ACES Asian Chemical Editorial Society

DOI: 10.1002/asia.201901324

CHEMISTRY AN ASIAN JOURNAL Communicatio

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Special Issue

Absolute Asymmetric Synthesis of an Aspartic Acid Derivative from Prochiral Maleic Acid and Pyridine under Achiral Conditions

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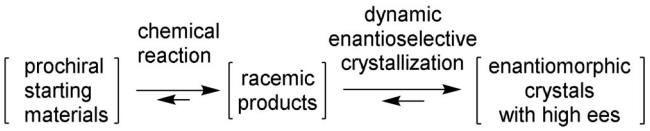
Abstract: The asymmetric synthesis of an aspartic acid derivative, *N*-succinopyridine, from prochiral starting materials involving dynamic enantioselective crystallization was accomplished without using any external chiral source. The aza-Michael addition reaction of prochiral maleic acid and pyridine afforded racemic conglomerate *N*-succinopyridine in water. Continuous stirring of the suspension of the reaction mixture with acetic acid promoted gradual deracemization to afford a crystal with an excellent optical purity of 99% in 71% yield.

Reactions in which optically active products are obtained from prochiral starting materials without using chiral sources, i.e., absolute asymmetric synthesis, have been linked to the homochirality of living matter and the origin of life, and are of interest in many research fields.[1] To date, absolute asymmetric synthesis has been limited to the application of physical chiral forces such as circularly polarized light[2] and chiral magnetic fields.[3] The Soai reaction[4] and asymmetric synthesis using the chirality of crystals generated by the crystallization of prochiral materials are also considered to be methods for absolute asymmetric synthesis.[5,6] Recently, an asymmetric synthetic methodology has been developed that combines the generation of a chiral center from prochiral materials with deracemization via dynamic crystallization (Scheme 1). Some valuable examples have been reported for the Mannich reaction,[7] aldol reaction,[8] desymmetrization from *meso* compounds via stereoisomerization,[9] aza-Michael addition reaction,[10] Strecker reaction,[11] photoisomerization followed by ring-closing and ring-opening reactions,[12] photodimerization reaction,[13] and Diels–Alder reaction.[14] All processes involved deracemization by dynamic crystallization and either a reverse reaction or a direct racemization of the generated chiral center of the product.[15]



Scheme 1. Asymmetric synthesis involving dynamic crystallization from prochiral starting materials under achiral conditions.

Here, we describe the asymmetric synthesis of amino acid derivatives using this methodology. The basic requirements are: (1) a racemic conglomerate crystal and (2) fast racemization under crystallization conditions. So far, most essential amino acids except asparagine[16] and glutamic acid[17] have either not given conglomerate crystals, or gave a conglomerate as one of multiple polymorphs.[18] It is not easy to control polymorphism in dynamic crystallization. We focused on one aspartic acid derivative, *N*-succinopyridine, synthesized by Michael addition of pyridine to maleic acid, crystallized as a conglomerate in a chiral space group of $P2_12_12_1$.[19] Therefore, we investigated the asymmetric synthesis of *N*-succcinopyridine from prochiral starting materials and the conditions for its deracemization. *N*-Succinopyridine can be converted to aspartic acid,[20] and is also a useful second-order nonlinear optical material.[21]

N-Succinopyridine **2** was effectively obtained by aza-Michael addition of maleic acid **1** and pyridine in a water solution (Scheme 2). The aza-Michael addition is a well-established reversible reaction, and it has been suggested that racemization may possibly occur through the reverse reaction.[10] It is also plausible that racemization is promoted through the enol form or enolate anion, because the acidity of the α-position of the protonated amino acid is relatively high, and it is easily deprotonated under acidic and basic conditions. Therefore, this reaction system is suitable for dynamic crystallization using a conglomerate crystal.

