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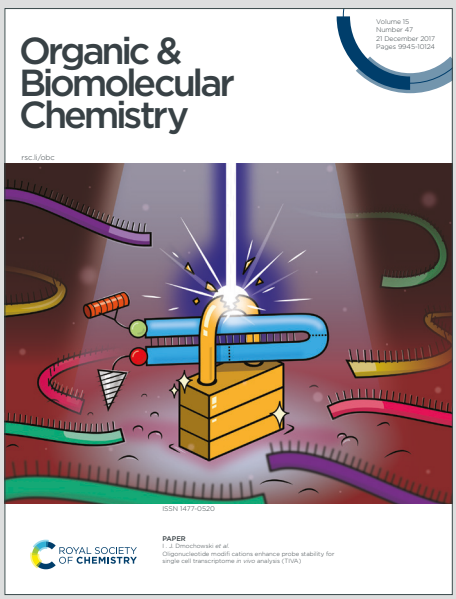

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ARTICLE

Replication of chiral α-hydroxy acid *via* induction and amplification through an enantioenriched cyanohydrin conglomerate

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A spontaneous absolute asymmetric synthesis of cyanohydrins has been developed without any external chiral source through the combination of conglomerate formation and solution-phase racemization. This method integrates HCN addition reaction to an aldehyde with subsequent Viedma ripening; consequently, spontaneous deracemization and enantioselective reactive crystallization of cyanohydrins are achieved for the first time. Importantly, the hydrolysis products of the cyanohydrin—namely, the corresponding α-hydroxy acid and hydroxyamide—serve as chiral inducer that direct the handedness of solid-state asymmetric amplification, leading to highly enantioenriched cyanohydrins with matching chirality. This feedback between product formation and asymmetric amplification establishes a reaction network in which chirality is propagated and reinforced across molecular transformations. In combination with cyanohydrin hydrolysis, this system constitutes a chemically coupled process that approaches the replication of chiral α-hydroxy acid and hydroxyamide, key products in abiotic Strecker-type synthesis, and is therefore relevant to the origin of biological homochirality.

Introduction

Biological systems on Earth are mainly composed of a single enantiomer among possible mirror image molecules. How and when the current biological homochirality—exemplified by L-amino acids and D-sugars—was established remains a fundamental puzzle closely related to studies on the origin of life. Since Louis Pasteur discovered the molecular chirality by separating the enantiomorphs of sodium ammonium tartrate,[1] various chiral factors and mechanisms have been proposed as possible source of chirality and its amplification to the overwhelming enantioenrichment.[2–21] Moreover, self-replication is a defining feature of biological systems, making the autoinductive synthesis of chiral molecules a central challenge in synthetic and systems chemistry.[22–24]

Meanwhile, Strecker-type synthesis[25] has long been considered one of the principal abiotic pathways for the formation of α-amino acids[26] and α-hydroxy acids.[27,28] Amino acids and hydroxy acids with the same alkyl groups have been detected in meteorite,[29–31] and their formations have been investigated.[32,33] Therefore, as in the case of enantioenriched α-amino acids,[34–38] research on the generation and amplification of enantioenriched α-hydroxy acids[39] should be regarded as an important chemical approach to understand the origin of chirality.

Previously we demonstrated a spontaneous absolute asymmetric Strecker synthesis of amino acids based on Viedma ripening of α-aminonitriles.[40,41] A slight enantiomeric imbalance can be amplified to near enantiopure in solid state[42] and corresponding amino acid, acting as chiral source, induce the asymmetric amplification of its own chiral intermediate, an aminonitrile. Based on this work, enantiotopic crystal faces of achiral imine,[43] chirally crystallized achiral imines,[44] chiral crystal of *rac*-cyanohydrin,[45] and chiral hydrogen isotopomers[46] have also been shown to induce the formation of enantioenriched aminonitriles. Consequently, after enhancement of aminonitrile ee, amino acids with high ee can be obtained *via* hydrolysis. Thus, internal chiral sources play a key role in producing highly enantioenriched amino acids *via* asymmetric amplification of the intermediates.

