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Article

Asymmetric Anisoin Synthesis Involving Benzoin Condensation Followed by Deracemization

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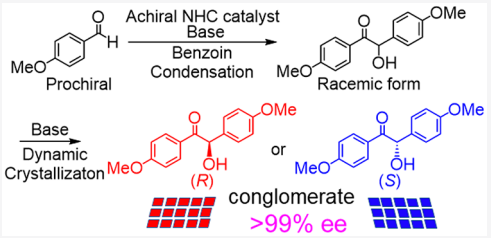
ABSTRACT: The highly enantioselective synthesis of *p*-anisoin was achieved via the benzoin condensation of a prochiral *p*-anisaldehyde using achiral NHC catalysts such as vitamin B1. In this reaction, *p*-anisoin crystallized as a conglomerate, and the deracemization of racemic *p*-anisoin under basic conditions was efficiently performed by Viedma ripening. Although the handedness of the enantioselective crystallization could not be controlled by spontaneous crystallization, it could be controlled by the coexistence of a catalytic amount of optically active valine. It was clarified that this is due to the asymmetric transformation of *p*-anisoin with enantiomeric valine in the mother liquor.



INTRODUCTION

Research on providing optically active materials with high enantioselectivities without the use of an external asymmetric source is related to the expression of the homochirality of biomolecules.[1−3] It is of interest in many academic fields. The crystallization-induced dynamic optical resolution method (CIDR), which utilizes the chirality of crystals, is an excellent optical resolution method capable of generating a one-handed enantiomer from a racemic mixture with a high optical purity and simple filtration.[4,5] Furthermore, a reaction that gives a conglomerate-forming product in one pot from a prochiral starting material combined with deracemization enables asymmetric synthesis without the use of an external asymmetric source (Figure 1).[6−8] In this method, a racemic mixture is generated in the reaction system, and one-handed enantiomer crystals are preferentially crystallized with racemization. When one enantiomer crystallizes, the opposite isomers are present in excess in the mother liquor. However, since racemization proceeds sufficiently fast, the racemic balance can always be maintained. Finally, the racemic mixture converges into one-handed enantiomeric crystals. This asymmetric amplification method includes gradually growing crystals from a supersaturated solution (crystallization-induced enantiomer transformation)[9−11] or attrition-enhanced deracemization (Viedma ripening), which is performed by suspending and stirring the crystals with glass beads in a small amount of solvent.[12] In either method, the products must crystallize as a conglomerate, and rapid racemization must proceed under the conditions of crystal growth. It has been reported that the racemization of the products can be carried out directly via an achiral intermediate, such as an enolate anion,[13−15] using a reversible reaction such as the Michael addition reaction[16−18] or the Diels−Alder reaction.[19,20] Various new reaction systems are actively under development.[21−23]

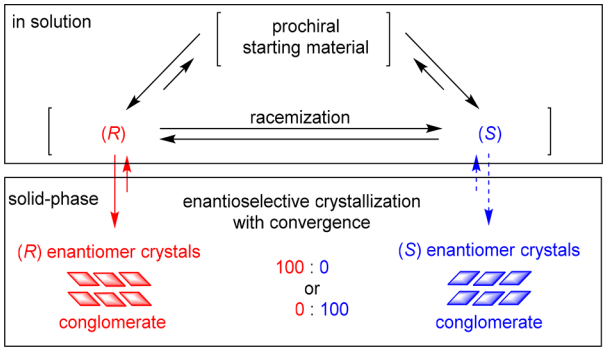


Figure 1. Asymmetric synthesis from prochiral starting materials via deracemization involving the dynamic enantioselective crystallization of conglomerates.