A single crystal obtained from a water/methanol solution by the vapor diffusion method was used for the XRD and high-performance liquid chromatography (HPLC) analysis. The perspective view in Figure S1(a) shows that the space group is $P2_12_12_1$, which is the same as that previously reported.[19] The packing diagram indicates that the carboxylic acid close to the pyridinium ion has a deprotonated structure. Carboxylic acid and carboxylate ions form intermolecular hydrogen bonds(OH–O, 1.695 Å) along the b-axis to produce a column as seen in Figure S1(b).

The space group was chiral $P2_12_12_1$ which indicated that the crystal was a conglomerate. However, the crystal data also indi-

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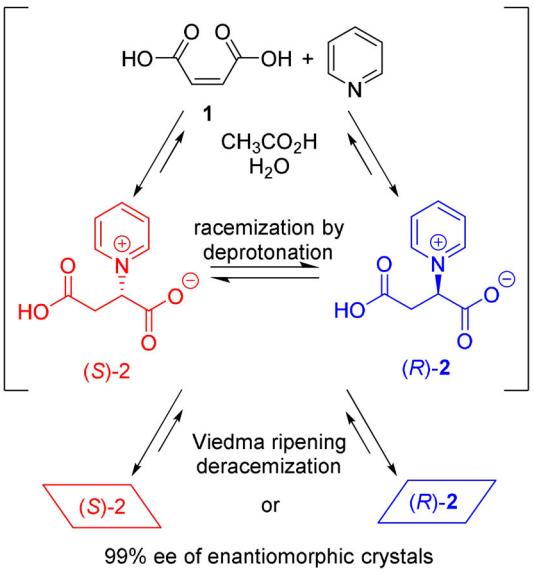
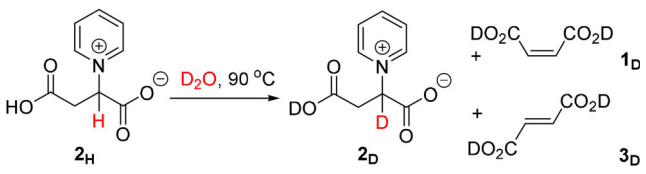


Scheme 2. Aza-Michael addition of pyridine to maleic acid followed by deracemization via dynamic crystallization.

cated that the crystal was twinned and the HPLC analysis of the single crystal showed that it was composed of a 73:27 mixture of enantiomers (Figure S2).

Next, we analyzed the crystal structure by powder XRD to elucidate the possibility of polymorphic crystal systems. The powdered crystalline **2** was produced by two methods. The first was crystallization by slow evaporation of water at 90 °C. The other solid sample was produced by the suspension of crystalline succinopyridine in water at 90 °C for seven days. Powder XRD analysis of both crystals showed the same spectra as the pattern simulated by single-crystal XRD analysis. These results suggest that *N*-succinopyridine is not polymorphic under these conditions (Figure S3).

Targeted deracemization requires fast racemization under the crystallization conditions. We examined the rate of racemization of succinopyridine in solution. There are two possible pathways for racemization: deprotonation at the chiral center of the α-position of the carbonyl group, or a reversible reaction (Scheme 2). To analyze the racemization pathway, a deuterium labeling experiment was carried out (Scheme 3). Succinopyridine ($\mathbf{2_H}$) was dissolved in D_2O and the time course of the change in the deuterated ratio at 90 °C was monitored by nuclear magnetic resonance (NMR) spectroscopy (Figure 1). After 90 min, around half of the starting succinopyridine ($\mathbf{2_H}$) was deuterated at the chiral center. Very small amounts of maleic acid $\mathbf{1_D}$ and fumaric acid $\mathbf{3_D}$ formed by the reverse reaction



Scheme 3. Investigation of racemization pathways by the deuterium labelling reaction in D_2O.