We report here the replication of a chiral hydroxy acid coupled with the deracemization of its own chiral intermediate, a cyanohydrin, *via* the reaction between an aldehyde with hydrogen cyanide (HCN). The hydroxy acid and its corresponding hydroxyamide, acting as a source of chirality, can induce the asymmetric amplification in solid-state, affording highly enantioenriched cyanohydrin with the same handedness as that of the chiral source (Fig. 1). Combined with conglomerate formation and solution-phase racemization of the cyanohydrin, this system achieves total spontaneous resolution[47] of the cyanohydrin *via* Viedma ripening.[48,49]

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Subsequent hydrolysis yields the corresponding hydroxyamide and hydroxy acid, enabling spontaneous absolute asymmetric synthesis without external chiral sources. Enantioselective reactive crystallization of the cyanohydrin further allows its auto-multiplication, providing a model for replicating asymmetric systems to give large amount of biologically relevant chiral compounds. Although the deracemization of conglomerate crystals under racemizing conditions has been extensively studied using Viedma ripening, to the best of our knowledge, this is the first example of the generation, amplification, and multiplication of chiral cyanohydrins.

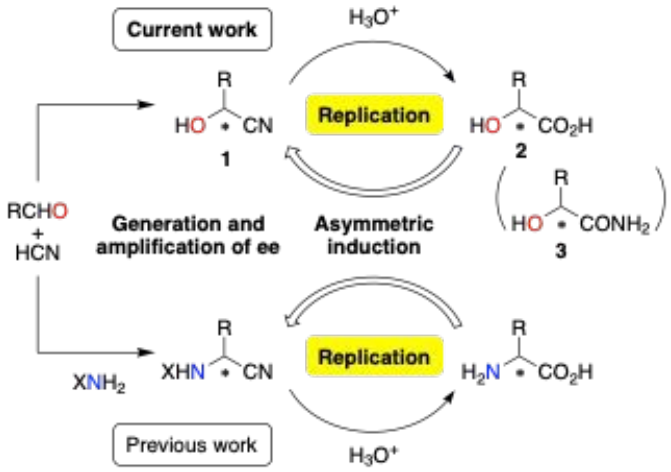


Fig. 1 Concept of this work: approaches to the replication of a chiral α-hydroxy acid **2** *via* asymmetric induction and amplification of its own chiral intermediate, an α-cyanohydrin **1** in comparison with our previous work on the formation of α-amino acid.

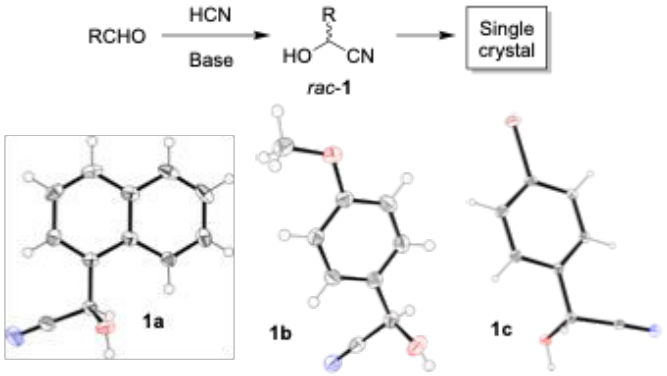
Results and discussion

First, racemic cyanohydrins **1** were prepared from the corresponding aldehydes and HCN, and their single-crystal X-ray structures are summarized in Table 1. Screening revealed that cyanohydrins **1a** and **1b**, derived from 1-naphthaldehyde and 4-anisaldehyde, respectively, crystallize in the space groups *R*3 and $P2_12_12_1$ and form conglomerates. Although the single-crystal structures of *p*-bromo and *o*-bromobenzaldehyde cyanohydrins (**1c** and **1d**) have been reported,[50] we found that both form conglomerates when crystallized from racemic solutions (toluene or toluene/hexane). A single-crystal structure of racemic compound **1d** in the achiral space group *Pbca* has also been reported from an ethereal solution.[51]

