Chirality

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Asymmetric Strecker Reaction Arising from the Molecular Orientation of an Achiral Imine at the Single-Crystal Face: Enantioenriched L- and D-Amino Acids

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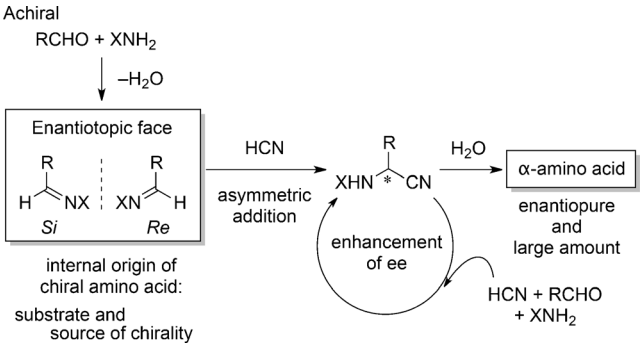
Abstract: *Strecker synthesis has long been considered one of the prebiotic reactions for the synthesis of α-amino acids. However, the correlation between the origin of chirality and highly enantioenriched α-amino acids through this method remains a puzzle. In the reaction, it may be conceivable that the handedness of amino acids has been determined at the formation stage of the chiral intermediate α-aminonitrile, that is, the enantioselective addition of hydrogen cyanide to an imine. Herein, an enantiotopic crystal surface of an achiral imine acted as an origin of chirality for the enantioselective formation of α-aminonitriles by the addition of HCN. In conjunction with the amplification of the enantiomeric excess and multiplication of enantioenriched aminonitrile, a large amount of near enantiopure α-amino acids, with the* L- *and* D- *handedness corresponding to the molecular orientation of the imine, is reported.*

One of the mysteries of the origin of life is the origin and amplification leading to biological homochirality, that is, how biology is almost predominantly composed of L-amino acids and D-sugars.[1] Chiral factors[2] have been suggested as candidates for the origin of chirality, such as circularly polarized light,[3] the chiral surface of minerals,[4] chiral crystallization,[5] spontaneous absolute asymmetric synthesis,[6] and extra-terrestrial factors such as enantioenriched meteoritic compounds.[7] Even if the initially induced chiral compounds by these factors have extremely small enantiomeric excess (*ee*), the compounds might acquire overwhelming enantioenrichment, as seen in L-amino acids, by the appropriate amplification and multiplication processes.[8]

Among the proposed chiral factors, the enantioselective reactions at the enantiotopic surface of an achiral compound should also be an entry because enantioenriched compounds could be synthesized from achiral compounds,[9] as exemplified by oxidation[10a] and reduction[10b] to give enantiomerically imbalanced chiral products. Moreover, highly enantioselective C–C bond formation has been achieved in combination with asymmetric autocatalysis (Soai reaction). Therefore, the synthesis of a 5-pyrimidyl alkanol with greater than 99.5% *ee* was triggered by the treatment of the enantiotopic crystal face of an achiral aldehyde with a dialkylzinc vapor.[11]

The Strecker reaction has been considered one of the mechanisms for prebiotic synthesis of amino acids. Therefore, the enantioselective addition of hydrogen cyanide (HCN) to an achiral imine would be a challenge and could become one of the approaches towards discovering the origin of chiral amino acids. In this presentation (Scheme 1), an achiral



Scheme 1. The concept of this work: enantioselective Strecker amino acid synthesis induced by the molecular orientation of a prochiral intermediate imine.

intermediate imine, prepared from a carbonyl compound and amine, provides its own molecular orientation as a source of asymmetric HCN addition to give an enantioenriched chiral intermediate α-aminonitrile. In conjunction with enhancement of the *ee* value and the amount of enantioenriched aminonitrile, a large amount of near enantiopure α-amino acid could be synthesized by hydrolysis. Different from the suggested external chiral factors, such as those mentioned above, the present method approaches the internal origin of chiral amino acids, thus, an achiral imine with an enantiotopic crystal face acts as both substrate and source of chirality inside the prebiotic mechanism, that is, Strecker amino acid synthesis.[12] To our knowledge, this is the first example of the direct link between the molecular orientation of a prochiral imine and L- and D-amino acids with high enantioenrichment mediated by the asymmetric Strecker reaction.