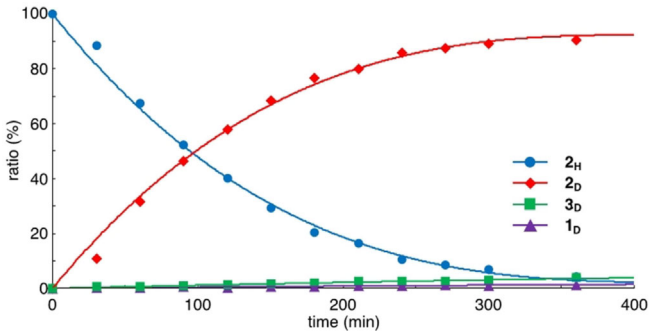


Figure 1. Time course for the deuterium labelling experiment of suc-cinopyridine in D_2O at 90 °C.

pathway were observed. Even after almost all the starting succinopyridine ($\mathbf{2_H}$) was consumed, less than 6% of the reverse reaction products were formed. This indicates that racemization occurred by a deprotonation mechanism as the major pathway. Although succinopyridine has two types of α-protons, only the chiral carbon was deuterated, because there was very little exchange of methylene protons with deuterium. These results closely correlate with the racemization mechanism that was involved in the deprotonation process.

Next, we explored the conditions under which faster racemization is promoted. Racemization of enantiopure succinopyridine in water or mixed solvent in the presence of various acids was studied (Figure 2). In water without an additive, the half-

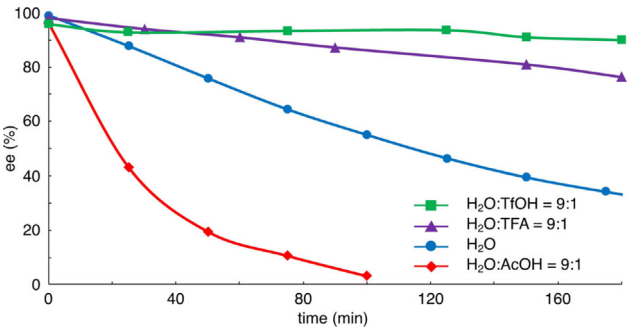


Figure 2. Time course for racemization of optically active succinopyridine at 90 °C in H_2O in the presence of acetic acid, trifluoroacetic acid, or trifluoromethanesulfonic acid.

life for racemization at 90 °C was 115 min. An investigation of different acids revealed that acetic acid was the most suitable catalyst for racemization. The half-life for racemization was reduced to 20 min in 10% (v/v) aqueous acetic acid at 90 °C. On the other hand, the strong acids TFA (trifluoroacetic acid) and TfOH (trifluoromethanesulfonic acid) reduced the racemization rate, and the half-life using 10% (v/v) water was 501 min and 1400 min, respectively. Using a base such as aqueous sodium hydroxide or 1,8-diazabicycloundec-7-ene (DBU), decomposition of succinopyridine occurred along with racemization.

These results strongly suggested the possibility of applying dynamic enantioselective crystallization to these systems as shown in Scheme 2. We could easily obtain a few millimeter

square crystals by the usual recrystallization method from hot water; however, the *ee* value was quite low since it was a twinned crystal. In contrast, the *ee* values for small single crystals were high. By regulating the crystal size to be relatively small, the possibility of convergence to a crystal with high optical purity is expected.

We examined the asymmetric synthesis of **2** involving attrition-enhanced deracemization (Viedma ripening).[22,23] When an aqueous solution of maleic acid (0.595 g, 5.12 mmol) and pyridine (0.405 g, 5.12 mmol) was stirred at 90 °C for 1 h, **2** precipitated by the aza-Michael addition reaction. Subsequently, acetic acid and glass beads (0.5 g) were added, and the solution was kept in suspension with stirring at the same temperature for several days. The change in the *ee* value for **2** for both the crystalline phase and the mother liquor was analyzed by HPLC using CHIRALPAK ZWIX(+) (Figure 3).

