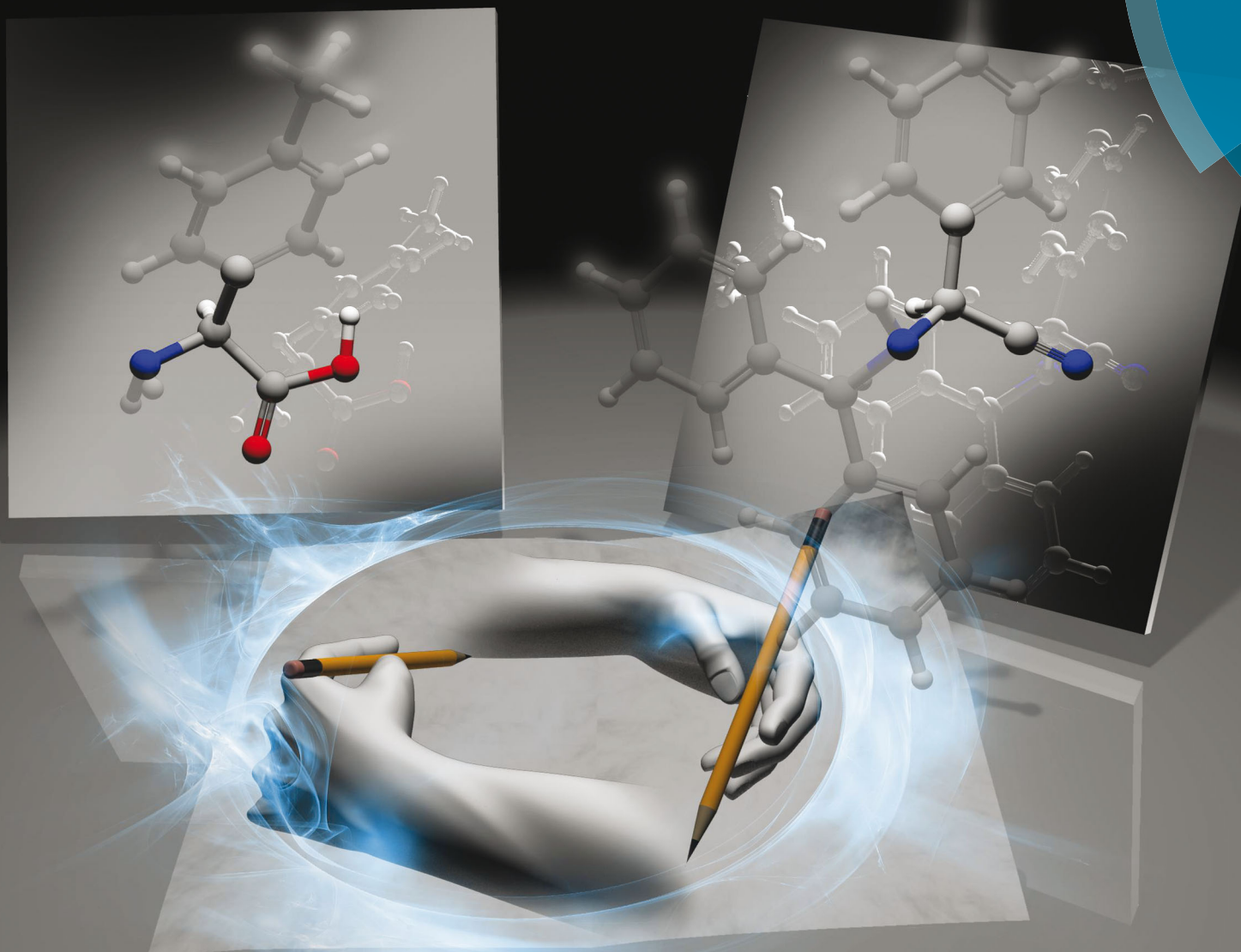


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## Replication of $\alpha$ -amino acids *via* Strecker synthesis with amplification and multiplication of chiral intermediate aminonitriles†

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Replication of chiral L- and D- $\alpha$ -(*p*-tolyl)glycine has been achieved in combination with the asymmetric induction, amplification and multiplication of their own chiral intermediates, L- and D-aminonitriles, in the solid-phase *via* the Strecker reaction between three achiral components, which is a plausible prebiotic mechanism for amino acid synthesis.

