Enantioselective synthesis mediated by chiral crystal of achiral hippuric acid in conjunction with asymmetric autocatalysis

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Enantiomorphous crystals composed of achiral hippuric acid, *i.e.*, naturally occurring *N*-benzoylglycine, have been used successfully as chiral inducers in enantioselective synthesis in combination with asymmetric autocatalysis to afford the product with extremely high enantiomeric excess.

The origin of biological homochirality in biomolecules such as L-amino acids and D-sugars is a significant topic of interest.[1] Inorganic chiral crystals such as quartz and sodium chlorate have been proposed as one of the origins of chirality. We previously reported the asymmetric autocatalysis induced by chiral quartz[2a] and sodium chlorate.[2b,c]

It has been recognized that some achiral organic compounds crystallize in a chiral space group to give enantiomorphous crystals.[3] Stereospecific reactions using these chiral organic crystals of achiral compounds as reactants have been reported.[3] However, enantiomorphous crystals formed from achiral organic compounds have rarely been used as a chiral inducer (or a catalyst) in enantioselective synthesis of external compounds. To the best of our knowledge, the only exception is asymmetric autocatalysis using a chiral two-component molecular crystal of achiral tryptamine and *p*-chlorobenzoic acid as a chiral inducer.[4] From a prebiotic point of view, to investigate the highly enantioselective reaction utilizing the crystal chirality of achiral biomolecules is an important experimental approach to understand the origin of biological homochirality.

Hippuric acid **1**, *i.e.*, *N*-benzoylglycine, is an achiral naturally occurring amino acid derivative, and is formed in mammals when the toxicity of benzoic acid is removed by conjunction with glycine. It has been reported that the single crystal of hippuric acid **1** forms enantiomorphous $P2_12_12_1$ crystals,[5] which belong to a chiral space group.

We report here that the enantiomorphous one-component single crystals of achiral hippuric acid **1** induce enantioselective addition of diisopropyl zinc (*i*-Pr_2Zn) to pyrimidine-5-carbaldehyde **2** to afford, in combination with asymmetric autocatalysis, pyrimidyl alkanol **3** with significant high enantiomeric excess. The absolute configuration of the corresponding 5-pyrimidyl alkanol **3** was controlled efficiently by the chirality of these single crystals (Scheme 1).

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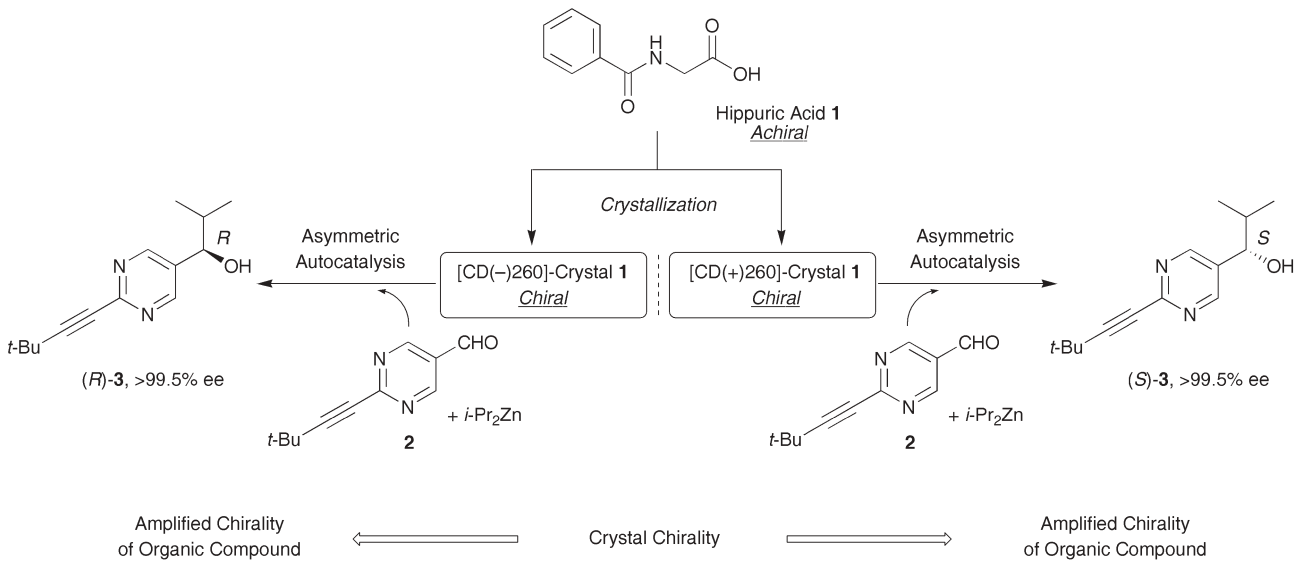
The results of the asymmetric autocatalysis mediated by the chiral single crystals of hippuric acid **1** are summarized in Table 1. The single crystals of **1** used in the asymmetric autocatalysis were grown from methanol solutions by slow evaporation at room temperature under atmospheric pressure. It is possible to discriminate between the enantiomorphs of the obtained single crystals by using solid state circular dichroism (CD) spectroscopic analysis with Nujol mulls (Fig. 1). One crystal **1** exhibits a positive Cotton effect at 260 nm ([CD(+)260]),[6] while the other shows a negative Cotton effect ([CD(−)260]) (Fig. 1).

