



# Highly enantioselective synthesis of organic compound using right- and left-handed helical silica<sup>☆</sup>

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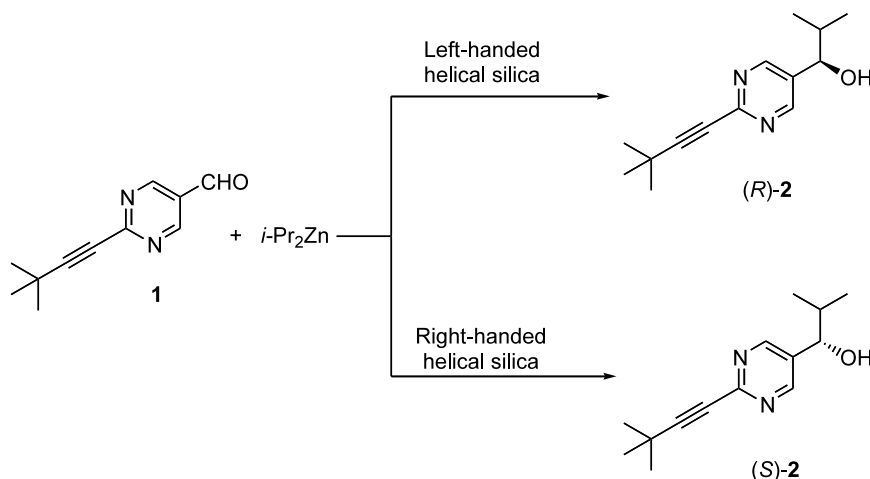
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**Abstract**—Highly enantiomerically enriched (up to 96–97% ee) 5-pyrimidyl alkanol was obtained by the addition of diisopropylzinc to pyrimidine-5-carbaldehyde in the presence of the artificially designed chiral inorganic material, right- and left-handed helical silica. © 2003 Elsevier Science Ltd. All rights reserved.

Inorganic heterogeneous solid materials such as silica, zeolite, and metal oxides play an important role in organic synthesis because they provide suitable environments such as appropriately sized cavities for certain reactions, and they work as catalysts.<sup>1</sup> They usually have greater (especially thermal) stability than organic heterogeneous catalysts. Their insolubility in solvents facilitates separation of the catalyst from the reaction

mixture. Enantioselective reaction of organic compounds using chiral inorganic materials has been one of the emerging areas for inorganic solid materials.<sup>2–4</sup> However, most of the existing methods employ inorganic–chiral organic hybrid materials,<sup>3</sup> in other words, chirality is based on the chiral organic moiety.<sup>5</sup> In this context, a chiral inorganic solid whose chirality is due to its inorganic framework has rarely been used in



Scheme 1.

**Keywords:** asymmetric induction; asymmetric synthesis; addition reactions; asymmetric autocatalysis; silica.

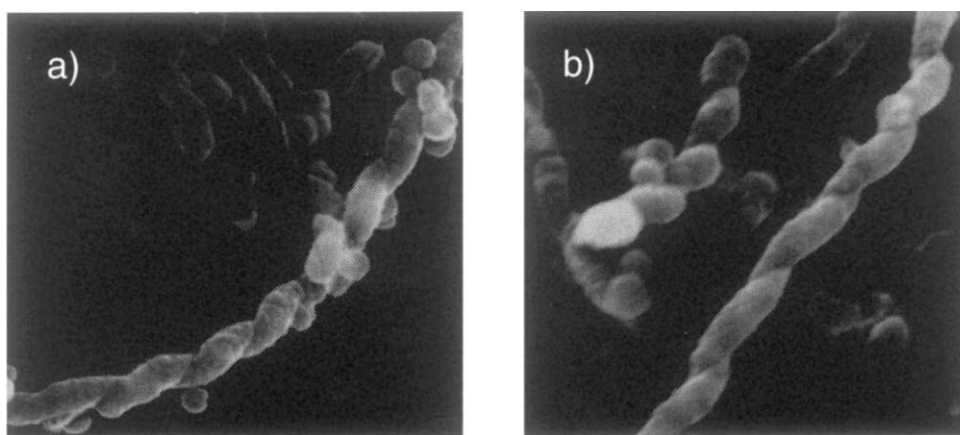
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enantioselective synthesis.<sup>2,4</sup> Davis and Lobo first reported the use of artificially tuned chiral zeolite beta in an enantioselective synthesis, although the enantiomeric excess (ee) was low (5%).<sup>2a</sup> Thus, highly enantioselective synthesis using artificially tuned chiral inorganic materials is a challenging problem.<sup>4</sup> We have recently reported the preparation of right- and left-handed silica by a sol-gel method.<sup>6</sup> We became interested in using right- and left-handed helical silica, an amorphous chiral inorganic material, as a chiral inducer in enantioselective synthesis.

We report here a highly enantioselective synthesis using right- and left-handed helical silica, a chiral amorphous material. We found that right- and left-handed helical silica induce asymmetric synthesis of chiral pyrimidyl alkanol **2** (Scheme 1). Helical silica (Fig. 1) was pre-

pared, according to a method reported previously,<sup>6a,b</sup> by sol-gel method followed by calcination at 500°C. When 2-(3,3-dimethyl-1-butynyl)pyrimidine-5-carbaldehyde **1**<sup>7a,b</sup> was reacted with diisopropylzinc (*i*-Pr<sub>2</sub>Zn) in the presence of left-handed helical silica, (*R*)-5-pyrimidyl alkanol **2** with 97% ee was isolated in 93% yield (Table 1, run 1). In contrast, in the presence of right-handed helical silica, the opposite enantiomer (*S*)-**2** with 96% ee was obtained in 92% yield (run 2). As shown in runs 3–5, the reaction was reproducible. These results show that right- and left-handed helical silica controls the absolute configuration of the pyrimidyl alkanol formed. Right- and left-handed helical silica were stable at room temperature for over a year. Right- and left-handed helical silica, even after standing for 14 months at room temperature, worked as a chiral initiator. Thus, the reaction using left-handed helical



**Figure 1.** SEM pictures of (a) left-handed and (b) right-handed helical silica prepared by a sol-gel method. Diameters of the helical silica are 100–110 nm.