We aimed to develop a new asymmetric reaction system that fuses the benzoin condensation reaction, which uses *N*-heterocyclic carbene (NHC) catalysts such as vitamin B1, with deracemization via dynamic crystallization. The benzoin condensation reaction is one of the fundamental reactions of organic chemistry. It is a dimerization reaction that occurs by the umpolung reaction of aromatic aldehydes catalyzed by

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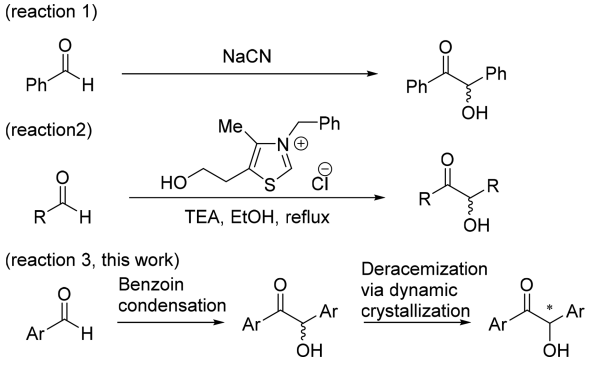
cyanide ions (Scheme 1, reaction 1).[24,25] The reaction has been developed for various substrates using NHC catalysts

Scheme 1. Historical Benzoin Condensation and Our Proposal for the Asymmetric Synthesis of Benzoin Derivatives



modeled on vitamin B1 (Scheme 1, reaction 2).[26−29] We expected that benzoin derivatives could be asymmetrically synthesized from prochiral aromatic aldehydes via deracemization by dynamic crystallization because the substrates have an enolizable acidic proton at the chiral center (Scheme 1, reaction 3).

The benzoin or acyloin structure exists widely in natural products and pharmaceuticals and is one of the most critical groups used as synthetic intermediates; thus, many asymmetric catalytic reactions have been developed for its synthesis.[28,29] We studied a method of providing optically active benzoins using only crystal chirality as a chirality source. To employ deracemization with dynamic crystallization, benzoin derivatives must crystallize as conglomerates. A search of the CCDC database revealed that the crystal structure of *p*-anisoin **1** had been analyzed 35 years ago, and its crystal space group was $P2_12_12_1$.[30] In this study, we reanalyzed the crystal structure of *p*-anisoin **1** and then investigated deracemization by dynamic crystallization from racemic *p*-anisoin **1**, its one-pot asymmetric synthesis from prochiral *p*-anisaldehyde, and the addition of chiral amino acids to control the handedness for enantiomeric crystallization.

RESULTS AND DISCUSSION

The single-crystal X-ray structure analysis of *p*-anisoin **1** was re-examined to confirm the absence of polymorphism. Indeed, the crystals obtained by recrystallization from either EtOH or a mixture of $CHCl_3$/hexane exhibited the same crystal structure, and polymorphism was not observed.[31] The crystal space group is $P2_12_12_1$, and the crystal parameters are almost the same as those from the previously reported data. It was thus expected that the conglomerate could be used for dynamic crystallization.

Since the hydroxyl group has an intramolecular hydrogen bond with the carbonyl group's oxygen atom (distance for OH—O=C of 2.168 Å), the twist angle of O1−C1−C2-O2 is small, 16.26°. The molecule also has an intermolecular hydrogen bond with the MeO group of the neighboring molecule (distance for OH−OMe of 2.304 Å), which forms a C_2 spiral along the *a*-axis (Figure 2).

Next, we investigated the rate of racemization, which is vital for obtaining high enantiomeric crystals via dynamic crystallization. Since the molecule has an acidic proton at the