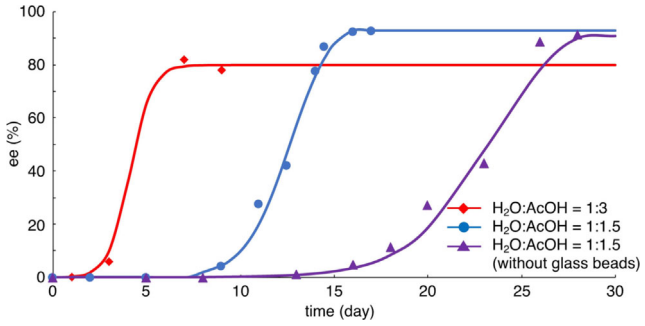


Figure 3. Asymmetric synthesis of **2** from prochiral maleic acid and pyridine involving attrition-enhanced deracemization in aqueous acetic acid at 90 °C.

Using a mixed solvent of water and acetic acid in a ratio of 1:3 by volume (water 0.25 mL: acetic acid 0.75 mL), deracemization began after 3 days and the *ee* value increased to 80% *ee* after 6 days (Figure 3, red line). The analyzed sample included both crystalline and dissolved compound in the mother liquor. On the other hand, the filtered solid of **2** was obtained in 22% chemical yield with 99% *ee*.

To increase the chemical yield and the *ee* value, the ratio of acetic acid was reduced, because acetic acid is the good dissolving solvent. Following the addition reaction in water, the ratio was adjusted to 1:1.5 water (0.4 mL) and acetic acid (0.6 mL), whereupon the deracemization rate became a little slower. The *ee* value started to increase at the ninth day and reached 93% after 16 days (Figure 3, blue line). In this case, the yield of the solid product after filtration was improved to 47% yield with 99% *ee*.

A control experiment was carried out to confirm the effect of the glass beads. Under the same conditions as the blue line using the solvent (water:acetic acid = 1:1.5), asymmetric synthesis followed by deracemization was examined without glass beads. The rate of deracemization became slower and 28 days were required to reach 91% *ee*. The solid succinopyridine after filtration was obtained in 51% yield with 99% *ee* (Figure 3, purple line).

Asymmetric synthesis of the aspartic acid derivative with very high optical purity was performed; however, the chemical yield still needed improvement. Finally, ethanol (1.0 mL) was added as a poor solvent to promote precipitation during deracemization, and the continuous suspension gave 99% *ee* for the solid in 71% chemical yield after filtration.

The experiment was repeated several times, and it was confirmed that the probability of tilting to either enantiomer was about 1:1 and that the directionality of the asymmetric amplification could be controlled by adding a small amount of enantiomorphic crystals during attrition-enhanced deracemization.

In conclusion, we developed the first example of asymmetric synthesis of an aspartic acid derivative from prochiral starting materials involving dynamic enantioselective crystallization with excellent optical purity of 99% *ee* without using any external chiral source. This reaction system is an absolute asymmetric synthesis and will be of interest to many researchers because the reaction is strongly linked to homochirality on Earth. Furthermore, this reaction process involving a chemical reaction generating a chiral center followed by deracemization via dynamic crystallization is simple and applicable to industrialization.

Experimental Section

General: NMR spectra were recorded in D_2O solutions on a BRUKER 300 operating at 300 and 75 MHz, respectively, for ^{1}H- and ^{13}C-NMR spectroscopy. Chemical shifts are reported in parts per million (ppm). IR spectra were recorded on a JASCO FT/IR-230 spectrometer. HPLC analyses were performed on a JASCO HPLC system (JASCO PU-1580 pump, DG-1580-53, LG-2080-02, MD-2015, and CD-2095 detector). X-ray single crystallographic analysis was conducted using a SMART APEX II ULTRA (Bruker AXS). Powder XRD analysis was conducted using a D8 ADVANCE (Bruker AXS).