In contrast, cyanohydrins **1e** (*o*-methoxyphenyl) and **1f** (*p*-nitrophenyl) crystallize as racemic compounds. The cyanohydrin **1g**, derived from phenylacetaldehyde, also crystallizes as a racemic compound. Notably, racemic compound **1h** adopts the space group $P2_12_12_1$ as a kryptoracemate, as reported in our previous work.[45] We have reported that imine and aminonitrile, derived from achiral 1-naphthaldehyde and benzhydrylamine, also crystallize in chiral forms and can be used to develop enantioselective reactions and chiral amplification.[41,44]

Next, racemization was investigated to establish the present crystallization-based deracemization method. For example, acetic acid stabilizes the cyanohydrins; therefore, we found that the strong organic base DBU (1,8-diazabicyclo[5.4.0]-7-undecene) efficiently promotes the racemization of cyanohydrins derived from aldehydes. The deprotonation/protonation equilibrium of the α-proton, as well as the HCN elimination/addition equilibrium is proposed as a possible mechanism. When **1a** with 98% ee (22 mM) was treated with DBU (13 mM) in toluene, the ee disappeared within 5 min (see SI Fig. S1), and the half-life ($t_{1/2}$) under the condition was calculated to be 42 s, which is sufficiently fast for deracemization *via* Viedma ripening. Racemization of **1b** with 95% ee (61 mM) in the presence of DBU (6.7 mM) showed a $t_{1/2}$ of 9 s. However, under the same condition in the presence of HCN (31 mM), the half-life $t_{1/2}$ decreased to nearly half, contrary to the expectation that DBU would be inhibited by neutralization with HCN. The addition of HCN is expected to shift the equilibrium toward cyanohydrin formation, thereby reducing the amount of aldehyde in solution. This result indicates that the HCN addition/elimination process contributes significantly to the racemization.

Table 1 Single-crystal X-ray structures of cyanohydrins **1** from their racemic solution.



Substituent R		Space group	CCDC
1-Naphthyl	**1a**	*R*3 (conglomerate)	2543998
p-Methoxyphenyl	**1b**	$P2_12_12_1$ (conglomerate)	2543999
p-Bromophenyl	**1c**	$P2_12_12_1$ (conglomerate)	2544000
o-Bromophenyl	**1d**	$P2_12_12_1$ (conglomerate)	2544001
o-Methoxyphenyl	**1e**	$P2_1/n$ (racemic compound)	2544002
p-Nitrophenyl	**1f**	*P*–1 (racemic compound)	2544003
Benzyl	**1g**	$P2_1/c$ (racemic compound)	2544004
p-Tolyl	**1h**	$P2_12_12_1$ (kryptoracemate)	2117047[a]

[a] See also ref.45 and the corresponding enantiomorphic structure (CCDC 2204872).

Next, we first attempted the spontaneous formation[47] of enantioenriched cyanohydrins in combination with the HCN addition reaction to aldehydes. However, no detectable enantiomeric imbalance was observed in the initial precipitation as a result of reaction progress, even though the solution-phase racemization in the presence of DBU. Therefore, temperature cycling coupled with Viedma ripening[52–54] was employed.

1-Naphthaldehyde was reacted with HCN in toluene in the presence of catalytic amount of DBU, which promotes not only the racemization but also the HCN addition (Fig. 2). After several

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hours, the reaction mixture was cooled to induce precipitation, which also shift the reaction equilibrium toward formation of **1a**. The resulting suspension was then heated to dissolve approximately 80–90% of the solid **1a**, followed by gradual cooling to room temperature to allow regrowth of **1a**. This temperature-cycling process was repeated.[42] For example, after three cycles, (*S*)-**1a** was obtained as solid product in 34% yield with 96% ee by filtration. In another experiment, oppositely configured (*R*)-**1a** was obtained in 36% yield with 88% ee after two cycles. Additional **1a** with low ee is isolable from the filtrate, however, it has not included in the yield. Importantly, the isolated cyanohydrin was stable at ambient temperature, and no deterioration of its ee was observed during storage or workup.

