

d- and *l*-Quartz-Promoted Highly Enantioselective Synthesis of a Chiral Organic Compound

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Heterogeneous inorganic solid catalysts play an important role in organic chemical reactions.¹ However, no overwhelming asymmetric synthesis of organic molecules using chiral inorganic solid catalysts has been described. On the other hand, since the discovery of chirality of organic molecules by Pasteur,² the origin of chirality of organic molecules has been an intriguing puzzle.^{2–14} Quartz (inorganic) displays morphologically chiral crystals^{15,16} which exist naturally as either dextrorotatory (*d*) or levorotatory (*l*) enantiomorphs.¹⁷ There is a theory that chiral quartz is the source of chirality for the first chiral organic molecule formed.¹⁴ However, apparently no asymmetric synthesis using quartz is known,¹⁸ although a very small imbalance of chirality was observed by Bonner et al. in an asymmetric adsorption of chiral molecules by quartz.¹⁹ Thus, chiral quartz-catalyzed asymmetric synthesis of chiral organic molecule with high enantiomeric excess (ee) is a challenging problem.

We report here that *d*- and *l*-quartz promote the asymmetric addition of diisopropylzinc (*i*-Pr₂Zn) to 2-alkynylpyrimidine-5-carbaldehyde **1** to afford, in combination with asymmetric autocatalysis,²⁰ chiral pyrimidyl alkanol **2** possessing *S* (from *d*-quartz) and *R* (from *l*-quartz) configurations, respectively, with significantly high (93–97%) enantiomeric excess (Scheme 1). This is the first example of asymmetric synthesis of an organic compound with high enantiomeric excess using a chiral inorganic crystal as catalyst. In the course of our continuing study on enantioselective alkylation of aldehydes²¹ and on asymmetric autocatalysis,^{22,23} we reported that a tiny imbalance of chirality

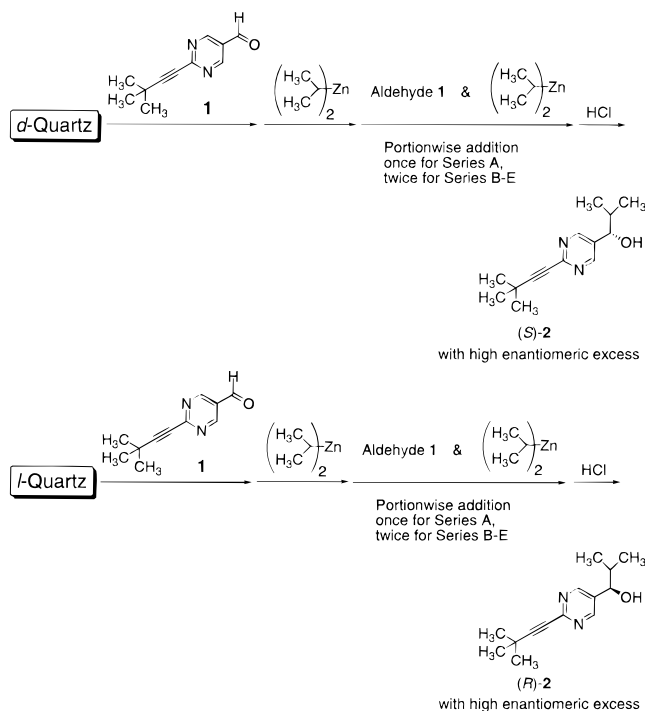
Table 1. Enantioselective Synthesis of Pyrimidyl Alkanol **2** in the Presence of *d*- or *l*-Quartz