The origin and amplification of chirality leading to biological homochirality, as exemplified by the L-amino acids and D-sugars, have attracted much attention. Starting from the discovery of molecular chirality,<sup>1</sup> original research studies<sup>2</sup> on the origin of chirality have been conducted including the effect of chiral physical factors<sup>3</sup> such as circularly polarized light,<sup>4</sup> the chiral surface of inorganic crystals<sup>5</sup> such as quartz, chiral crystallization of achiral compounds<sup>6</sup> including stereospecific solid-state reactions<sup>2d,7</sup> and the spontaneous absolute asymmetric synthesis.<sup>8</sup> The induced small chirality by the suggested mechanisms should be significantly enhanced toward high enantioenrichment as seen in biological compounds by the appropriate mechanisms<sup>9</sup> including the phenomenon of self-disproportionation of enantiomers.<sup>10</sup> Asymmetric autocatalysis with amplification of enantiomeric excess (ee)<sup>2e,11</sup> should be strongly correlated with the homochirality of organic compounds. In addition, it has been reported that chiral amino acids including meteoritic compounds<sup>12</sup> could act as a source of chirality to synthesize the enantioenriched compounds<sup>13</sup> such as sugars and related compounds.<sup>14</sup>

On the other hand, the Strecker reaction<sup>15</sup> (Fig. 1) has long been considered as one of the methods for the synthesis of  $\alpha$ -amino acids on primitive Earth before the origin of life.<sup>16</sup> Therefore, replicative generation of highly enantioenriched amino acids *via* this mechanism is an emerging research subject in the fields of prebiotic, synthetic, and systems chemistry<sup>17</sup> and could be one of the possible approaches to achieving biological homochirality.

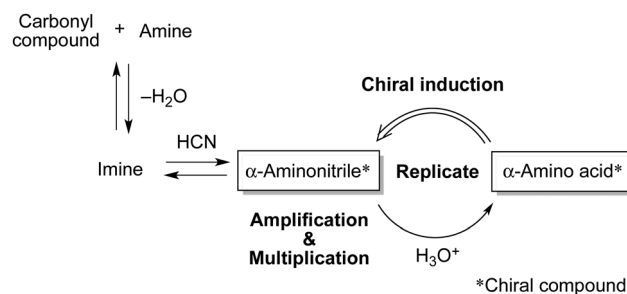


Fig. 1 Concept of the present research: replicative Strecker amino acid synthesis.

Here we report the selective formation of a nearly enantiomerically pure  $\alpha$ -aminonitrile, which is a chiral intermediate of the Strecker amino acid synthesis. It is produced by the reaction between hydrogen cyanide (HCN), a carbonyl compound and an amine. We found that an amino acid could induce the enantiomeric imbalance toward the formation of its own chiral intermediate (Fig. 1). Therefore, as a result of the combination of the amplification and multiplication of aminonitrile, a more near enantiopure amino acid could be newly synthesized after the hydrolysis of aminonitrile. The present reactions demonstrate one of the models in which the chiral intermediate  $\alpha$ -aminonitrile plays a key role in the generation and evolution of homochirality of amino acids *via* the Strecker synthesis.

We have previously reported<sup>18</sup> the formation of enantioenriched  $\alpha$ -(*p*-tolyl)glycine nitrile **1** *via* spontaneous crystallization<sup>8b,19</sup> after a three-component Strecker reaction between achiral HCN, *p*-tolualdehyde (**3**) and benzhydramine (**4**). The stochastic distribution in the formation of L- and D-enriched enantiomorphs **1** was observed. In this work, the formation of a selected enantiomer between L- and D- $\alpha$ -(*p*-tolyl)glycine nitrile **1** was achieved by using chiral amino acids, *i.e.*, L- and D- $\alpha$ -(*p*-tolyl)glycine (**2**), as a source of chirality (Fig. 2). As the enantiomeric imbalance of **1** induced by amino acid **2** can be significantly enhanced by the dissolution/crystallization-mediated amplification of ee,<sup>20,21</sup> and the amount of enantioenriched **1** can also be multiplied, a large

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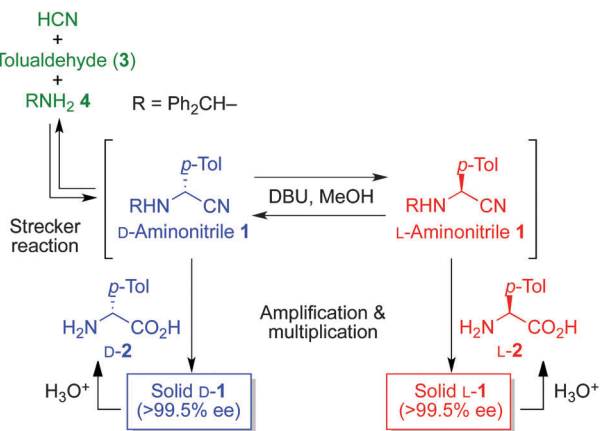


Fig. 2 Replicative formation of L- and D- $\alpha$ -(*p*-tolyl)glycine (**2**) via asymmetric induction in the formation of an enantioenriched conglomerate of aminonitrile **1**.

amount of near enantiomerically pure amino acid **2**, with the same molecular handedness as that of the original, could be newly synthesized in a highly enantioselective manner after the hydrolysis of aminonitrile **1**.