The results of the spontaneous formation of enantioenriched cyanohydrin **1a** are summarized in the histogram shown in Fig. 2. Across 38 independent experiments, cyanohydrin (*R*)-**1a** was obtained 20 times, whereas (*S*)-**1a** was obtained 18 times. This stochastic formation of enantiomers fulfils one of the key requirements for spontaneous absolute asymmetric syntheses without the intervention of any chiral factors.[55] Thus, we achieved the spontaneous absolute asymmetric Strecker-type synthesis of a cyanohydrin coupled with HCN addition to an aldehyde and Viedma ripening by temperature cycling.

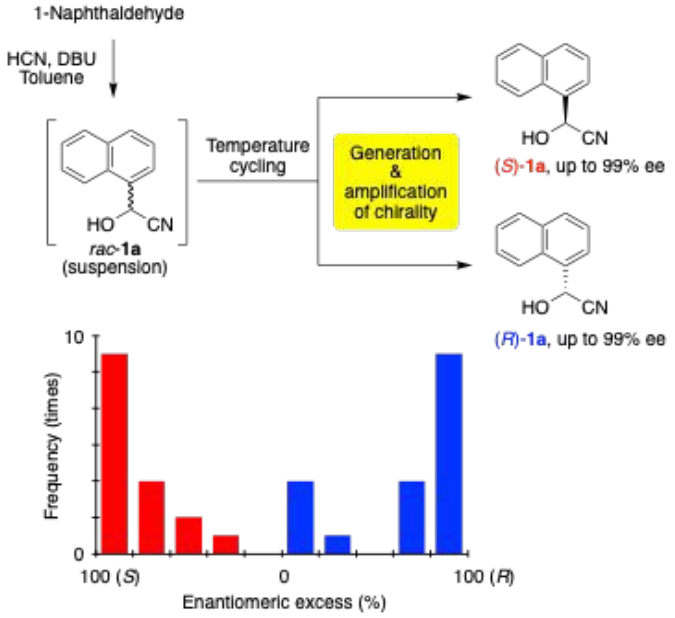

Fig. 2 Spontaneous formation of enantioenriched cyanohydrin **1a** in combination with temperature cycling *via* Viedma ripening.

The distribution of ee, along with the solid yield, is broad (see SI Table S2). This variability is attributed to the heterogeneous nature of the process, in which the efficiency of ee generation and amplification in the solid state depends on the fraction of crystals dissolved during heating. Because the enantiomeric imbalance is concentrated in the residual solid, its presence is essential for efficient deracemization.

The more the suspended solid dissolves, the higher the ee of the remaining solid, likely because approximately equal amounts of each enantiomorph of **1a** dissolve during heating.[42] Although it cannot be directly measured, the magnitude of the enantiomeric imbalance in the initial precipitation is also likely to influence the subsequent development of measurable ee. It should also be noted that the inherent instability of the cyanohydrin leads to low solid yields under elevated temperatures and repeated temperature cycling. Additionally, polymerization of HCN, which produces dark-coloured, highly polar compounds, further contributes to the decrease in solid yield.

The ee of **1a** during the process were monitored by sampling a portion of the suspension (Fig. 3a; see Table S3 in the SI for the numerical data). After the first cycle, a detectable 20% ee with the *R*-configuration was observed. After the second cycle, the ee amplified to 90% ee, and finally, (*R*)-**1a** with 99% ee was obtained as solid product. In another experiment, oppositely configured (*S*)-**1a** with 93% ee was isolated after five thermal cycles.

Next, cyanohydrin **1b** bearing a *p*-methoxyphenyl substituent was subjected to deracemization (Fig. 3b; see Table S3 in the SI for the numerical data). (*R*)-**1b**, pre-adjusted to 4% ee, was suspended in toluene in the presence of catalytic amount of DBU and subjected to temperature cycling. The ee was amplified from 29% to 59%, then 70%, and finally to 97% ee, affording (*R*)-**1b** in 43% yield. Starting from (*S*)-**1b** with 3% ee, (*S*)-**1b** with 96% ee was obtained in 43% yield after three thermal cycles. We also confirmed that **1c** with a *p*-bromophenyl substituent ($t_{1/2}$ = 18 s) underwent chiral amplification, with the ee increasing from 10% to 98% ee in 48% yield using the same technique.