**Table 1.** Enantioselective synthesis of 5-pyrimidyl alkanol **2** using left- or right-handed helical silica<sup>a</sup>

Entry	Helical silica		5-Pyrimidyl alkanol <b>2</b>		
		Sample set	Yield (%)	Ee (%)	Config.
1	Left-handed	A	93	97	<i>R</i>
2	Right-handed	A	92	96	<i>S</i>
3	Left-handed	A	91	97	<i>R</i>
4	Right-handed	A	92	96	<i>S</i>
5	Left-handed	A	91	94	<i>R</i>
6 <sup>b</sup>	Left-handed	A	97	97	<i>R</i>
7 <sup>b</sup>	Right-handed	A	94	96	<i>S</i>
8	Left-handed	B	93	50	<i>R</i>
9	Right-handed	B	93	67	<i>S</i>

<sup>a</sup> Experimental procedure: Helical silica was prepared according to Ref. 6b. After the calcination (at 200°C for 2 h then at 500°C for 2 h under a nitrogen atmosphere, and heated further at 500°C), helical silica was washed with diethyl ether and dried in vacuo at ca. 400°C. 0.15 ml of a toluene solution (1.0 M) of *i*-Pr<sub>2</sub>Zn (0.15 mmol) was added at 0°C over a period of 30 min to a toluene suspension (0.1 ml) of pyrimidine-5-carbaldehyde **1** (9.4 mg, 0.05 mmol) and right- or left-handed helical silica (30 mg). After the mixture was stirred for 12 h at 0°C, toluene (4.75 ml), *i*-Pr<sub>2</sub>Zn (0.4 mmol, 0.4 ml of 1.0 M toluene solution), and a toluene solution (1.5 ml) of aldehyde **1** (37.5 mg, 0.2 mmol) were added successively, and the mixture was stirred for 3.5 h. Then, toluene (14.4 ml), *i*-Pr<sub>2</sub>Zn (1.6 mmol, 1.6 ml of 1.0 M toluene solution) and a toluene (4.0 ml) solution of aldehyde **1** (150.6 mg, 0.8 mmol) were added successively, and the mixture was stirred at 0°C for 2.5 h. The reaction was quenched by adding 1 M hydrochloric acid (5 ml), and then satd. aq. sodium hydrogencarbonate (15 ml) was added. The mixture was filtered through Celite, and the filtrate was extracted with ethyl acetate. The combined organic layers were dried over anhydrous sodium sulfate, and evaporated under reduced pressure. Purification of the residue by silica gel thin layer chromatography (developing solvent, hexane:ethyl acetate=2:1 v/v) gave pyrimidyl alkanol **2**. The ee was determined by HPLC using a chiral stationary phase (Chiralcel OD).

<sup>b</sup> Silica was used after standing for 14 months.

silica produced (*R*)-**2** with 97% ee and right-handed helical silica (*S*)-**2** with 96% ee (runs 6 and 7). Helical silica prepared independently also worked. Left-handed helical silica gave (*R*)-**2** (run 8), and right-handed helical silica (*S*)-**2** (run 9). Although there is a difference in ee between the reactions using two sets of samples A and B (runs 1–7 and 8, 9), it should be emphasized that the moderate ee of **2** (runs 8 and 9) can be enhanced significantly by further asymmetric autocatalysis with amplification of ee.<sup>7–9</sup>

It should be mentioned that the helical silica is prepared under the conditions using chiral organogel systems derived from 1,2-diaminocyclohexane.<sup>6</sup> However, the existence of the residue of organogel in the helical silica is not probable by the following reasons: (i) any carbon or nitrogen atom was not detected by the elemental analysis (chamber temp. 950°C) of calcinated (500°C) right-handed helical silica used in Table 1 (entries 2, 4 and 6. Anal. found: C, 0.00; H, 1.69; N: 0.00). The value of hydrogen content showed good correlation to the representative values (3–6) of ignition-loss of amorphous silica prepared by sol-gel method; (2) when *trans*-1,2-bis(dodecanoylamino)cyclohexane, the template molecule, was independently heated at 500°C under an ambient atmosphere, the substrate evaporated with partial decomposition and no substrate was remained as the residue; (3) when helical silica was prepared, calcination at 500°C was employed; (4) the helical silica was calcinated at 500°C again just before use. Therefore, the chirality of inorganic architecture is considered to contribute to the asymmetric induction.

The transmission electron microscope (TEM) pictures of helical silica show that the silica not only possesses supramolecular helical structure but also has inner tubular helicity with the same handedness.<sup>6b,10</sup> In addition, the presence of chiral sites imprinted by the chiral organogel is also plausible.<sup>2c</sup> Although it is not clear whether the helicity and/or the imprinted chiral site of silica which is/are responsible for the asymmetric induction, right- or left-handed helical silica induces an imbalance of enantiomers of (the isopropylzinc alkoxide of) 5-pyrimidyl alkanol **2** with high ee in conjunction with the subsequent asymmetric autocatalysis.<sup>7,8</sup>

In summary, we have demonstrated a highly enantioselective synthesis using artificially tuned chiral inorganic amorphous material, right- and left-handed helical silica. We believe that the results reported here significantly enhance the opportunities for artificially tuned chiral inorganic materials whose chirality is based on their frameworks.

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