Previously, we reported the significant amplification of α-aminonitrile **2**[13a] (for structure see Scheme 2) in the solid state from about 0.05% *ee* to near enantiopure by thermal dissolution/recrystallization cycles, and the replicative formation of α-*p*-tolylglycine has been achieved in which L- and D-

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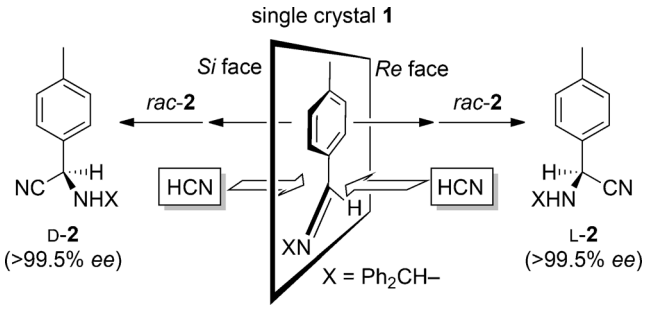
amino acids induce the amplification of its own L- and D-intermediate **2**, respectively.[13b] Herein, we show the asymmetric addition of HCN to the enantiotopic single-crystal face of achiral imine **1** to afford the corresponding L- and D-aminonitrile **2** with up to greater than 99.5% *ee*, in combination with the asymmetric amplification and multiplication of the solid product, which can be hydrolyzed to give L- and D-amino acids without a decrease in enantiopurity (Scheme 2).



Scheme 2. The asymmetric addition of hydrogen cyanide (HCN) to the imine **1** at the enantiotopic surface to afford the corresponding L- and D-aminonitriles **2**.

The achiral imine **1** was prepared by dehydrative condensation between achiral *p*-tolualdehyde and benzhydrylamine, and its well-defined single crystals could be synthesized by recrystallization from the mixed solvent of *n*-hexane and toluene by slow concentration (Figure 1 a). Single-crystal X-ray structure analysis demonstrated that the crystal **1** belongs to the achiral space group $P\bar{1}$.[14] When molecule **1** was projected along the *a*-axis in the packing diagram, the *Re* face of the imino group was oriented towards the red-colored *a*-face on the outside of the crystal (Figure 1 b). In turn, the *Si* face was oriented towards the opposite blue-colored face. The X-ray analysis showed reproducibly the single-crystal surfaces having the largest surface areas to be enantiotopic (100) or its back side (−100) faces. These crystal planes were parallelograms with an acute angle of about 60°, which could be absolutely differentiated and defined morphologically to be (100) or (−100) planes based on the non-superimposable parallelogram face shapes as indicated, respectively (Figures 1 a; see Figure S1 in the Supporting Information). The single crystal **1**, other than the single reactive (100) or (−100) faces, was coated with an epoxy resin to select one enantiotopic face from which HCN could approach (Figure 1 c), thus leading to enantioselective addition. It was assumed that racemic transformation would proceed when the cyanide addition occurred at both enantiotopic faces with the same probability.

The enantiotopic (100) and (−100) faces were independently reacted with HCN to form enantioenriched L- and D-aminonitriles **2**, respectively (Figure 1 d and Table 1). Upon treatment of HCN at the enantiotopic (100) face (area: 8.0 mm^2) of the single crystal **1** (crystal **A**, 0.026 mmol) in a methanol suspension of *rac*-**2** (lot number **I**), the enantioenriched L-aminonitrile **2** with 99% *ee* was synthesized in the yield of 0.195 mmol after the amplification of the solid-state *ee* value (Table 1, entry 1). In contrast, when the

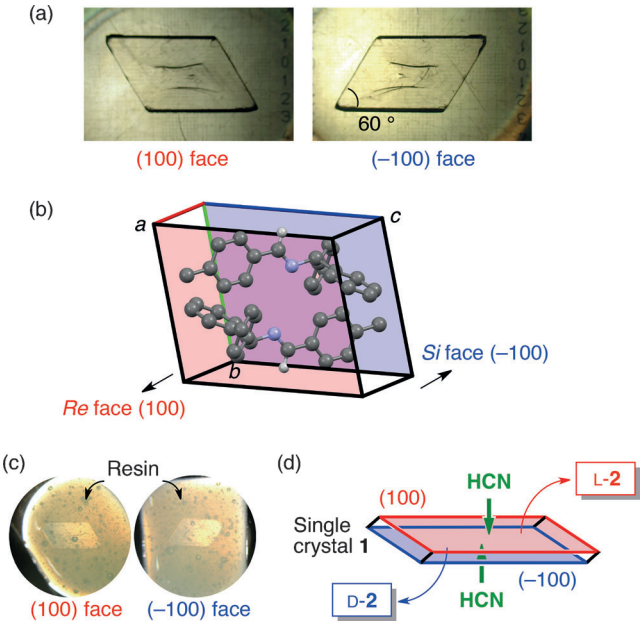


Figure 1. Single crystal of achiral imine **1**. a) Microscope image of a single crystal **1** from the (100) and its back side of (−100) planes with enantiotopic parallelogram face shapes. See also Figure S1. b) A packing diagram of imine **1**. The red and blue planes correspond to the enantiotopic (100) and (−100) faces, respectively. The hydrogen atoms other than those of the imino group were removed for clarity. See also Figure S1. c) Microscope image of single crystals **1**. One crystal was coated with a resin other than the indicated (100) face and the other crystal was coated with a resin except for the indicated (−100) face. d) Asymmetric addition of HCN at the enantiotopic faces.