Enantioselective reactive crystallization of **1b** was then demonstrated (Fig. 3c). Using a crystal seed of (*R*)-**1b**, portionwise addition of *p*-anisaldehyde, HCN, DBU and toluene afforded a large amount of highly enantioenriched solid (*R*)-**1b** with the same absolute configuration as the seed, without the need for temperature cycling (see the SI for the experimental procedure and the results using (*S*)-**1b** as the seed crystal). Thus, the amount of solid cyanohydrin with high ee can be auto-multiplied through the consecutive addition of achiral compounds.

Hydrolysis of cyanohydrin **1a** is shown in Fig. 3d. Treatment of (*S*)-**1a** with concentrated HCl afforded (*S*)-amide **3a** in 91% yield, whose structure was confirmed by X-ray single-crystal analysis (see SI for details (CCDC 2544005)). And the following hydrolysis of the isolated **3a** using H_2SO_4 furnished (*S*)-hydroxy acid **2a** in nearly enantiomerically pure form after recrystallization. A direct transformation from cyanohydrin **1a** to hydroxy acid **2a** resulted in a significant decrease in ee.

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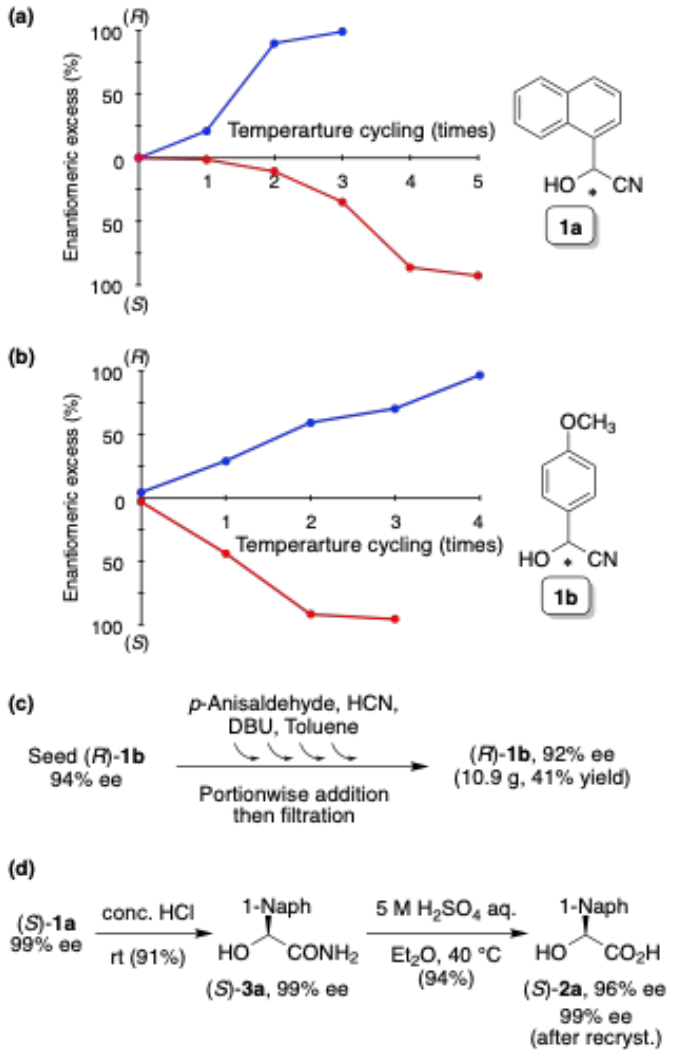


Fig. 3 (a) Generation and amplification of ee in suspended conglomerate **1a** and (b) in **1b**. (c) Enantioselective reactive crystallization of **1b**. (d) Hydrolysis of (*S*)-cyanohydrin **1a**, affording (*S*)-hydroxyamide **3a** and (*S*)-hydroxy acid **2a**.

