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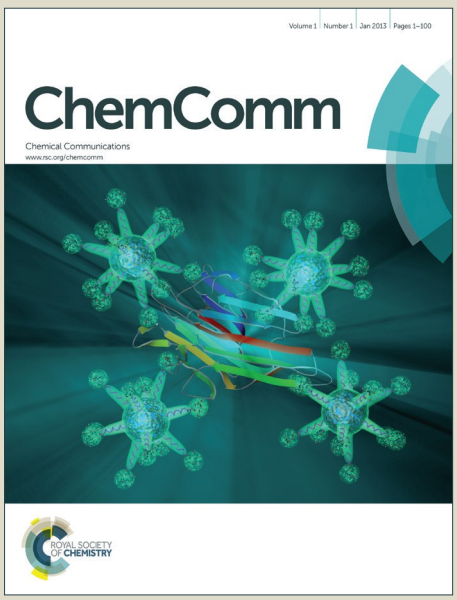

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Spontaneous formation and amplification of enantioenriched α-amino nitrile, a chiral precursor of Strecker amino acid synthesis†

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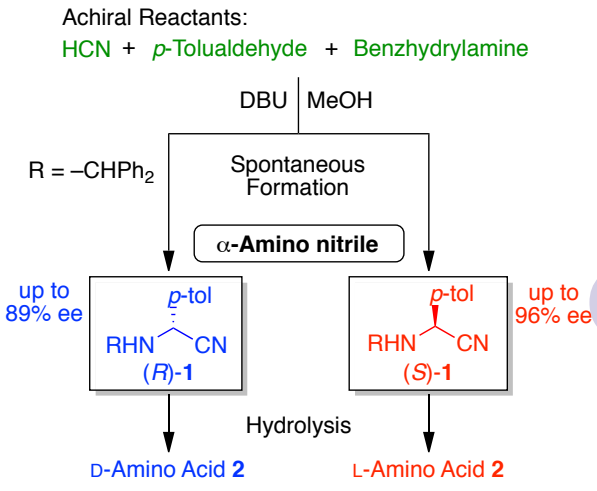
Without adding any chiral substances, spontaneous formation of enantioenriched α-amino nitrile (up to 96% ee), which is a chiral precursor of Strecker amino acid synthesis, has been achieved in combination with the conglomerate formation. The frequency of the formation of enantiomorphs exhibits the approximate stochastic distribution, *i.e.*, L-form occurred 21 times and D-form occurred 22 times, which fulfil the conditions necessary for spontaneous absolute asymmetric synthesis.

L-Amino acids are the main building blocks of proteins. Therefore, their origin—specifically, how enantioenriched amino acids emerged in the achiral or racemic world before the origin of life—is one of the great research topics. Following the discovery of molecular chirality by Pasteur, pioneering work by a number of researchers has led toward an understanding of the origin of chirality.[1–4] Among the proposed theories, the spontaneous generation of enantioenriched compounds under achiral or racemic conditions is a possible route under terrestrial circumstances.[5] The first experimental realization in homogeneous solution was the enantioselective synthesis of 5-pyrimidyl alkanol by asymmetric autocatalysis with amplification of enantiomeric excess (the Soai reaction).[1k,1l,6–8] In the heterogeneous process, the deracemization of chiral quaternary ammonium salts was reported.[9] Furthermore, enantiomorphous sodium chlorate[10] and 1,1′-binaphthyl[11] were resolved under stirred condition.[2f]

We now report on the spontaneous crystallization of enantioenriched α-amino nitrile with up to 96% enantiomeric excess (ee) from the reaction solution of three achiral compounds, hydrogen cyanide (HCN), *p*-tolualdehyde, and benzhydrylamine. Almost the same probability of the generation of L and D-forms was observed. In addition, applying attrition-enhanced ripening,[12–14] the amplification of solid phase ee was realized. Thus, in combination with hydrolysis, the present reaction would become one of the efficient ways to access highly enantioenriched α-amino acids[15] without intervention of chiral materials. To our knowledge, this is the first example of enantioenriched α-amino nitrile, a chiral precursor of Strecker amino acid synthesis,[16,17] being obtained spontaneously.