run ^{a,b}	quartz ^c	pyrimidyl alkanol 2	
		isolated yield (%)	ee (%) (configuration) ^d
Series A			
A1	<i>d</i>	90	89 (<i>S</i>)
A2	<i>l</i>	97	85 (<i>R</i>)
A3	<i>d</i>	88	86 (<i>S</i>)
A4	<i>l</i>	96	84 (<i>R</i>)
A5	<i>d</i>	93	80 (<i>S</i>)
A6	<i>l</i>	96	89 (<i>R</i>)
Series B ^e			
B1	<i>l</i>	97	95 (<i>R</i>)
B2	<i>l</i>	97	93 (<i>R</i>)
B3	<i>d</i>	96	95 (<i>S</i>)
B4	<i>d</i>	97	95 (<i>S</i>)
Series C ^e			
C1	<i>d</i>	93	97 (<i>S</i>)
C2	<i>l</i>	97	97 (<i>R</i>)
C3	<i>l</i>	95	97 (<i>R</i>)
Series D ^e			
D1	<i>l</i>	95	93 (<i>R</i>)
D2	<i>d</i>	95	94 (<i>S</i>)
Series E ^e			
E1	<i>d</i> : <i>l</i> = 9:1 (w/w)	96	95 (<i>S</i>)
E2	<i>d</i> : <i>l</i> = 1:9 (w/w)	95	95 (<i>R</i>)
Series F			
F1	<i>d</i>	5	<1 (<i>S</i>)
F2	none	trace	BDL ^f

^a All of the experiments were reproducible. Reaction temperature was 0 °C. Molar ratios were quartz (as SiO₂):aldehyde **1**:*i*-Pr₂Zn = 1.9:1.0:2.0 for series B–E (aldehyde **1** and *i*-Pr₂Zn were added in three portions), 8.0:1.0:2.5 for series A (aldehyde **1** and *i*-Pr₂Zn were added in two portions), 8.2:1.0:3.0 for run F1 (aldehyde **1** and *i*-Pr₂Zn were added in one portion). For run F2, aldehyde **1**:*i*-Pr₂Zn = 1.0:3.0. Reaction time was 1 min for series F; see footnote *e* for the reaction time of series B–E. ^b To exclude any effect other than quartz, in series A–D, each reaction was run in the order of run numbers using the same equipment. ^c Synthetic *d*- and *l*-quartz crystals (products of Toyo Communication Equipment Co., Japanese Industrial Standard (JIS) quality; *d*- and *l*-quartz form hemihedral crystals, and they can be identified by their shapes) were powdered by Dalton Co. (for series A, B, C, E, and F; average particle sizes were 4.4 μm for *d*-quartz and 7.6 μm for *l*-quartz) and by Seishin Enterprise Co. (for series D; average particle sizes were 2.9 μm for *d*-quartz and 3.4 μm for *l*-quartz), independently. The surface of quartz was cleaned and activated by the following procedures: (i) 2 M hydrochloric acid for 10 h at 100 °C, (ii) methanol for 10 min, (iii) washed with acetone three times and then with water three times, (iv) 11% hydrofluoric acid for 15 min at room temperature, (v) washed with water until the pH of the supernatant water became neutral, (vi) dried in vacuo (0.5 mmHg) at 100 °C for 10 h. In each step, quartz was collected and recovered by centrifugation. ^d Ee was determined by HPLC analysis using a chiral column (Chiralcel OD). ^e Typical experimental procedure is as follows: To a mixture of *d*- or *l*-quartz (120 mg, 2.0 mmol calculated as SiO₂) and aldehyde **1** (9.4 mg, 0.05 mmol) was added toluene (0.1 mL) under an argon atmosphere. The mixture was stirred for 15 min at room temperature and for 5 min at 0 °C. Then a 1.0 M toluene solution (0.15 mL) of *i*-Pr₂Zn (0.15 mmol) was added to the mixture at 0 °C using a syringe at a rate of one drop per 30 s, and the mixture was stirred for 12 h. Toluene (4.75 mL), *i*-Pr₂Zn (0.4 mmol, 0.4 mL of 1.0 M toluene solution), and a toluene (1.5 mL) solution of aldehyde **1** (37.6 mg, 0.2 mmol) were added successively, and the mixture was stirred for 5 h. Then, toluene (14.4 mL), *i*-Pr₂Zn (1.6 mmol, 1.6 mL of 1.0 M toluene solution), and toluene (4.0 mL) solution of aldehyde **1** (151 mg, 0.8 mmol) were added successively, and the mixture was stirred at 0 °C for another 5 h. The reaction was quenched by addition of 1 M hydrochloric acid (4 mL) and then was made alkaline by saturated aqueous sodium bicarbonate (12 mL). The mixture was filtered using Celite, and the filtrate was extracted with ethyl acetate. The combined organic layer was dried over sodium sulfate and evaporated under reduced pressure. Purification of the residue by silica gel thin-layer chromatography (developing solvent, hexane:ethyl acetate = 2:1) gave pyrimidyl alkanol **2**. ^f Below the detection level.