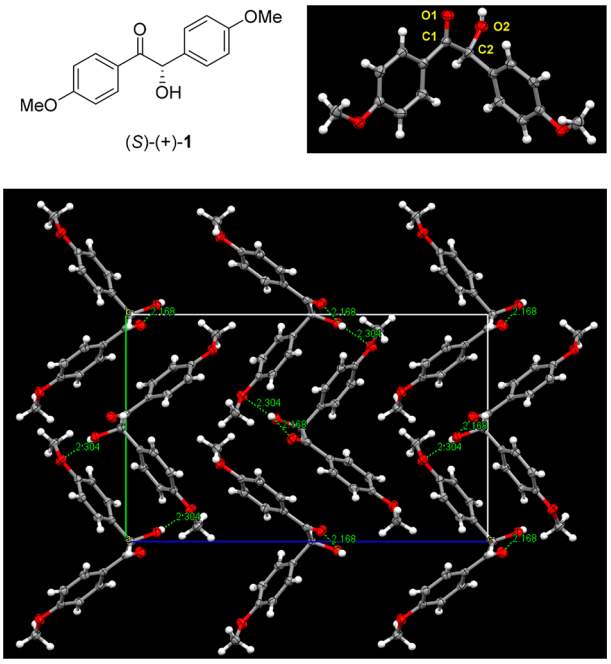


Figure 2. Perspective view and packing diagram along the *a*-axis of *p*-anisoin **1**.

α-position of the carbonyl group, sufficiently fast racemization can be expected under basic crystallization conditions.

The stability of the asymmetric center is also crucial for isolation. **1** hardly racemizes at room temperature regardless of the solvent, but racemization occurs slowly when it is heated to 60 °C in ethanol, with a half-life of 54.7 h ($\Delta G^{\ddagger}$ = 28 kcal mol^{-1}) (Table 1, entry 4). The asymmetric center is fairly stable under neutral conditions; however, in the presence of a catalytic amount of base, racemization via the enolate anion proceeds at a considerable rate even at room temperature (Scheme 2). When the racemization rate was measured in various solvents and bases, the use of NaOH in ethanol was found to be the most suitable. A sufficient racemization rate was also shown with DBU (Table 1 and Figure 3).

Based on these results, the dynamic optical resolution from racemic **1** was examined. We used EtOH as the solvent and conducted experiments using three types of bases. To a sealed glass tube (ø20 mm) were added **1** (272 mg, 1.0 mmol), EtOH (0.5 mL), base (0.10 mmol), and glass beads (ø2 mm, 20 pieces), and the mixture was suspended with stirring at 600 rpm using a cross-shaped stirring bar (15 mm) at 60 °C. Crystals obtained by filtration at regular intervals were subjected to HPLC (CHIRALPAK OD-H) to determine the enantiomeric purity. Asymmetric amplification was observed from the second day onward, and a sigmoid curve was drawn that eventually converged to 94−99% ee crystals (Figure 4a). Finally, crystals were recovered by filtration in 90−91% yields using any of the bases (Table 2). The rate of asymmetric amplification appears to be related to the racemization speed, reaching the boundary fastest in seven days with NaOH but even converging in 10 days with K_2CO_3. It was also suggested that deracemization progressed via first-order kinetics in the initial stage regardless of the nature of the base, as shown in Figure 4b. Thus, we discovered one of the ideal environmentally friendly asymmetric amplification systems.

This deracemization of **1** could be applied to a gram-scale experiment. When *p*-anisoin **1** (2.2 g, 8.0 mmol) in EtOH (2.0

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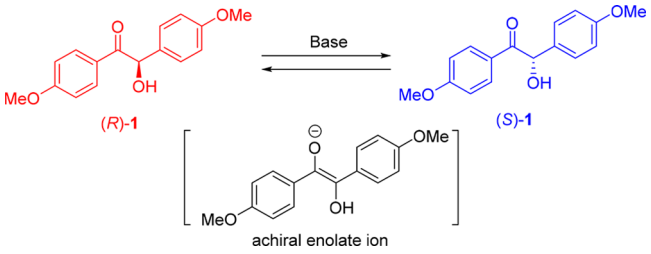
Table 1. Thermodynamic Parameters for the Rate of Racemization of 1[a]

entry	solvent	base	temperature (°C)	$\tau_{1/2}$ (min)	k_{rac} (s^{-1})	$\Delta G^{\ddagger}$ (kcal mol^{-1})
1	toluene	DBU	25	39.4	1.5×10^{-4}	22.7
2	MeCN	DBU	25	20.5	2.8×10^{-4}	22.3
3	EtOH	DBU	25	14.7	3.9×10^{-4}	22.1
4	EtOH	none	60	3.28×10^{3}	1.7×10^{-6}	28.3
5	EtOH	K_2CO_3	25	33	1.7×10^{-4}	22.6
6	EtOH	NaOH	25	9.9	5.8×10^{-4}	21.7