The enantioenriched *N*-benzhydryl-α-*p*-tolylglycine nitrile (**1**)[18] was obtained *via* Strecker synthesis in combination with the conglomerate formation (Scheme 1). The reaction between HCN, *p*-tolualdehyde, and benzhydrylamine proceeded in the presence of DBU (1,8-diazabicyclo[5.4.0]undec-7-ene). Upon addition of these three reagents to a 1 M DBU solution in methanol, crystals of **1** appeared in enantioenriched form after some reaction time. In one reaction, the crystalline product of (*S*)-amino nitrile **1** with up to 96% ee was isolated in 33% yield. In sharp contrast, crystalline product (*R*)-**1** with up to 89% ee was produced in another reaction vessel. The subsequent hydrolysis of **1** proceeded without any decrease in enantiopurity to afford *p*-tolylglycine (**2**).



Scheme 1 Spontaneous crystallization of enantioenriched α-amino nitrile **1** in combination with Strecker reaction of three achiral reactants in the presence of DBU followed by the hydrolysis to give L and D-α-*p*-tolylglycine (**2**).

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In the reactions under discussion, dehydrative condensation between *p*-tolualdehyde and benzhydrylamine affords the corresponding achiral imine intermediate and subsequent nucleophilic addition of HCN gives chiral *N*-benzhydryl-α-*p*-tolylglycine nitrile (**1**). Progression of the reaction leads to the supersaturation of **1** in the solution, which induces the spontaneous crystallization of **1**. The single crystal **1**, which belongs to the monoclinic space group $P2_1$, has been obtained from the present reaction solution, thus, forming a conglomerate (Fig. S1, ESI†). DBU accelerates the racemization of α-amino nitrile **1** by the deprotonation of acidic α-proton and the reverse reaction, *i.e.*, formation of the achiral imine intermediate by the elimination of HCN (Scheme S1, ESI†); thus, both processes of α-deprotonation/protonation and elimination/addition of HCN may be included in the racemization mechanisms (racemization half-life ($t_{1/2}$) ca. 0.5 min at room temperature) (Fig. S2, ESI†). Since the amino nitrile in solution phase is near racemic, spontaneous resolution and deracemization[19] would be included.

Rapid racemization of **1** in the solution phase ensures sufficient supply of the preferred enantiomer to the solid phase after the primary nucleation of enantioenriched **1**. In addition, considering the reaction equilibrium between imine and amino nitrile,[20] the crystalline product (and HCN) drives the reaction in the forward direction forming amino nitrile **1** and DBU in the reverse direction forming imine intermediate. After the appearance of crystals, the formation of more amounts of amino nitrile and further crystal growth are associated with each other. Thus, in the presence of DBU promoting reverse reaction, slow and selective crystal growth can be realized in the present system, in which the synthetic reaction and crystallization are coupled. This controlled reactive crystallization prevents additional (random) primary nucleation reducing the crystal ee, and induces prompt secondary nucleation keeping the imbalance of enantiomer of the primary nuclei. In fact, the amount of suspended crystal increased gradually during the hours after the initial crystal appearance. We assume that the present reaction has a well-balanced equilibrium to maintain the minimum supersaturation of amino nitrile required for spontaneous crystallization and to provide the highly selective resolution during the crystal-growing step (Fig. S3, ESI†).

To examine the distribution of the sense of chirality and ee of amino nitrile **1**, further experiments were repeatedly conducted (Table 1). When the reaction and crystallization were performed under stirring, enantioenriched **1** was obtained in a powder-like form (Fig. S4, ESI†). In run 1, the solid product (*R*)-**1** with 25% ee was obtained in 38% yield and the *R* configured product with only 0.4% ee was isolated from the solution phase in 37% yield. By contrast, (*S*)-isomer **1** with 7.5% ee was formed as a crystalline product (run 2). As noted, (*R*)- and (*S*)-**1** with up to 89% and 96% ee were isolated in yields of 27 and 33%, respectively (runs 18 and 32), and (*R*)-**1** with 43% ee was isolated in 71% yield as the total product of the reaction mixture (run 31).