In the presence of L- or D- $\alpha$ -(*p*-tolyl)glycine (**2**), the formation and amplification of enantiomorphous aminonitrile **1** were performed *via* a Strecker reaction between three achiral substrates: HCN, aldehyde **3**, and amine **4** (Fig. 2 and Table 1). When highly enantioenriched L-**2** with 97% ee was used as a source of chirality, L-aminonitrile **1** with > 99.5% ee was isolated in 45% yield by filtration after the amplification of the solid-phase ee (entry 1). Near racemic **1** was isolated from the solution-phase (filtrate) in 24% yield. On the other hand, D-amino acid **2** led to the formation of near enantiopure D-**1** after four amplification

Table 1 Stereochemical relationship between  $\alpha$ -aminonitrile **1** and  $\alpha$ -amino acid **2** in the formation and amplification of enantiomorphs **1**

Entry <sup>a</sup>	Amino acid <b>2</b>		Aminonitrile <b>1</b>		
	% ee	Config.	% ee <sup>b</sup>	Config.	% Yield <sup>c</sup>
1 <sup>d</sup>	97	L	> 99.5	L	45
2 <sup>e</sup>	97	D	> 99.5	D	44
3	ca. 50	L	99	L	42
4 <sup>f</sup>	ca. 50	D	98	D	48
5 <sup>g</sup>	ca. 10	L	> 99.5	L	27
6	ca. 10	D	> 99.5	D	38
7 <sup>h</sup>	ca. 50	L	75	L	21
8 <sup>h</sup>	ca. 50	D	47	D	20

<sup>a</sup> The molar ratio used was 2 : 3 : 4 : HCN = 1 : 2 : 2 : 3 (mmol). The reactions were performed in a 1.0 M DBU solution in methanol in the presence of a stir bar without using glass beads. Amino acid **2** completely dissolves in the reaction medium containing DBU. <sup>b</sup> The ee value was determined by high performance liquid chromatography (HPLC), employing a chiral stationary phase. <sup>c</sup> The isolated yield of solid product **1** by filtration. <sup>d</sup> L-**1** with 75% ee was obtained after four cycles of amplification; two additional cycles enhanced the ee to > 99.5% ee. Near racemic **1** was isolated from the solution-phase (filtrate) in 24% yield. <sup>e</sup> D-**1** with 71% ee was obtained after three cycles of amplification; one additional cycle enhanced the ee to > 99.5%. Near racemic **1** was isolated from the solution-phase (filtrate) in 28% yield. <sup>f</sup> Eight cycles of amplification of solid-phase ee were performed. <sup>g</sup> Eleven cycles of amplification of solid-phase ee were performed. <sup>h</sup> The thermal cycle was started after the dissolution of amino acid **2** in a suspension of racemic conglomerate **1**.

cycles (entry 2). No other compounds such as the product of benzoin condensation of *p*-tolualdehyde could be isolated from the filtrate except for highly polar materials.

The enantiomeric purity of suspended solid **1** was enhanced by the subsequent heating/cooling cycles. After partial dissolution of suspended solid **1** (ca. 80–90%) in the reaction mixture at 45–50 °C, the remaining conglomerate **1** regrew during the gradual cooling to room temperature over a period of 1 hour. The repetition of this thermal dissolution/crystallization cycle amplified the ee of solid **1** significantly to afford **1** with up to > 99.5% ee.

Even when L- and D-**2** with as low as approximately 50 and 10% ee were provided as chiral triggers, highly enantioenriched L- and D-solids **1** could be isolated with the same stereochemical relationships, respectively (entries 3–6). Therefore, L-amino acid **2** induced the production of L-aminonitrile **1** and D-**2** initiated the propagation of D-**1**. When L- and D-**2** were dissolved in a prepared suspension of racemic conglomerate **1**, crystalline solid **1** acquired L- and D-excess, respectively, after an adequate number of thermal cycles (entries 7 and 8). Stereoselective adsorption<sup>22</sup> of amino acid **2** at the crystal surface of conglomerate **1** would be included as a source of asymmetric induction and amplification, which subsequently differentiates the rate of crystal growth and dissolution between L- and D-enantiomorphs **1**. As enantioenriched **1** can be hydrolyzed to **2** without a decrease in enantiopurity,<sup>18</sup> and the molecular handedness of the source and product is the same, replication of amino acid **2** is subsequently achieved.