Asymmetric synthesis of *N*-succinopyridine via attrition-enhanced deracemization: A solution of maleic acid (**1**) (595 mg, 5.12 mmol) and 1.0 equiv. of pyridine (405 mg, 5.12 mmol) in H_2O (0.25 or 0.40 mL) was stirred using an oval magnetic stirring bar with or without glass beads (∅2.0 mm, 500 mg) in a sealed tube at 90 °C. After crystalline **2** appeared, acetic acid (0.75 or 0.60 mL) was added. The solution was kept in suspension with stirring at the same temperature for several days.

The *ee* value of **2** was monitored by HPLC using a chiral column, CHIRALPAK ZWIX(+) (Daicel Ind.): eluent: MeOH/MeCN/H_2O/formic acid/diethyl amine = 490/490/20/1.9/2.6 (v/v/v/v/v).

Enantioselectivity of asymmetric reaction: Ten experiments were performed at optimized conditions (H_2O : AcOH = 1:1.5, with glass beads) in order to examine the probability of tilting to either enantiomer. As the result, 6 times (−)-**2** and 4 times (+)-**2** were obtained.

Control of chirality by seeding: We also attempted to control chirality of dynamic crystallization by adding seed crystals. Maleic acid (0.595 g), pyridine (0.405 g) and water (0.4 mL) were added to a sealed tube, and the aqueous solution was stirred at 90 °C. After crystalline *N*-succinopyridine **2** was appeared, acetic acid (0.6 mL), glass beads (∅2.0 mm, 500 mg), and powdered seed crystal of (−)-form (ca. < 5 mg) were added. Next day, the *ee* value of suspended solution increased to 14% *ee* (−) form, and *ee* value reached 89% *ee* (−) form after 4 days.

Single-crystal X-ray structure analysis of *N*-succinopyridine 2 : Colourless prism (0.20 × 0.10 × 0.10 mm^3), orthorhombic space group $P2_12_12_1$, a = 7.7020(2) Å, b = 7.7485(2) Å, c = 14.8933(5) Å, V =

888.82(4) Å^3, $Z=4$, $\lambda(Cu_{K\alpha})=1.54178$ Å, $\rho=1.459$ g cm^{-3}, $\mu(Cu_{K\alpha})=0.775$ cm, 5465 reflections measured ($T=173$ K, $5.7100^\circ<\theta<68.3124^\circ$), nb of independent data collected: 1621, nb of independent data used for refinement: 1615 in the final least-squares refinement cycles on F^2, the model converged at $R_1=0.0266$, $wR_2=0.0710$ [$I>2\sigma(I)$], $R_1=0.0265$, $wR_2=0.0710$ (all data), and GOF = 1.070, H-atom parameters constrained. CCDC 1952557 contains the supplementary crystallographic data for this paper. CCDC 1952557 contains the supplementary crystallographic data for this paper. These data are provided free of charge by The Cambridge Crystallographic Data Centre.

Acknowledgements

This work was supported by Grants-in-Aid for Scientific Research (Nos. 19H02708, 17K19114, and 16H04144) from the Ministry of Education, Culture, Sports, Science, and Technology (MEXT) of the Japanese Government. Mr. Uemura acknowledges financial support from Frontier Science Program of Graduate School of Science and Engineering, Chiba University.

Conflict of interest

The authors declare no conflict of interest.

Keywords: amino acids · asymmetric synthesis · attrition-enhanced deracemization · conglomerate · Michael addition

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Manuscript received: September 19, 2019
Revised manuscript received: October 9, 2019
Accepted manuscript online: October 9, 2019
Version of record online: ■■ ▮▮, 0000

COMMUNICATION

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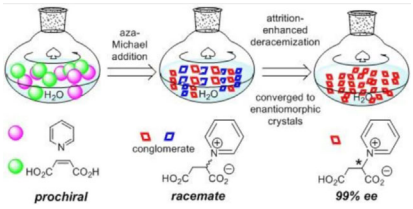

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