[a]The rate of racemization was measured under conditions of 1.0×10^{-2} mol L^{-1} **1** in a solvent with base (10 mol %).

Scheme 2. Racemization Mechanism for 1 via an Enolate Ion



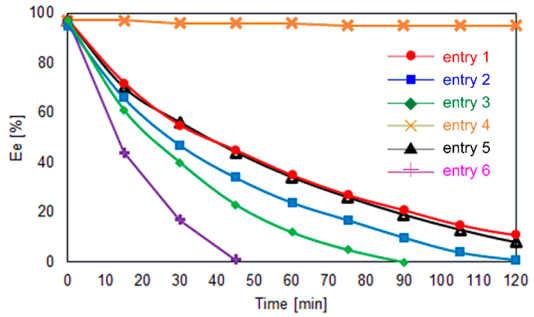


Figure 3. Racemization of **1** under various conditions. Entry numbers correspond to those in Table 1.

mL) was suspended with stirring at 600 rpm at 60 °C in a sealed glass tube in the presence of DBU (122 mg, 0.8 mmol) and glass beads, crystals were recovered by filtration in a 90% yield with a 99% ee.

In all experiments, which of the two enantiomers is predominantly amplified is random, and it is not possible to selectively obtain one enantiomer. Additional deracemizations of **1** confirmed that the enantioselectivity in these deracemizations was random (Figure S1). However, handedness could be controlled by starting the Viedma ripening from a low ee (5% ee) using NaOH or DBU as a base. Deracemization was immediately initiated, and the crystals with the same handedness as the slightly excess stereoisomer were efficiently obtained after four days.

Next, we examined the asymmetric synthesis of **1** by continuously performing benzoin condensation from prochiral *p*-anisaldehyde and chiral amplification by dynamic crystallization in one pot. **C1**, **C2**, and **C3**, all achiral NHC catalysts, were used as catalysts for benzoin condensation (Scheme 3). **C1** is vitamin B_1, a vital substance *in vivo*, and is commercially available.[26−29] The commercially available thiazolium salt **C2** and the imidazolium salt **C3**, which are commonly used as catalysts for the benzoin condensation reaction, were also examined.[32,33]

To a sealed glass tube were added *p*-anisaldehyde (272 mg, 2.0 mmol), EtOH (0.5 mL), **C1** (60 mg, 0.2 mmol), an