Table 1. Spontaneous generation of enantioenriched α-amino nitrile **1**.[a]

Run	Solid product **1** Yield/%[b]	ee/%[c]	Run		
—Stirred condition[d]—			23	37	19 (*R*)
1[e]	38	25 (*R*)	24[f]	nd	0.4 (*R*)
2	nd	7.5 (*S*)	25	41	6.2 (*S*)
3	16	6.0 (*S*)	26	41	2.7 (*S*)
4	37	17 (*S*)	27	35	4.7 (*R*)
5[f]	37	1.7 (*R*)	28	31	37 (*S*)
6	19	30 (*R*)	29	21	9.4 (*S*)
7	33	81 (*R*)	30	nd	5.1 (*S*)
8	nd	2.2 (*S*)	31[g]	71	43 (*R*)
9[f]	nd	0.7 (*R*)	32[h]	33	96 (*S*)
10	nd	2.1 (*S*)	33[i]	34	90 (*S*)
11	nd	6.0 (*S*)	34[j]	25	88 (*S*)
12	nd	9.3 (*R*)	35	37	37 (*R*)
13	nd	86 (*S*)	36	34	8.7 (*R*)
14	nd	22 (*S*)	37	35	2.3 (*R*)
15	44	17 (*R*)	38	52	52 (*S*)
16	32	2.4 (*S*)	39	38	38 (*R*)
17	44	6.0 (*R*)	40	nd	14 (*S*)
18	27	89 (*R*)	—Unstirred condition[k]—		
19	35	26 (*S*)	41[l]	29	82 (*S*)
20	35	17 (*R*)	42	26	64 (*R*)
21	nd	2.0 (*S*)	43	nd	11 (*R*)
22	28	4.5 (*R*)			

[a] The results are shown in entries 1–40 and 41–43, in the order in which the reactions were performed, respectively. The product **1** was isolated at least 6 h after initially noticing crystal formation (ca. 0.5 h to 72 h). [b] The isolated yield of crystalline product **1**. The product in the solution phase is not included unless otherwise stated. nd: not determined. [c] The ee value was determined by HPLC on a chiral stationary phase. [d] Constant stirring rate is between 300 to 1000 rpm. [e] (*R*)-**1** with 0.4% ee was isolated from the solution phase in 37% yield. [f] The ee values are below the detectable level. [g] (*R*)-**1** with 43% ee was isolated as the mixed product from both the solid and solution phases. The yield indicates the amount of amino nitrile **1** obtained from both phases. The data was ranged between 80–100% ee (*R*) in the histogram (Fig. 2). [h] (*R*)-**1** with 0.4% ee was isolated from the solution phase in 21% yield. [i] The product was isolated 18.5 h after the addition of all reagents. (*R*)-**1** with 1.4% ee was isolated from the solution phase in 43% yield. [j] (*R*)-**1** with 0.1% ee was isolated from the solution phase in 43% yield. [k] The reactions were performed without stirring. [l] The single crystal appeared after 48 h. (*S*)-**1** with 3.2% ee was isolated from the solution phase in 29% yield.

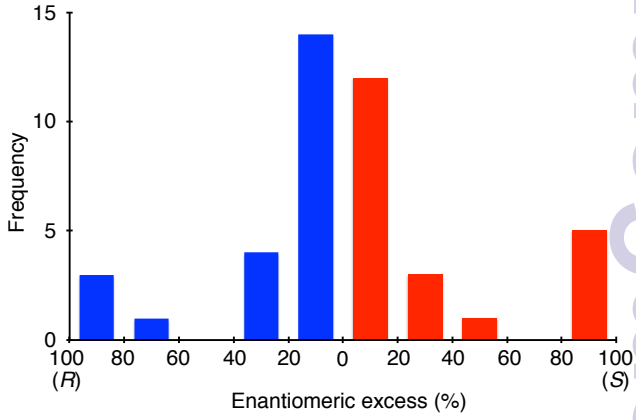

Fig. 1 Histogram of total experimental outcomes.