opposite (−100) plane of **1** (crystal **B**) was reacted with HCN in the suspension of *rac*-**2** with the same lot number **I**, the oppositely configured D-**2** with an amplified *ee* value of 98% was obtained in a yield of 0.198 mmol by filtration (entry 2). Although the *ee* value of the suspended **2** was below the detectable level after finishing the asymmetric HCN addition, and before the thermal cycles, the initial tiny enantiomorphic imbalance of **2** could be enhanced significantly to afford highly enantioenriched **2** by the thermal heating/cooling cycles.[13b] The suspensions of the *rac*-**2** used in each asymmetric reaction were prepared by dividing a solution of *rac*-**2**, obtained from a homogeneous reaction of **1** and HCN (see the Supporting Information). The original solution was identified with the indicated lot numbers **I**–**VI**. Further reactions disclosed that cyanide addition at the morphologically defined (100) and (−100) faces of **1** (crystals **C**, **D**, **E**, and **F**) reproducibly gives L- and D-aminonitrile **2**, respectively, with high *ee* values (entries 3–6). Because the stereochemical relationships are constant between the absolute configuration of the produced **2** and the parallelogram face shape of the reacting single crystal of **1**, the molecular orientation of prochiral **1** in the crystal should correlate to the handedness of the parallelogram face. Therefore, the absolute orientation of the imino group at the crystal surface can be determined from the absolute configuration of **2**.[15]

Moreover, for the purpose of making sure of the stereochemical outcomes further experiments were con-

Table 1: Stereochemical correlations between the enantiotopic face of **1** and absolute handedness of **2**.

Entry[a]	Single-crystal **1**		Reactive surface		Lot No. of	**2**		Number of
	No.	Amount (mmol)	Face index	Area (mm^2)	pre-suspended *rac*-**2**[b]	*ee* [%][c] (config.)	Amount[d] (mmol)	thermal cycles[e]
1	**A**	0.026	(100)[f]	8.0	**I**	99 (L)	0.195	10
2	**B**	0.028	(−100)[f]	8.8	**I**	98 (D)	0.198	10
3	**C**	0.0084	(100)	2.0	**II**	90 (L)	0.130	9
4	**D**	0.01	(−100)	3.2	**II**	92 (D)	0.227	9
5	**E**	0.019	(100)	7.0	**II**	93 (L)	0.232	11
6	**F**	0.036	(−100)	6.0	**II**	92 (D)	0.170	14
7	**G**	0.033	(100)	10.5	**I**	>99.5 (L)	0.198 (0.652)[g]	6
8	**G**	0.026	(−100)	9.6	**I**	>99.5 (D)	0.130 (0.698)[g]	13
9	**H**[h]	0.022	(100)	7.0	**III**	97 (L)	0.278	7
10	**H**[h]	0.023	(−100)	8.3	**III**	84 (D)	0.221	7
11	**I**	0.126	(100)	n.d.[i]	**IV**	91 (L)	n.d.[i]	7
12	**I**	0.093	(−100)	n.d.[i]	**IV**	95 (D)	n.d.[i]	8

[a] In a 5 mL screw vial, the single crystal **1**, coated with resin except for one enantiotopic face, was added to a suspension of *rac*-**2** (ca. 0.5 mmol) in methanol (1 mL) and includes HCN (0.036 mL, 0.85 mmol) at room temperature for entries 1, 2, 7, 8, 11, and 12 or 0 °C for entries 3–6, and 9 and 10. After gentle stirring for 1–2 h, the single crystal **1** disappeared and the resin was removed. After the addition of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU; 0.2 mL), the resulting mixture was submitted to a heating/cooling cycle to afford the enantioenriched **2** by filtration. See also the Supporting Information for the details. [b] The *rac*-**2** was synthesized by HCN addition to **1** in a homogeneous toluene solution in the presence of a catalytic amount of DBU. See also the Supporting Information for the details. [c] Determined by high-performance liquid chromatography (HPLC) on a chiral stationary phase. [d] The amount of isolated **2** by filtration. Near *rac*-**2** from the filtrate was not included in this value. [e] The *ee* value before the thermal amplification cycles was below the detectable level from the HPLC analysis of a part of the suspended solid **2**. [f] Photos of the single crystal **A** coated with a resin except for the (100) face and single crystal **B** coated with a resin except for the (−100) face are shown in Figure 1 c. [g] The amount of enantioenriched **2** could be increased by reactive crystallization. See also Ref. [13b]. [h] Photos of both the (100) and (−100) faces of the crystal **H**, which was cut and submitted to the reaction after coating with resin, are shown in Figure 1 a. [i] Not determined.