It should be noted that amino acids other than  $\alpha$ -(*p*-tolyl)glycine (**2**) could also work as chiral triggers for the formation of enantioenriched **1** (Table 2). Therefore, L-aminonitrile **1** was formed by the Strecker reaction between HCN, aldehyde **3** and primary amine **4** in the presence of L-alanine after the amplification of solid-phase ee (entry 1). Thus, the opposite D-alanine induced the formation of D-**1** (entry 2). L- and D-Phenylalanine also acted as a source of chirality for the production of L- and D-**1**, respectively (entries 3 and 4). When valine was subjected to this reaction, L-enantiomer affords D-**1** and D-valine gave the L-enantiomorph of **1** (entries 5 and 6). Unnatural phenylglycine that is a demethyl derivative of **2** also worked as an efficient chiral trigger to produce **1** (entries 7 and 8). In these reactions, chiral inducers, *i.e.*, amino acids completely dissolved in the reaction medium including DBU same as in the case when using L- and D-**2**.

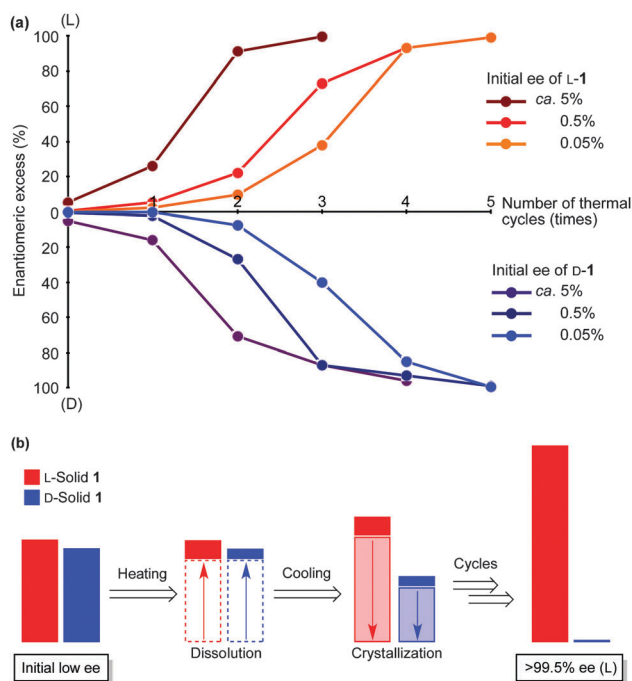
Next, we demonstrate the amplification of solid-phase ee from extremely low ee (ca. 0.05% ee) to a near enantiopure state (Fig. 3 and Table S1, ESI<sup>†</sup>). Solid **1** with the indicated ee was prepared by mixing racemic conglomerate **1** and near enantiopure L- or D-conglomerates **1**, and the resulting **1** (with indicated ee) was suspended in a 1 M DBU solution in methanol in the presence of a stir bar without glass beads. This mixture was then subjected to repeated dissolution/crystallization-induced amplification as mentioned above. When L-**1** with ca. 5% ee was subjected to the thermal cycle, the ee was amplified to 26% ee (L). The next cycle afforded L-solid **1** with 91% ee; finally, > 99.5% ee (L) was achieved. The recovered yield of **1** was 54%. The opposite D-**1** with ca. 5% ee could also be amplified to 96% ee (D) after



**Table 2** Stereochemical relationships between  $\alpha$ -amino acids and aminonitrile **1**

Entry <sup>a</sup>	Amino acid	Aminonitrile <b>1</b> <sup>b</sup>		
		% ee	Config.	% Yield
1	L-Alanine	92	L	54
2	D-Alanine	> 99.5	D	50
3	L-Phenylalanine	99	L	54
4	D-Phenylalanine	99	D	49
5	L-Valine	99	D	58
6	D-Valine	99	L	45
7	L-Phenylglycine	99	L	41
8	D-Phenylglycine	98	D	32

<sup>a</sup> The molar ratio used was amino acid : 3 : 4 : HCN = 1 : 2 : 2 : 3 (mmol). The reactions were performed in a 1.0 M DBU solution in methanol. All amino acids completely dissolve in the reaction medium containing DBU. <sup>b</sup> The ee value was determined by HPLC, employing a chiral stationary phase.