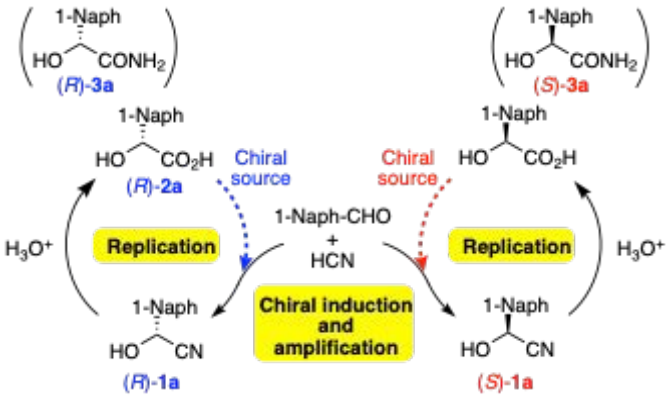
Next, we investigated the chiral amplification of cyanohydrin **1a** using a chiral additive capable of controlling the direction of amplification. In this study, we selected the α-hydroxy acid **2a** and the corresponding hydroxyamide **3a**, which are hydrolysis products of **1a**. If **2a**/**3a** induces an enantiomeric imbalance between suspended (*R*)- and (*S*)-**1a**, subsequent deracemization could enhance the ee to give **1a** with high enantiopurity. Therefore, the overall process would constitute replication of the hydroxy acid **2a** and hydroxyamide **3a**.

The stereochemical outcomes of temperature cycling using chiral sources **2a** and **3a** are summarized in Table 2. In the presence of catalytic amount of (*S*)-**2a**, 1-naphthaldehyde was allowed to react with HCN in toluene containing DBU. After the addition reaction, cyanohydrin **1a** precipitated, and the mixture was stirred overnight. During this incubation period, an amplifiable enantiomeric imbalance was induced in the suspended solid **1a**. Temperature cycling was then performed to promote the deracemization. Upon filtration, (*S*)-**1a** with 98% ee was obtained in 38% yield under the influence of (*S*)-**2a** (Table 2 entry 1). In contrast, (*R*)-**2a** induced the formation of (*R*)-**1a** with 98% ee in 36% yield after chiral amplification (entry 2). As shown in entries 3 and 4, the stereochemical relationships was reproducibly constant; therefore, upon hydrolysis of **1a**, hydroxy acid **2a** with the same absolute configuration as the initially used compound can be replicated in an enantioselective manner.

Moreover, hydroxyamide **3a** also efficiently acts as a chiral source that induces a chiral bias in the cyanohydrin **1a**. Deracemization was initiated using the corresponding (*S*)-**3a**, affording (*S*)-**1a** with 30% ee in 26% yield (entry 5). The temperature cycling was performed only three times; however, further cycling could enhance enantioenrichment, as discussed above. In contrast, in the presence of (*R*)-**3a**, (*R*)-**1a** was obtained with 99% ee in 26% yield (entry 6). The stereochemical relationship between the chiral source **3a** and product **1a** is consistent with that observed for hydroxy acid **2a** (entries 7 and 8).

It should be noted that hydroxy acid **2a** was introduced as its sodium carboxylate form, as neutralization of DBU inhibits its catalytic activity for the cyanide addition to the aldehyde. Increasing the amount of DBU to address this issue led to side reactions, resulting in a complex reaction mixture during thermal cycling. Despite the use of the sodium carboxylate, the initial reaction mixture remains homogeneous owing to the presence of excess HCN.

Table 2. Deracemization of **1a** by Viedma ripening in the presence of hydroxy acid **2a** and hydroxy amide **3a** with the corresponding molecular handedness.