When pyrimidine-5-carbaldehyde **2** was treated with *i*-Pr_2Zn in the presence of the powdered single crystal [CD(+)260]-**1**, (*S*)-pyrimidyl alkanol **3** with 73% ee was obtained in 88% yield (Table 1, entry 1). On the other hand, in the presence of [CD(−)260]-**1**, the opposite enantiomer (*R*)-**3** with 89% ee was isolated in 89% yield. The correlation between the chirality of crystal **1** and pyrimidyl alkanol **3** was reproducible (entries 3 and 4). In this system, after the crystal chirality induces the chirality of asymmetric carbon in the external organic compound, the subsequent asymmetric autocatalysis[7–9] gives an increased amount of enantiomerically amplified product.

When crystals grown from the stirred methanol solution of hippuric acid using each enantiomorph of **1** as the seed crystal were used in asymmetric autocatalysis, the same correlation between the chirality of crystal **1** and the produced 5-pyrimidyl alkanol **3** was observed with nice reproducibility (entries 5, 6, 7 and 8). To exclude any chiral effect other than that of the crystal chirality, the reactions were run using the same apparatus by changing only the chirality of crystal **1**. The results were found to be reproducible, *i.e.*, [CD(+)260]- and [CD(−)260]-**1** afforded (*S*)- and (*R*)-**3**, respectively (entries 9 and 10).

It should be noted that nearly enantiopure (*S*)- and (*R*)-pyrimidyl alkanols **3** with > 99.5% ee are obtained by applying the further consecutive asymmetric autocatalysis (entries 11 and 12).[7b]

Typical experimental procedure is as follows: A crystal of hippuric acid **1** was ground into a powder (particle size estimated from SEM images = 10–20 μm) using a pestle and mortar. Toluene solution of *i*-Pr_2Zn (0.08 mL, 0.08 mmol) was added dropwise at 0 °C with stirring to a mixture of finely powdered crystal **1** (13.4 mg, 0.075 mmol) and aldehyde **2** (4.7 mg, 0.025 mmol). After stirring overnight at 0 °C, toluene (0.75 mL) was added to the mixture, and then toluene solution of *i*-Pr_2Zn (0.3 mL, 0.3 mmol) was added dropwise over a period of 1 h. Then, toluene (0.75 mL) solution of **2** (18.8 mg, 0.1 mmol) was slowly added dropwise over a period of 1.5 h. After stirring for 3 h at 0 °C, toluene (5.0 mL) and toluene solution of *i*-Pr_2Zn (0.8 mL, 0.8 mmol) were added



Scheme 1 Asymmetric autocatalysis induced by chiral single crystal of hippuric acid.