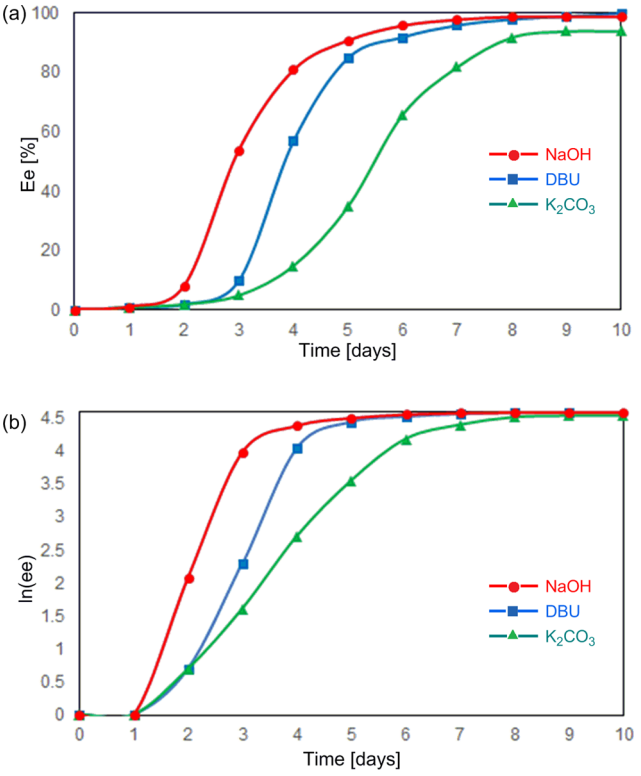


Figure 4. Time course of the deracemization of racemic **1** with Viedma ripening using various bases at 60 °C shown as (a) ee (%) vs time (days) and (b) ln(ee) vs time (days).

Table 2. Deracemization of 1 by Viedma Ripening[a]

entry	solvent	base	recovery (%)[b]	ee (%)[c]
1	EtOH	NaOH	90	99
2	EtOH	DBU	91	99
3	EtOH	K_2CO_3	91	94

[a]All experiments were performed in the presence of crystals of **1** (273 mg, 1.0 mmol), 0.5 mL of solvent, and a catalytic amount of base (10 mol %) at 60 °C. [b]Crystals were recovered by filtration. [c]One of the two enantiomers predominantly amplified was random.

aqueous sodium hydroxide solution (0.5 ml, 0.6 M), and glass beads, and the mixture was stirred at room temperature for 24 h. A small amount of water was needed for its dissolution of vitamin B1. After the condensation reaction was complete, the solvent was evaporated under reduced pressure to remove the water. To the crude racemic *p*-anisoin was added EtOH (0.5 mL), which was suspended with stirring at 600 rpm using a cross-shaped stirring bar (15 mm) at 60 °C. A small amount of the crystals obtained by filtration was subjected to HPLC analysis every day to determine the enantiomeric purity. Finally, crystals were filtered and washed with a small amount

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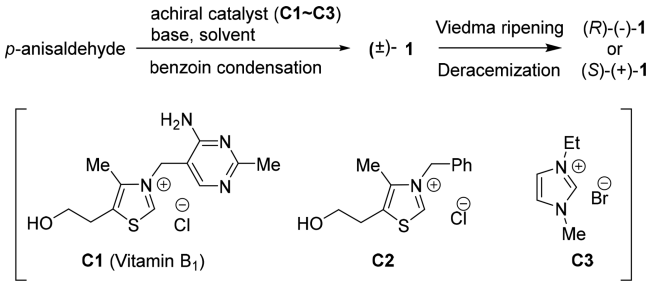
Scheme 3. One-Pot Asymmetric Synthesis of 1 By Combining Benzoin Condensation Using Achiral NHC Catalysts with Dynamic Crystallization



of cold ethanol to give a 70% yield of *p*-anisoin with a 93% ee (Table 3, entry 3, and Figure 5). When using DBU instead of NaOH, the chemical yield of **1** was low, and solids were not obtained for suspension (Table 3, entry 2).

Table 3. Asymmetric Synthesis of *p*-Anisoin from *p*-Anisaldehyde Involving Benzoin Condensation and Viedma Ripening[a]

entry	catalyst	solvent	base	yield (%)[b]	ee (%)[c]
1[d]	**C1**	EtOH/H_2O	NaOH	70	93
2	**C1**	EtOH/H_2O	DBU	n.a.[e]	
3	**C2**	EtOH	NaOH	75	99
4	**C2**	EtOH	DBU	50	94
5	**C3**	EtOH	NaOH	88	99
6	**C3**	EtOH	DBU	n.a.[e]	

[a]All experiments were performed in the presence of *p*-anisaldehyde (2.0 mmol), 0.5 mL of solvent, catalyst (10 mol %), and base (15 mol %). The solution was suspended with stirring. [b]Yield of crystallized **1** obtained by filtration. [c]One of the two enantiomers predominantly amplified was random. [d]After the reaction at rt for 24 h, the solvent was removed under reduced pressure. Next, EtOH (0.5 mL) was added and suspended with stirring at 60 °C. [e]Crystalline **1** was not obtained.

