Achiral Inorganic Gypsum Acts as an Origin of Chirality through Its Enantiotopic Surface in Conjunction with Asymmetric Autocatalysis

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Abstract: *Achiral inorganic gypsum ($CaSO_4 \cdot 2H_2O$) triggers the asymmetric autocatalysis of pyrimidyl alkanol on its two-dimensional enantiotopic faces to give highly enantioenriched alkanol products with absolute configurations corresponding to the respective enantiotopic surfaces. This is the first example of highly enantioselective synthesis on the enantiotopic surface of an achiral mineral.*

The origins of the homochirality of biological compounds such as L-amino acids and D-sugars have been the subject of great interest in chemistry, biology, physics, astrobiology, and studies on the origin of life.[1] There have been several theories proposed for the origins of the chirality of organic compounds.

Meanwhile, increasing attention has been focused on two-dimensional surface chirality.[1n,o,2] Although chiral inorganic minerals have been considered to be an origin of chirality, achiral natural minerals with an enantiotopic surface have rarely been considered as an origin of chirality. A spectacular example was reported by Hazen et al.[3] They reported the enantiomer-selective adsorption of racemic amino acids on the enantiotopic faces of the achiral mineral calcite ($CaCO_3$) with moderate enantiomeric excess (Scheme 1a). Certain metal surfaces, such as artificially cut Cu(643), become enantiotopic, and the enantiomer-selective decomposition of chiral compounds have been reported.[4] However, it has not yet been possible to control the enantioselective synthesis induced on the enantiotopic surface of achiral inorganic minerals to generate chiral molecules from achiral molecules.

We have been studying asymmetric autocatalysis of pyrimidyl alkanol with amplification of chirality.[5–8] Various chiral factors,[9] including circularly polarized light,[10] isotope chirality,[11] and chiral inorganic crystals[12] trigger asymmetric autocatalysis. However, to the best of our knowledge, no definitive report has appeared on asymmetric synthesis using achiral inorganic crystals.[13]

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(a) **Enantioselective Adsorption of Racemate**

(b) **This work: Enantioselective Synthesis** (Gypsum)

Enantioselective synthesis induced by surface (2-dimensional) chirality of inorganic achiral crystal
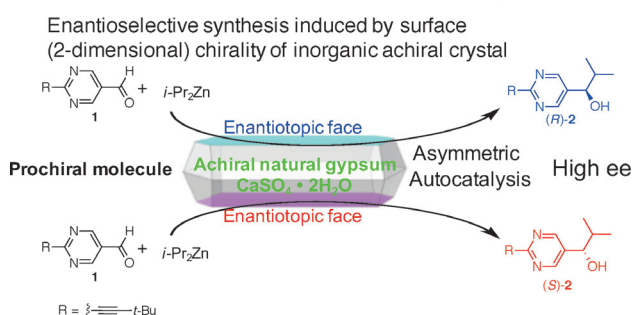
Scheme 1. The enantiotopic faces of an achiral mineral as an origin of chirality.

Gypsum is a common mineral that has been used in a wide range of applications, including materials for sculpture, plasterboard in buildings, and plaster casts for medical use. The crystal structure of gypsum is achiral, but its large grown face and its habit of cleavage make it enantiotopic. Although Cody and Cody have reported asymmetric crystal growth of the enantiotopic surface of gypsum in the presence of a chiral organic compound,[14] and Viedma, Cintas, et. al. have reported oriented aggregation growth of gypsum crystals,[15] no example has been reported of asymmetric synthesis on gypsum enantiotopic surfaces.
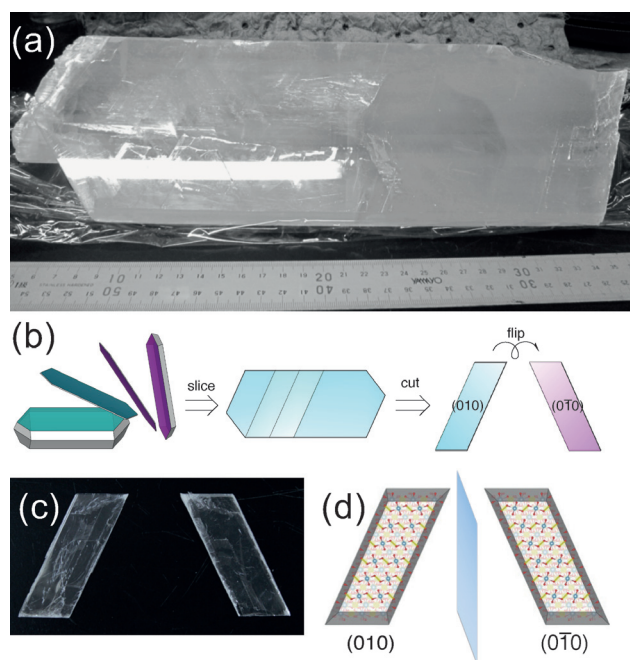
Herein, we report enantioselective synthesis using the two-dimensional enantiotopic face of an achiral inorganic crystal (Scheme 1b). The achiral inorganic mineral gypsum (calcium sulfate dihydrate, $CaSO_4 \cdot 2H_2O$) triggers asymmetric autocatalysis on its enantiotopic face, thereby providing highly enantioenriched alkanol product with chirality corresponding to that of the enantiotopic face of the gypsum.