Entry	Chiral source	Cyanohydrin **1a**		Temperature cycling/times
		% ee (Config)	Yield/%	
1	(*S*)-**2a**	98 (*S*)	38	6
2	(*R*)-**2a**	98 (*R*)	36	6
3	(*S*)-**2a**	72 (*S*)	18	12
4	(*R*)-**2a**	88 (*R*)	11	7
5	(*S*)-**3a**	30 (*S*)	26	3
6	(*R*)-**3a**	99 (*R*)	26	3
7	(*S*)-**3a**	98 (*S*)	5	3
8	(*R*)-**3a**	98 (*R*)	12	3

[a] Highly enantioenriched (98–99% ee) **2a** and **3a** were used as chiral sources. [b] Determined using HPLC on a chiral stationary phase.

This sequence appears to operate under the concept of "tailor made additives," as introduced by Lahav and co-

workers.[56–58] In this context, the structurally related additives—namely hydroxy acid **2a** and amide **3a**—selectively adsorb on the crystal surfaces of cyanohydrin **1a** and regulate the enantioselective crystal growth, thereby inducing a slight enantiomeric imbalance between the suspended enantiomorphs **1a**. Subsequent Viedma ripening by temperature cycling enhances the enantiopurity of crystalline **1a**.

The more efficient chiral induction observed with **3a** than with **2a** may arise from differences in their interactions with the crystal surface of **1a**, as reflected by the fewer temperature-cycling repetitions required to obtain enantioenriched **1a**. The neutral hydroxyamide **3a** may interact more favourably with the crystal surface, for example through hydrogen bonding, than the ionic sodium carboxylate of **2a**, thereby providing a more effective stereochemical bias during crystal growth. Further mechanistic studies will be required to clarify the origin of this difference.

Conclusions

We have demonstrated that cyanohydrins **1a–c** crystallize as conglomerates and undergo efficient asymmetric amplification *via* DBU-mediated partial dissolution and recrystallization, allowing the ee to increase from an undetectable level to near enantiopure state. In addition, enantioselective reactive crystallization enables the amount of enantioenriched cyanohydrin to be auto-multiplied on a larger scale. Furthermore, coupling Strecker-type cyanohydrin formation with this amplification in the presence of hydroxy acid **2a** or hydroxyamide **3a** establishes a self-replicating process. The chiral source dictates the product configuration, with (*S*)-hydroxy acid or hydroxyamide selectively yielding (*S*)-enriched cyanohydrin, and vice versa. Given that the cyanohydrin serves as a direct precursor to the corresponding hydroxy acid and can be converted, this system constitutes an effective chiral propagation cycle. These results demonstrate that hydroxy acid and corresponding hydroxyamide can propagate their own chirality through precursor formation and amplification, providing a new insight into the origin of homochirality.

Author contributions

The manuscript was written through contributions of all authors. Conceptualization: T. Kawasaki; Supervision: T. Kawasaki; Funding acquisition: T. Kawasaki; Investigation: S. Aiba, K. Niikura, Y. Tsunomori; Methodology: N. Takamatsu, S. Aiba, Y. D. Kim, S. Okumura; Formal analysis: T. Inoue, Y. Tanaka, M. Kato; Writing – original draft: S. Aiba, K. Niikura; Writing – review & editing: T. Kawasaki, K. Nemoto, Y. Tokunaga; Resources: Y. Tokunaga.

Conflicts of interest

There are no conflicts to declare.

Data availability

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The data supporting the findings of this study are available within the article and it's Supplementary Information.

All experimental procedures and characterization data, including NMR spectra, HRMS data, IR spectra, and HPLC analyses, are provided in the Supplementary Information (SI).

CCDC 2543998–2544005 contain the supplementary crystallographic data for this paper. The data supporting this article have Supplementary Information (SI): methods, experimental data and characterization of the compounds. See DOI: 10.1039/x0xx00000x

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The data supporting the findings of this study are available within the article and its Supplementary Information.

All experimental procedures and characterization data, including NMR spectra, HRMS data, IR spectra, and HPLC analyses, are provided in the Supplementary Information (SI).

Crystallographic data for the reported structures have been deposited with the Cambridge Crystallographic Data Centre (CCDC), and can be obtained free of charge via www.ccdc.cam.ac.uk (CCDC deposition numbers: 2543998–2544005). Further data that support the findings of this study are available from the corresponding author upon reasonable request.