ducted using both enantiotopic faces originating from one specific single crystal, which was cut into two pieces. The (100) face of almost one-half of the crystal **G** was reacted with HCN to afford L-**2** with greater than 99.5 % *ee*, after the amplification of the *ee* value (entry 7). In contrast, the reaction at the opposite (−100) face of the same crystal **G** gave the oppositely configured D-**2** with greater than 99.5 % *ee* (entry 8). It should be noted that further Strecker reaction between achiral HCN, *p*-tolualdehyde, and benzhydrylamine using the obtained **2** as a seed could increase the amount of near enantiomerically pure **2**, as shown here.[13b] The reproducibility of the formation of the major enantiomer was also checked by using pieces of the single crystals **H** and **I** to afford the highly enantioenriched **2** with the corresponding molecular handedness (entries 9–12). Therefore, the present enantioselectivity of HCN addition would be induced by the direct reaction of HCN at a single-crystal face, either *Re* or *Si* enantioface, of the imino group because the dissolution of **1** causes disappearance of the chirality. Because the reaction proceeds at one specific plane of the crystal, the direction of the preferential approach of cyanide to the *Re* and *Si* faces can be absolutely controlled.

During the HCN addition reaction, pre-suspended L- and D-**2** (racemic conglomerate) were grown according to the formation of **2** because the solution was saturated in *rac*-**2**. It was supposed that the crystals of L- and D-**2** grew depending on the enantioenrichment of newly formed **2**. Therefore, the enantioselectivity of HCN addition to **1** could be caught as an imbalance of the L- and D-enantiomorphs **2**. After finishing the HCN addition, that is, the disappearance of the single crystal **1**, the enantiomerically imbalanced solid **2**, including initially added racemic conglomerate, was subjected to thermal amplification[13b] thus affording the highly enantioenriched solid **2**, as observed here. Therefore, a larger molar amount of **2** than that of the submitted **1** could be isolated by filtration in a highly enantioselective manner. The present thermal cycle is a highly sensitive and efficient method to amplify the tiny enantio-imbalance induced by the asymmetric HCN addition on the crystal surface of imine.

In addition, it should be noted that the absence of any chiral factors which can chirally influence the asymmetric amplification was confirmed by checking the pre-existing *rac*-**2** (see Table S1). Therefore, the present results support that the asymmetric Strecker reaction solely arose from the two-dimensional molecular orientation of the achiral imine **1**.

In summary, we have demonstrated the enantioselective addition of HCN to the enantiotopic surface of the imine **1** to form the α-aminonitriles **2** in enantioenriched form with the absolute configurations corresponding to the prochirality of **1**. In conjunction with the amplification of the solid-state *ee* value and multiplication of the enantioenriched intermediate **2**, a large amount of near enantiopure L- and D-amino acids could be synthesized. Therefore, a possible origin for chiral amino acids has been found by using the suggested Strecker reaction.

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Conflict of interest

The authors declare no conflict of interest.

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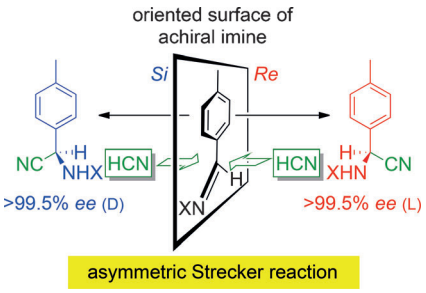
Communications

Chirality

S. Miyagawa, K. Yoshimura, Y. Yamazaki, N. Takamatsu, T. Kuraishi, S. Aiba, Y. Tokunaga, T. Kawasaki* _____ ■■■■–■■■■

Asymmetric Strecker Reaction Arising from the Molecular Orientation of an Achiral Imine at the Single-Crystal Face: Enantioenriched L- and D-Amino Acids



Face off: The correlation between the molecular orientation of an achiral imine and highly enantioenriched amino acids has been achieved for the Strecker synthesis. A highly enantioenriched aminonitrile was formed by the asymmetric addition of HCN at one surface of a single crystal of the imine, in combination with amplification of the *ee* value and multiplication of the enantioenriched product. Therefore, a possible entry for the origin of chiral amino acids has been found by using the Strecker reaction.