Asymmetric Synthesis

Asymmetric Amplification Using Chiral Cocrystals Formed from Achiral Organic Molecules by Asymmetric Autocatalysis**

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The origin and amplification of chirality leading to the overwhelming enantioenrichment of organic compounds, such as the L-amino acids and D-sugars on Earth, is a significant topic of interest.[1] One of the proposed mecha-

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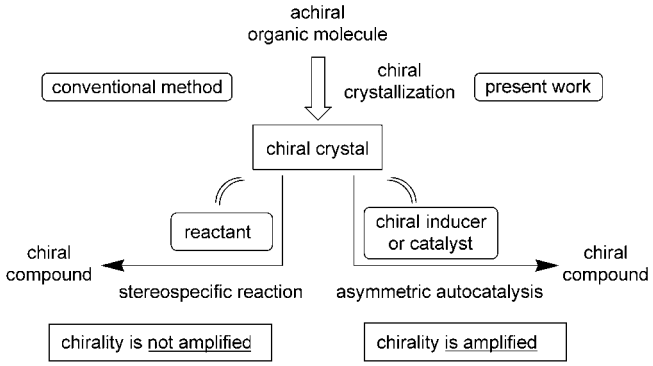
nisms for the origin of chirality is the generation of chiral crystals formed from achiral organic compounds, with each crystal exhibiting one of the two possible enantiomorphs.[2] Of the 230 possible space groups, 65 are chiral, and it is worth noting that among the five most common space groups of organic crystalline compounds, on the basis of a survey of approximately 29000 crystal structure determinations, about 18% of crystals belong to the two chiral space groups $P2_12_12_1$ and $P2_1$.[3] Moreover, the formation of chiral cocrystals of a quaternary ammonium salt from an equimolar solution of an achiral carboxylic acid with amine components has been reported.[4] These crystals belong to a typical chiral space group and have both clockwise (*P*) and counterclockwise (*M*) helicities.

Although examples of highly stereospecific reactions that use chiral crystals of achiral compounds have been reported, these reactions are limited as these chiral crystals were only used as reactants, and so that the amount of chirality did not increase (Scheme 1).[5–7] Amplification of the amount of chirality is required for significant quantities of the desired chiral compounds to be obtained. To the best of our knowledge, no highly enantioselective reactions using chiral crystals as chiral initiators (or catalysts) have been reported. Thus, a challenging problem to be addressed is the development of a highly enantioselective synthesis using chiral cocrystals formed from achiral organic molecules as chiral inducers or catalysts, whereby the enantioselective synthesis enables significant amplification of the amount of the chirality in the system (Scheme 1).



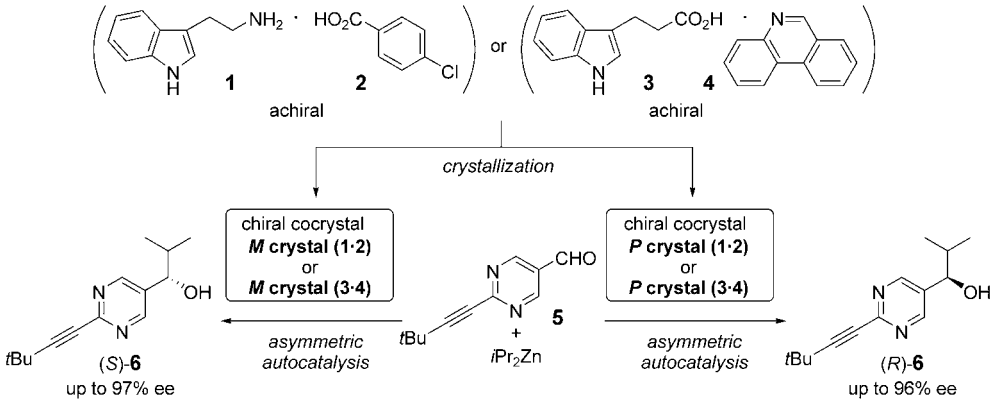
Scheme 1. A comparison of the concept of utilizing chiral crystals composed of achiral organic molecules as chiral inducers or catalysts in asymmetric autocatalysis with their conventional use as reactants in stereospecific reactions.