Gypsum exhibits a perfect enantiotopic cleavage face that easily appears upon slicing of the crystal (Scheme 2). The crystal structure of gypsum belongs to the achiral space group $C2/c$.[16] Ideal surface images of gypsum looking along the b and $-b$ axes are shown in Scheme 2d. It should be noted that the (010) and (0$\bar{1}$0) faces of gypsum form enantiotopic faces and cannot be superimposed on each other with two-dimen-
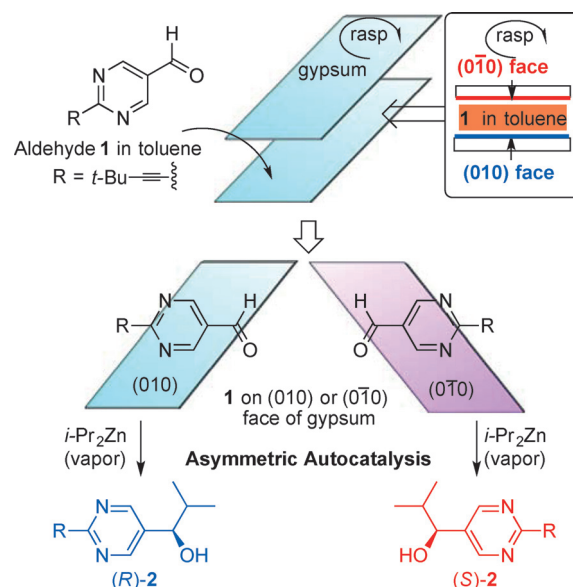
Scheme 2. The achiral gypsum ($CaSO_4 \cdot 2H_2O$) crystal and its enantio-topic faces. a) A naturally grown achiral crystal of gypsum. b) Habit of cleavage. c) A photograph of the enantiotopic faces of (010) and (0$\bar{1}$0). d) The surface structures of the enantiotopic faces are mirror images of each other.

Scheme 3. Asymmetric autocatalysis initiated on the enantiotopic surfaces of achiral mineral gypsum.

Table 1: Asymmetric autocatalysis initiated on the enantiotopic faces of gypsum.

Entry	Reaction set[a]	Enantiotopic face of gypsum	Pyrimidyl alkanol **2**		
			Amount [mg][b]	*ee* (%)	Configuration
1	A	(010)	1.0	72 (>99.5[c])	*R*
2	A	(0$\bar{1}$0)	1.0	71 (>99.5[c])	*S*
3	B	(010)	1.2	42	*R*
4	B	(0$\bar{1}$0)	0.8	18	*S*
5	C	(010)	0.9	36	*R*
6	C	(0$\bar{1}$0)	1.4	51	*S*
7	D	(010)	1.0	58	*R*
8	D	(0$\bar{1}$0)	0.7	50	*S*
9	E	(010)	0.8	72	*R*
10	E	(0$\bar{1}$0)	1.1	44	*S*
11	F	(010)	1.5	19	*R*
12	F	(0$\bar{1}$0)	1.3	38	*S*

[a] Aldehyde **1** was rubbed gently between the opposite surfaces belonging to the same reaction set to be adsorbed onto the enantiotopic faces. [b] Each reaction set uses ca. 4.7 mg of aldehyde on the surface. The conversion of aldehyde is typically high, although estimation of the exact yield was difficult owing to loss during the rubbing process. [c] The *ee* value for **2** after further asymmetric autocatalytic reactions with amplification of *ee*.

sional movement. When considering only one side of the crystal, the reaction environment becomes chiral. We anticipated that if only one side of the crystal can be used for the reaction, it may become a chiral source, even though the crystal structure itself is achiral.