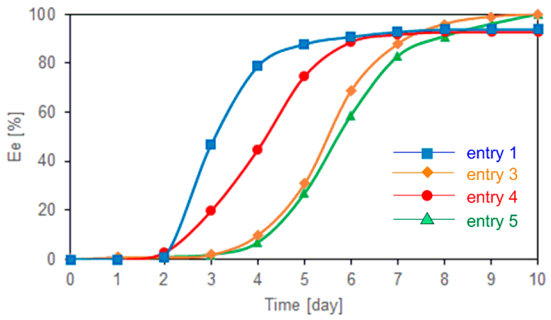


Figure 5. Time course of the asymmetric synthesis of **1** involving deracemization by Viedma ripening. Entry numbers correspond to those in Table 3.

In the case of the reaction using catalyst **C2**, we could use EtOH as a solvent without water, and it was possible to carry out the reaction and the asymmetric amplification at the same time. In a sealed glass tube, *p*-anisaldehyde (272 mg, 2.0 mmol), EtOH (0.5 mL), **C2** (0.2 mmol), powdered NaOH (12 mg, 3.0 mmol), and glass beads were reacted At 60 °C. Crystals of **1** immediately precipitated and were suspended with stirring at the same temperature. The changing ee value of the crystals was analyzed using the above method, and **1** was finally obtained by filtration in a 75% yield with a 99% ee (Table 3, entry 3, and Figure 5). In the reaction using **C2** and DBU, crystals were filtered and washed with a small amount of cold ethanol to give a 50% yield of **1** with a 94% ee (Table 3, entry 4, and Figure 5).

In the reaction using catalyst **C3**, it was also possible to carry out the reaction simultaneously with the asymmetric amplification. The use of NaOH as a base gave an 88% yield of **1** in a 99% ee (Table 3, entry 5, and Figure 5). When using DBU as a base, we could not obtain the crystalline **1** (Table 3, entry 6).

As described above, the formation of racemic **1** by the benzoin condensation of prochiral *p*-anisaldehyde was followed by deracemization via Viedma ripening. It is plausible that racemization is promoted through the enolate ion such as in the case of the deracemization of anisoin shown in Table 2. On the other hand, benzoin condensation is a well-established reversible reaction, and it has also been suggested that racemization possibly occurs through the reverse reaction. Therefore, this reaction system is suitable for dynamic crystallization using a conglomerate crystal.

It was possible to isolate a 99% ee of **1** by simple filtration from the reaction mixture without using an external asymmetric source. These crystals could be easily purified into 100% ee by a recrystallization from chloroform/hexane. It was possible to isolate 100% ee *p*-anisoin from prochiral *p*-anisaldehyde simply by filtering the crystals twice.

Next, the control of the handedness of the chirality was examined. In dynamic optical resolution by spontaneous crystallization, it was impossible to predict which enantiomer crystal would converge (Figure S1). In this case, it was possible to control the handedness by starting from slightly enriched crystals or adding enantiomer crystals as a seed; however, we examined another approach to control the handedness of the deracemization using optically active amino acids.

A catalytic amount of L- or D-valine crystals was added during the Viedma ripening of racemic **1**. In a sealed glass tube, **1** (272 mg, 1.0 mmol), EtOH (0.5 mL), DBU (15 mg, 0.10 mmol), glass beads, and L- or D-valine (12 mg, 0.1 mmol) were suspended with stirring at 600 rpm using a cross-shaped stirring bar at 60 °C. Deracemization began immediately and reached an enantiomeric excess of 99% in just five days (Table 4, entries 1 and 2, and Figure S2). The configuration of the obtained **1** matched that of the added valine. When L-valine was used, (*R*)-**1** was obtained, while the addition of D-valine caused the handedness of the deracemization to converge to (*S*)-**1**. The experiments were repeated five times each.