During our studies into asymmetric autocatalytic processes we found that the asymmetric autocatalysis of a 5-pyrimidyl alkanol in the enantioselective addition of diisopropylzinc to pyrimidine-5-carbaldehyde (**5**) proceeds with an amplification of enantiomeric excess.[8–10]

Herein, we report on a highly enantioselective addition of $i\mathrm{Pr}_2\mathrm{Zn}$ to **5** in the presence of chiral cocrystals of tryptamine/*para*-chlorobenzoic acid (**1**/**2**)[3c] and 3-indolepropionic acid/phenanthridine (**3**/**4**; Scheme 2)[3a] The enantioselective addition of $i\mathrm{Pr}_2\mathrm{Zn}$ to **5** in the presence of powdered *P* or *M* crystals gave the pyrimidyl alkanol **6** with high enantioselectivity in high yield. The absolute configuration of the corresponding 5-pyrimidyl alkanol **6** was controlled by the chirality of these cocrystals, which had been prepared from achiral organic molecules. The molar amount of the prepared chiral compounds in this reaction was increased by a factor of up to 30, which was calculated from the molar ratio of the chiral cocrystal and the resulting chiral 5-pyrimidyl alkanol **6**. Moreover, chiral 5-pyrimidyl alkanol **6** can be automultiplied by subsequent asymmetric autocatalysis, as we have previously reported.[8a]

The (*R*)-pyrimidyl alkanol **6** was obtained in a 90% yield and with 89% *ee* (Table 1, entry 1) when the reaction was performed in the presence of the *P* crystal of **1**/**2**. Repeated reactions in the presence of *P*-(**1**/**2**) led to (*R*)-**6** being obtained in 82–96% *ee*, thus showing that the results are reproducible (Table 1, entries 3, 5, and 7). On the other hand, the reaction between **5** and $i\mathrm{Pr}_2\mathrm{Zn}$ in the presence of the *M*-(**1**/**2**) crystal instead of the *P* crystal always gave (*S*)-**6** in 82–95% *ee* and 86–94% yield (Table 1, entries 2, 4, 6, and 8). Both reactions were performed using the same apparatus and gave the same results, thus excluding any effect other than that of the chiral cocrystal (Table 1, entries 7 and 8).

Next, we examined the addition of $i\mathrm{Pr}_2\mathrm{Zn}$ to **5** under the same conditions using the **3**/**4** chiral cocrystal. The enantioselective preparation of (*R*)-pyrimidyl alkanol **6** was induced in the presence of the *P* crystal of **3**/**4** and was obtained with 72–92% *ee* in 92–99% yield (Table 1, entries 9, 11, 13, and



Scheme 2. Highly enantioselective asymmetric autocatalysis using chiral cocrystals **1**/**2** and **3**/**4**.

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Table 1: The highly enantioselective synthesis of pyrimidyl alkanols in the presence of chiral cocrystals **1/2** and **3/4**.

Entry[a]	Chiral cocrystal[b]	Pyrimidyl alkanol **6**		
		yield [%]	*ee* [%][c]	config.
1	*P*-(**1/2**)	90	89	*R*
2	*M*-(**1/2**)	86	89	*S*
3	*P*-(**1/2**)	92	87	*R*
4	*M*-(**1/2**)	88	82	*S*
5[d]	*P*-(**1/2**)	99	96	*R*
6	*M*-(**1/2**)	92	95	*S*
7[d,e]	*P*-(**1/2**)	88	82	*R*
8[e]	*M*-(**1/2**)	94	92	*S*
9	*P*-(**3/4**)	93	92	*R*
10	*M*-(**3/4**)	89	89	*S*
11	*P*-(**3/4**)	92	86	*R*
12	*M*-(**3/4**)	91	85	*S*
13	*P*-(**3/4**)	94	72	*R*
14	*M*-(**3/4**)	93	93	*S*
15[e]	*P*-(**3/4**)	99	87	*R*
16[e]	*M*-(**3/4**)	90	97	*S*

[a] The molar ratio used was cocrystal/**5**/iPr$_2$Zn = 0.05:1.55:3.25 unless otherwise noted. Compound **5** and iPr$_2$Zn were added in four separate portions. [b] The cocrystals were ground into a powder using a pestle and mortar. The chirality of the cocrystals was verified from solid-state CD spectra using nujol. The powder of cocrystal **1/2** was washed with diethyl ether and then with hexane several times and dried in vacuo before use. The powder of cocrystal **3/4** was washed several times using only hexane because of its solubility in diethyl ether. [c] The *ee* value was determined by HPLC on a chiral stationary phase (chiralcel OD column, eluent = 3% 2-propanol in hexane, flow rate = 1.0 mL min^{-1}, 254 nm UV detector, retention time = 18.1 min for (*S*)-**6**, 26.9 min for (*R*)-**6**). [d] The molar ratio used was cocrystal/**5**/iPr$_2$Zn = 0.05:1.05:2.25. Compound **5** and iPr$_2$Zn were added in three separate portions. [e] Each reaction was performed using the same apparatus to exclude any effect other than that of the chiral cocrystal.