Table 1 The relationship between the crystal chirality of hippuric acid **1** and the obtained 5-pyrimidyl alkanol **3** in conjunction with asymmetric autocatalysis[a]

		Pyrimidyl alkanol **3**		
Entry	Chiral crystal **1**[b]	Isolated yield (%)	ee (%)[c]	Config.
1	[CD(+)260]	88	73	*S*
2	[CD(−)260]	89	89	*R*
3	[CD(+)260]	86	81	*S*
4	[CD(−)260]	82	23	*R*
5[d]	[CD(+)260]	90	62	*S*
6[d]	[CD(−)260]	89	89	*R*
7[d]	[CD(+)260]	87	87	*S*
8[d]	[CD(−)260]	88	89	*R*
9[d,e]	[CD(+)260]	86	73	*S*
10[d,e]	[CD(−)260]	92	72	*R*
11[d,f]	[CD(+)260]	90	> 99.5	*S*
12[d,f]	[CD(−)260]	93	> 99.5	*R*

[a] The molar ratio of **1** : **2** : *i*-Pr_2Zn = 0.075 : 1.325 : 2.78. Aldehyde **2** and *i*-Pr_2Zn were added in four separate portions. The aldehyde **2**, which was added to the reaction mixture in the first and second portions, was purified by sublimation. [b] The chirality of the crystals was verified from solid-state CD spectra using Nujol. [c] The ee value was determined by HPLC on a chiral stationary phase. [d] The powder-like crystals, which were grown by a seeding method using the fragment of native single crystals with stirring, were used as the chiral sources. [e] Each reaction was performed using the same apparatus to exclude any effect other than that of the chiral crystal. [f] After the typical experimental method, an additional three rounds of consecutive asymmetric autocatalyses were performed as previously described (see ref. 7*b*).

successively. Then, toluene (2.0 mL) solution of **2** (75.3 mg, 0.4 mmol) was added dropwise over a period of 1.5 h and the mixture was stirred for 1 h at 0 °C. Once again, toluene (14.0 mL) and toluene solution of *i*-Pr_2Zn (1.6 mL, 1.6 mmol) were added, and toluene (4.0 mL) solution of **2** (150.6 mg, 0.8 mmol) was added dropwise over a period of 1.5 h. After the mixture was stirred for 1 h at 0 °C, the reaction was quenched with 1 M hydrochloric acid (5 mL) and neutralized with a saturated solution of sodium hydrogen carbonate (15 mL). The resulting mixture was filtered through Celite and the filtrate extracted with ethyl acetate. The combined organic layers were dried over anhydrous sodium sulfate and concentrated *in vacuo*. Purification of the residue by thin-layer chromatography on silica gel gave the 5-pyrimidyl alkanol **3**.

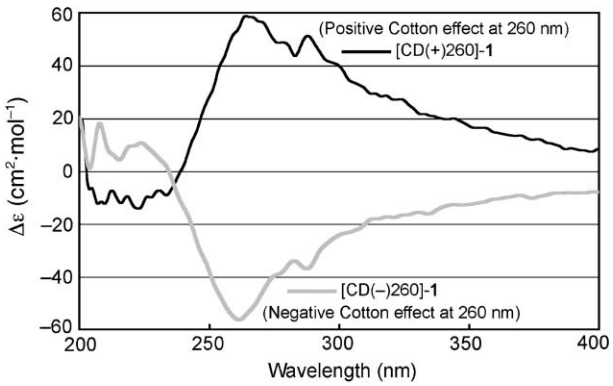


Fig. 1 Solid state CD spectroscopic analysis of two enantiomorphous crystals of hippuric acid (**1**) as Nujol mulls.

The initial reaction of the pyrimidine-5-carbaldehyde **2** and *i*-Pr_2Zn proceeded on the chiral surface of the chiral crystal **1** so that a small imbalance of enantiomeric excess was induced. Then, the subsequent consecutive asymmetric autocatalysis[7b] with an amplification of chirality afforded 5-pyrimidyl alkanol **3** in a high enantiomeric excess.

In conclusion, the enantioselective addition of *i*-Pr_2Zn to pyrimidine-5-carbaldehyde **2** was achieved by utilizing the chirality of single crystals of achiral hippuric acid **1**. The enantiomeric excess was amplified to > 99.5% ee in conjunction with asymmetric autocatalysis. These results clearly demonstrate that the crystal chirality of achiral **1** is responsible for the enantioselective addition of *i*-Pr_2Zn to pyrimidine-5-carbaldehyde **2**. This is the first example in which the crystal chirality of an achiral biological single compound induces the chirality of another organic compound and this is amplified to significantly high enantiomeric excess.

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