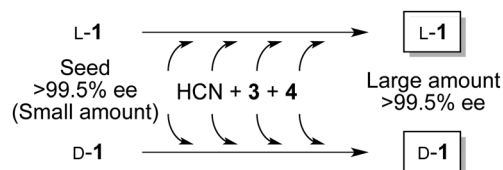
**Fig. 3** (a) Amplification of solid-phase ee of L- and D- $\alpha$ -aminonitrile **1** from extremely low ee (*ca.* 0.05% ee) to near enantiopurity (> 99.5% ee) by the heating/cooling cycles. (b) Simplified model for the production of highly enantioenriched solid **1** (L-enantiomorph).

four thermally controlled amplifications. Even when the enantio-enrichment was reduced to *ca.* 0.5% ee, the initially existing major enantiomorph **1** dominated; up to > 99.5% ee was achieved after five heating/cooling cycles. Furthermore, the initial very small L- and D-imbalances, approximately 0.05% ee, were also significantly enhanced during five amplification cycles; up to > 99.5% ee was achieved.

A linear relationship was observed between the initial ee and the number of thermal cycles required to achieve high ee, therefore, it was assumed that near racemate **1** dissolved during the heating step to afford a reduced amount of suspended solid **1** with amplified ee (Fig. 3b). In turn, cooling-induced deracemization may occur during gradual crystal growth without a decrease in the amplified ee. In the simple calculations (Fig. S1, ESI<sup>†</sup>), dissolution of 80% of *rac*-**1** from enantioenriched solid **1** with 5% ee (enantiomeric ratio (er) = 52.5/47.5) affords solid **1** with 25% ee (er = 12.5/7.5). After the ideal deracemization of **1** (er = 62.5/37.5, 25% ee), the next cycle affords a near enantiomerically pure solid (er = 100/0, 100% ee). It was calculated that four and five thermal cycles afford enantiopure solids starting from solid **1** with 0.5% ee and 0.05% ee, respectively. Since the initial very low ee (*ca.* 0.05%) could be enhanced to become a near enantiopure state, it was supposed that exact racemic dissolution during the heating step and efficient deracemization during the cooling step are key to this process. Therefore, this practically perfect thermal cycle is a highly sensitive and powerful method to improve an extremely small imbalance of L- and D-enantiomorphs of **1** toward a near enantiopure state (> 99.5% ee).

In addition, reactive crystallization of selected enantiomer **1** was realized; thus, seed crystal **1** gave a further amount of a near enantiomerically pure crystalline solid **1** by the portion-wise addition of three achiral reagents (Fig. 4 and Table S2, ESI<sup>†</sup>). For example, using L-**1** (0.08 g) with > 99.5% ee as a seed, five consecutive additions of HCN, aldehyde **3**, and amine **4** were conducted to precipitate L-**1** (46.5 g) with > 99.5% ee in 76% isolated yield, without thermal amplification. On the other hand, the amount of D-**1** with > 99.5% ee could also be increased as a result of the three-component Strecker reaction. Therefore, automultiplication of near enantiopure L- and D- $\alpha$ -aminonitrile **1** has been achieved in a highly stereospecific manner. To the best of our knowledge, this is the first example of highly enantioselective reactive crystallization *via* a three component reaction involving C–C bond formation.

In summary, we have demonstrated one of the reaction models for the replication of chiral  $\alpha$ -amino acids *via* the proposed prebiotic mechanism—the Strecker synthesis. Amino acids, *i.e.*, L- and D- $\alpha$ -(*p*-tolyl)glycine (**2**), acting as a source of chirality, asymmetric induction, amplification, and multiplication, were realized at the formation stage of the chiral intermediate  $\alpha$ -aminonitrile **1**, and amino acid **2** with the same structure and configuration as those of the original amino acid was newly synthesized by the subsequent hydrolysis. Even if a small amount of amino acid with low ee was induced by the proposed origin



**Fig. 4** Amplification of solid-phase ee of L- and D- $\alpha$ -aminonitrile **1** from extremely low ee (*ca.* 0.05% ee) to near enantiopurity (> 99.5% ee) by the heating/cooling cycles.



of chirality initially, it is possible to obtain both quantitatively and enantiomerically enhanced amino acids by the reaction sequence discussed here. These results should contribute to one of the approaches toward understanding the origin and amplification of homochirality such as seen in L-amino acids.

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