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Scheme 1 *d*- and *l*-Quartz-Promoted Asymmetric Synthesis of (*S*)- and (*R*)-**2**

of organic molecule can be enhanced by the mechanism of asymmetric autocatalysis.²⁴ We then carefully examined the quartz-promoted asymmetric synthesis.

We found that chiral quartz promotes asymmetric synthesis of chiral pyrimidyl alkanol **2** (Table 1). When 2-(*tert*-butylethynyl)pyrimidine-5-carbaldehyde **1**²³ was treated with *i*-Pr₂Zn in the presence *d*-quartz powder in toluene (aldehyde **1** and *i*-Pr₂Zn were added in 2 portions), (*S*)-2-(*tert*-butylethynyl)pyrimidyl alkanol **2** with 89% ee was isolated (run A1). On the other hand, in the presence of *l*-quartz, the opposite enantiomer (*R*)-**2** with 85% ee was obtained (run A2). The reproducibility of the reaction is shown in Table 1 (series A). To examine the effect of quartz clearly, each quartz sample was used only once. A series of reactions was performed in the presence of, alternatively, *d*-, *l*-, *d*-, *l*-, *d*-, and *l*-quartz, using exactly the same reaction vessel, magnetic stirring bar, argon balloon, and injection syringes.

When aldehyde **1** and *i*-Pr₂Zn were added in three portions (series B, C, and D), (*S*)- and (*R*)-**2** with significantly high ee's, i.e., 95–97% and 93–97% ee, were obtained in the presence of *d*- and *l*-quartz, respectively. To examine the generality of the quartz crystal catalysis, the quartz powder was produced in two

different places (for series A, B, C, E and for series D, see footnote of Table 1). Both sets of powdered quartz crystals gave **2** with almost the same ee. These results show that the chirality of quartz determines the absolute configuration of **2** formed. In addition, when a mixture of *d*- and *l*-quartz (9:1, w/w) was utilized, (*S*)-**2** with 95% ee was obtained in 96% yield (run E1). On the other hand, the reaction in the presence of a mixture of *d*- and *l*-quartz (1:9, w/w) afforded (*R*)-**2** with 95% ee in 95% yield (run E2). Thus, the absolute configuration of **2** formed is dependent on the quartz of the major enantiomorphs in the mixture. In control experiments (series F), reaction between **1** and *i*-Pr₂Zn at 0 °C afforded **2** in 5% yield in the presence of *d*-quartz (run F1), while only a trace amount of **2** was formed in the absence of quartz (run F2).

Because quartz is morphologically chiral^{15,16} and acidic, it may differentiate the enantioface of aldehyde **1** when it coordinates with the oxygen and nitrogen atoms of aldehyde **1**. This differential coordination of quartz may cause the difference in the reactivity toward *i*-Pr₂Zn between the two enantiofaces of aldehyde **1**.²⁵ Thus, an initial (probably very small) asymmetric induction may occur when *i*-Pr₂Zn adds to the aldehyde **1** coordinated with chiral quartz (*d*-quartz affords (*S*)-**2**, *l*-quartz (*R*)-**2**).²⁶ Subsequently, the ee of **2** (even though it may be very small in the early stage) is enhanced by the asymmetric autocatalytic reaction to afford **2** with very high ee. The overall process constitutes a chiral quartz-promoted enantioselective synthesis of **2** with very high ee by the reaction of *i*-Pr₂Zn with aldehyde **1**.

As described, we have shown that chiral quartz promotes the reaction of **1** with *i*-Pr₂Zn to afford optically active pyrimidyl alkanol **2** with very high enantiomeric excess. The present results provide chemical evidence that chiral quartz may be involved in the origin of the chirality of organic molecules through catalytic asymmetric synthesis.

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(26) It may be also possible that the enantioselective adsorption of initially formed product, i.e., zinc alkoxide of **2**, on chiral quartz induces a small imbalance of the enantiomers.