It should be noted that enantiomerically enriched crystalline products **1** were obtained without stirring (runs 41–43). Under unstirred conditions, several single crystals in water-clear form were found to form spontaneously in the reaction vessel (Fig. S4, ESI†). (*S*)-**1** with up to 82% ee was formed in 29% yield (run 41). The opposite configured (*R*)-α-amino nitrile **1** with 64% and 11% ee were formed in runs 42 and 43, respectively.

Among the 160 experiments that were performed, spontaneous crystallizations occurred in 43 cases. No crystal formation was observed in 117 reactions, even after more than 2 weeks.[21] Fig. 1 summarizes the results shown in Table 1, and shows that the absolute handedness of **1** exhibited an approximate stochastic distribution, *i.e.*, the *S*-enantiomer occurred 21 times and the opposite *R*-form occurred 22 times. Because the reaction was initiated by mixing achiral reagents without adding any chiral materials, present observation constitutes one of the conditions necessary for spontaneous absolute asymmetric synthesis. Furthermore, from the low frequency of moderate ee observed in the histogram, it could be assumed that the initial crystalline product with higher ee possesses the larger amplification effect in ee during the crystal formation step.

Next, we examined the amplification of crystal ee by applying Viedma ripening.[14–16] Amino nitrile **1** with low ee was suspended in a DBU and HCN solution of methanol, which was saturated with *rac*-**1**, and the mixture was vigorously stirred in the presence of glass beads. The ee of the solid phase was monitored over time by sampling a part of the crystalline product (Figure 2). (*R*)-**1** with 7.0% ee was amplified to be 11% ee after 15 h. The value finally achieved was 93% ee after 98 h and a sigmoidal shape was observed. In the same manner, (*S*)-amino nitrile **1** with 9.0% ee was amplified to become 93% ee after 114 h. When the crystal with higher ee was submitted as initial solid, the ee value was enhanced to reach high ee more rapidly.

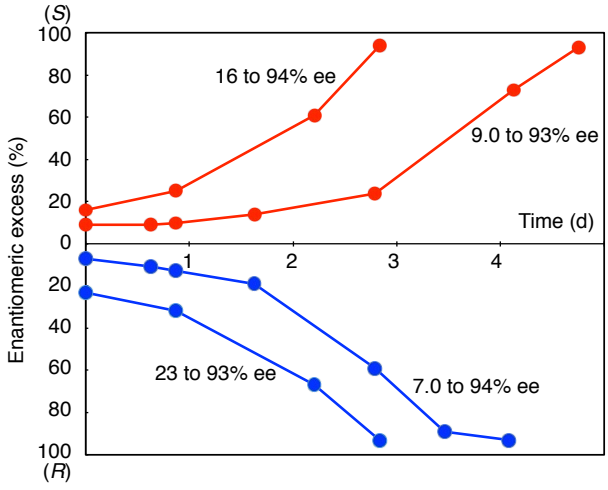

Fig. 2 Amplification of solid phase ee of α-amino nitrile **1** starting from low ee in the presence of glass beads under grinding condition.

In summary, spontaneous generation of enantioenriched α-amino nitrile **1** was realized in combination with a Strecker reaction between achiral substrates and subsequent spontaneous crystallization. We have demonstrated the stochastic distribution of a handedness of spontaneously generated enantioenriched (*S*) and (*R*)-α-amino nitrile **1**. The enhancement of solid phase ee was observed by the attrition of crystalline product; therefore, in combination with hydrolysis, the synthesis of highly enantioenriched L and D-amino acid, α-*p*-tolylglycine (**2**) was achieved without intervention of any chiral materials. We believe that the present results highlighting spontaneous formation and amplification of enantioenriched α-amino nitrile are one approach to understanding the origins of chirality such as seen in L-amino acids.

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21 When larger amount of *p*-tolualdehyde and benzhydrylamine (ca. 1.0 mmol) were submitted to the reaction, the higher probability of crystal formation after shorter incubation time was observed with ee of up to 21%.