The addition reaction of diisopropylzinc (i-Pr$_2$Zn) was performed with pyrimidine-5-carbaldehyde (**1**) on an enantiotopic surface of gypsum. The natural mineral gypsum was sliced along the (010) perfect cleavage face and cut into an approximately 2 cm × 7 cm parallelogram (Scheme 2 b,c). A toluene solution of pyrimidine-5-carbaldehyde **1** was dropped onto a freshly cleaved gypsum surface and gently rubbed on the opposite enantiotopic face with another gypsum piece until the toluene was almost evaporated. After removal of the toluene under reduced pressure, the aldehyde **1** on each enantiotopic surface was exposed to i-Pr$_2$Zn vapor to perform the addition reaction on the surface (Scheme 3). The pyrimidyl alkanol **2** was obtained through extraction with ethyl acetate from the surface and the *ee* of alkanol **2** was determined using chiral HPLC analysis.

The results are summarized in Table 1. In each reaction set (A–F), a new piece of gypsum was used and the two parts of the crystal pairs were rubbed against each other for the adsorption of aldehyde **1**. The reaction of adsorbed aldehyde on the (010) surface of gypsum afforded alkanol **2** in the *R* configuration. On the other hand, (*S*)-alkanol **2** was obtained through the reaction on the opposite (0$\bar{1}$0) face. Although the *ee* values for the pyrimidyl alkanol product vary, we attribute this to different conditions on the enantiotopic surfaces of gypsum. It should be noted that the *ee* values of pyrimidyl alkanol **2** increase to more than 99.5% *ee* during

further asymmetric autocatalysis (entries 1 and 2). Rubbing of the crystal surfaces is important for good reproducibility.

Although the mechanism of the present enantioselectivity is not yet fully understood, one possibility is that the initial orientation of the aldehyde on the gypsum surface may have a slight imbalance with regard to the *Re* and *Si* face orientations as a result of interactions between the enantiotopic face of gypsum and the enantiotopic *Re* and *Si* faces of the aldehyde. This may induce enantioselective addition of the i-Pr$_2$Zn reagent. The initially induced *ee* could then be

amplified by the subsequent asymmetric autocatalytic process.

In conclusion, we have achieved enantioselective synthesis by using the enantiotopic surface of the achiral natural mineral gypsum. This reaction is the first example of asymmetric synthesis using the surface chirality of achiral natural minerals. Furthermore, the present results expand the possibility of natural achiral minerals as the origin of homochirality

Experimental Section

A gypsum crystal was sliced along a perfect cleavage face and cut into an approximately $2\,cm \times 7\,cm$ parallelogram. Unstained clear crystals were selected for the reaction. A toluene solution of pyrimidine-5-carbaldehyde **1** (4.7 mg in 0.15 mL) was dropped onto the crystal and each enantiotopic face was gently rubbed on the opposite enantiotopic face of another crystal until the toluene was almost evaporated. After further evaporation of the toluene under reduced pressure, the two crystals were placed separately in a 100 mL flask and the flask was cooled in an ice bath. Diisopropylzinc (*i*-Pr$_2$Zn) in cumene (1.0 M, 0.4 mL) was added carefully to the flask so as not to contact the crystal face directly. The vapor of *i*-Pr$_2$Zn reacted with the aldehyde **1**. The flask stood undisturbed at 0°C overnight. The reaction was then quenched with NH_3/NH_4Cl buffer solution (5 mL) and the products were washed and collected from the crystal surfaces with EtOAc. The crude product was purified using silica-gel column chromatography (Hexane/EtOAc = 2:1) to give the pyrimidyl alkanol **2**. The *ee* was determined using HPLC with a chiral column (Daicel Chiralpak-IB, 5% IPA in hexane, 1.0 mLmin^{-1}, 254 nm).

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Keywords: asymmetric catalysis · autocatalysis · gypsum · homochirality · surface chirality

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