15). On the other hand, the reaction between **5** and iPr$_2$Zn in the presence of the *M*-(**3/4**) cocrystal always gave (*S*)-**6** with 85–97% *ee* in 89–93% yield (Table 1, entries 10, 12, 14, and 16). Again, the same equipment was used in this series of reactions to exclude any effect other than that of the chiral cocrystal (Table 1, entries 15 and 16).

The enantioselectivity observed in this asymmetric reaction may be explained as follows: The initial reaction of the aldehyde **5** and iPr$_2$Zn proceeded on the chiral surface of the cocrystal so that a small enantiomeric excess was induced. Then, subsequent asymmetric autocatalysis with an amplification of chirality afforded alkanol **6** (as zinc alkoxide) in a high enantiomeric excess, and with the corresponding absolute configuration. Further mechanistic details are now under investigation.

In summary, the highly enantioselective addition of iPr$_2$Zn to pyrimidine-5-carbaldehyde (**5**) was achieved by utilizing the chirality of two-component molecular crystals of tryptamine/*para*-chlorobenzoic acid (**1/2**) and 3-indolepropionic acid/phenanthridine (**3/4**). These results clearly demonstrate that the chirality of the cocrystals **1/2** and **3/4** is responsible for the enantioselective addition of iPr$_2$Zn to **5**. We believe that the insight that chiral crystals composed of achiral compounds offer into the origin and evolution of chirality is significantly increased by asymmetric autocatalysis.

Experimental Section

A typical experimental procedure: A cocrystal (single crystal = 50 mg) was ground into a powder using a pestle and mortar (particle size estimated from SEM images = 2–10 μm). The two enantiomorphous *P* and *M* crystals of **1/2** and **3/4** were discriminated by solid-state circular dichroism (CD) spectroscopic analysis (nujol). The powder of **1/2** was washed with diethyl ether and hexane several times and then dried in vacuo before use.

iPr$_2$Zn (0.25 mmol, in solution with hexane (1.0 M, 0.25 mL)) was added dropwise at 0 °C to a finely powdered sample of cocrystal **1/2** (15.8 mg, 0.05 mmol). The hexane was immediately removed by distillation under reduced pressure (3.0 mm Hg, 5 min) to leave a white powder of cocrystal **1/2**, whose surface was coated with iPr$_2$Zn. A solution of **5** (9.4 mg, 0.05 mmol) in methylcyclohexane (1.5 mL) was then added over a period of 30 min at 0 °C and the mixture was stirred for 16 h at 0 °C. Toluene (0.7 mL), iPr$_2$Zn (0.2 mmol, in solution with toluene (1.0 M, 0.2 mL)), and a solution of **5** (18.8 mg, 0.1 mmol) in toluene (0.75 mL) were added successively, and the reaction mixture stirred at 0 °C for 3 h.

Then, toluene (5.0 mL), iPr$_2$Zn (0.8 mmol, 0.8 mL of a 1 M toluene solution), and a solution of aldehyde **5** (75.2 mg, 0.4 mmol) in toluene (2.0 mL) were added successively and the mixture was stirred at 0 °C for 1 h. Once again, toluene (14 mL), iPr$_2$Zn (2.0 mmol, in solution with toluene (1.0 M, 2.0 mL)), and a solution of aldehyde **5** (188.2 mg, 1.0 mmol) in toluene (5.0 mL) were added successively, and the mixture was stirred at 0 °C for 1 h. The reaction was quenched with hydrochloric acid (1 M, 5 mL) and neutralized with a saturated sodium hydrogen carbonate solution (15 mL). The mixture was then filtered through celite and the filtrate extracted with ethyl acetate (×3). The combined organic layers were dried over anhydrous sodium sulfate and evaporated in vacuo. Purification of the residue by thin-layer chromatography on silica gel (hexane/ethyl acetate, 2:1) gave the 5-pyrimidyl alkanol **6**.

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