The same asymmetric control was observed when valine coexisted in the benzoin condensation from *p*-anisaldehyde. Deracemization proceeded efficiently and faster than that without valine. (*R*)-Anisoin **1** was obtained in 68−70% yield with a >99% ee by adding L-valine (Table 4, entry 3), while the reaction in the presence of D-valine gave (*S*)-**1** in all five experiments (Table 4, entry 4).

To clarify this phenomenon, we first investigated the crystal growth of **1** in the presence of optically active valine. However, a clear difference was not observed in the growth rate between (*R*)-**1** and (*S*)-**1** in the presence of L-valine, and both enantiomer crystals were grown.[34] Additionally, to investigate the possibility of forming mixed crystals with optically active valine, the crystals obtained from recrystallization in the presence of valine were analyzed by NMR spectroscopy. It was found that valine was not included in the crystals of **1**.[35]

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Table 4. Control of the Handedness of the Deracemization of 1 in the presence of L- or D-Valine

entry	material	additive	time (days)	configuration of **1**	ee of **1**
1[a]	(±)-**1**	L-valine	5	*R*[b]	>99%
2[a]	(±)-**1**	D-valine	5	*S*[b]	>99%
3[c]	*p*-anisaldehyde	L-valine	6	*R*[d]	>99%
4[c]	*p*-anisaldehyde	D-valine	6	*S*[d]	>99%

[a]In a sealed glass tube (⌀20 mm), **1** (272 mg, 1.0 mmol), EtOH (0.5 mL), DBU (15 mg, 0.10 mmol), glass beads (⌀2 mm, 20 pieces), and L- or D-valine (12 mg, 0.1 mmol) were suspended with stirring at 600 rpm using a cross-shaped stirring bar at 60 °C. [b]Crystals were recovered in 89−91% yields in all five experiments. [c]In a sealed glass tube, *p*-anisaldehyde (272 mg, 2.0 mmol), EtOH (0.5 mL), **C1** (60 mg, 0.2 mmol), a sodium hydroxide aqueous solution (0.5 mL, 0.6 M), and glass beads were combined, and the mixture was stirred at room temperature for 24 h. After the solvent was evaporated under reduced pressure, EtOH (0.5 mL) was added and suspended with stirring at 600 rpm at 60 °C. [d]Crystals were recovered in 68−70% yields in all five experiments.

Next, we studied the asymmetric transformation of **1** with chiral valine.[36−38] When racemic **1** and L-valine (0.1 equiv) were dissolved in ethanol with DBU (0.5 equiv) and left to stand at rt for 24 h, it was observed that the racemic equilibrium moved to the enrichment of (*R*)-**1** in a 5% ee. Similarly, the addition of D-valine under the same conditions led to an asymmetric transformation to (*S*)-**1** in a 5% ee. These results indicate that chiral valine resulted in an asymmetric equilibration in the basic solution of racemic anisoin. This bias caused the dynamic crystallization to converge on the excess enantiomeric crystals.

CONCLUSION

Efficient deracemization from racemic *p*-anisoin was achieved by Viedma ripening in 99% ee. The asymmetric synthesis from prochiral *p*-anisaldehyde in one pot by benzoin condensation using an NHC catalyst, such as vitamin B1, followed by deracemization via Viedma ripening afforded a 99% ee of the product without the use of any external chiral source. We succeeded in controlling the handedness of the asymmetric amplification by adding a catalytic amount of optically active valine. These results provide not only the asymmetric transformation of *p*-anisoin, which is important as an intermediate for medical and agrochemical products, but also essential information deeply related to the expression of the homochirality of biomolecules on Earth.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.cgd.1c00036.

Experimental procedure, x-ray structure analysis, and HPLC analysis (PDF)

Accession Codes

CCDC 2053909 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Author Contributions

The manuscript was written through contributions by all authors.

Notes

The authors declare no competing financial interest.

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