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Asymmetric Autocatalysis Initiated by Chiral Ephedrine Immobilized on Silica Gel in a Diisopropylzinc Addition to Pyrimidine-5-carbaldehyde

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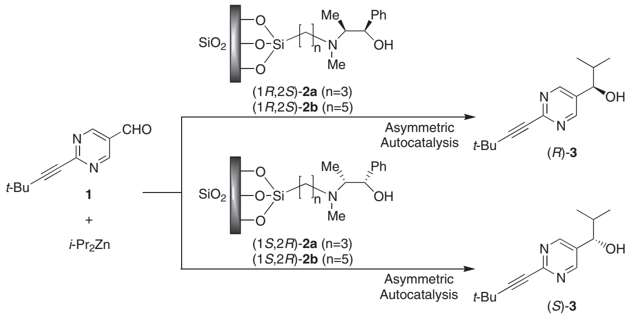
5-Pyrimidyl alkanol with up to 97% ee was formed using chiral ephedrine immobilized on silica gel in the enantioselective addition of diisopropylzinc to pyrimidine-5-carbaldehyde in conjunction with asymmetric autocatalysis.

The enantioselective addition of dialkylzincs to aldehydes using chiral catalysts is a useful method for the preparation of enantioenriched *sec*-alcohols.[1] Homogeneous chiral catalysts such as β-amino alcohols have been employed most often. Although heterogeneous chiral catalysts have been developed for the enantioselective addition of dialkylzincs to aldehydes, most of them are polystyrene-bound and organic polymer based chiral catalysts.[1,2] Meanwhile, silica gel is an easily available inorganic compound and has been widely used as the chiral and achiral stationary phases in chromatographic separations. However, it has rarely been employed as a support of chiral catalysts in asymmetric carbon–carbon bond forming reactions.

In 1990, we reported the first use of silica gel as a support of chiral catalysts for the enantioselective addition of dialkylzincs to aldehydes.[3] Since then, chiral catalysts supported on mesoporous silica and silica gel have been developed by several groups.[4] However, compared to the chiral catalysts bound to organic polymers[1,2] and dendrimers,[5] the enantioselectivity observed in the dialkylzinc addition to aldehydes has remained low to moderate by the use of these chiral catalysts immobilized on silica gel. Meanwhile, we have been studying asymmetric autocatalysis with amplification of ee[6,7] in which the chiral product acts as the chiral catalyst for its own production.

We here report a successful use of chiral inorganic–organic hybrid materials, i.e., ephedrine immobilized on silica gel, as a chiral catalyst and initiator in asymmetric autocatalysis: highly enantioenriched 5-pyrimidyl alkanol with the corresponding absolute configurations to those of chiral inorganic–organic hybrid materials was achieved.

Chiral inorganic–organic hybrid materials were prepared as follows: activated silica gel was functionalized with either 3-chloropropylsilyl or 5-bromopentylsilyl groups.[3,8] The subsequent immobilization of (1*R*,2*S*)- and (1*S*,2*R*)-ephedrine on the functionalized silica gels afforded chiral inorganic–organic hybrid materials **2a** and **2b** bearing tri- and penta-methylene chains, respectively.



Scheme 1. Highly enantioselective asymmetric autocatalysis using ephedrine immobilized on silica gel.

Table 1. Highly Enantioselective Synthesis of Pyrimidyl Alkanol **3** in the Presence of Inorganic–Organic Hybrid Materials **2a**, **b**[a)]

Entry	Hybrid silica	Pyrimidyl alkanol **3**		
		Yield/%	Ee/%[b)]	Config.
1	(1*R*,2*S*)-**2a**	86	93	*R*
2	(1*R*,2*S*)-**2a**	90	92	*R*
3	(1*S*,2*R*)-**2a**	91	95	*S*
4	(1*S*,2*R*)-**2a**	93	93	*S*
5	(1*R*,2*S*)-**2b**	86	97	*R*
6	(1*R*,2*S*)-**2b**	87	90	*R*
7	(1*S*,2*R*)-**2b**	84	93	*S*
8	(1*S*,2*R*)-**2b**	85	93	*S*
9[b)]	(1*S*,2*R*)-**2b**	88	95	*S*

a) For detailed reaction conditions, see the Experimental. b) Recovered hybrid silica **2b** from Entry 8 was used.

In the presence of chiral inorganic–organic hybrid materials, the enantioselective addition of i-Pr_2Zn to 2-alkynylpyrimidine-5-carbaldehyde **1** was examined (Scheme 1). As shown in Table 1, in the presence of (1*R*,2*S*)-**2a**, (*R*)-5-pyrimidyl alkanol **3** with 92–93% ee was formed (Entries 1 and 2). In sharp contrast, in the presence of (1*S*,2*R*)-**2a**, (*S*)-5-pyrimidyl alkanol **3** with 93–95% ee was obtained in 91–93% yields (Entries 3 and 4). The length of the methylene chains of inorganic–organic hybrid materials didn't have a considerable effect on the enantiomeric excess of product **3**. The reaction in the presence of hybrid silica (1*R*,2*S*)-**2b** gave (*R*)-5-pyrimidyl alkanol **3** with 90–97% ee (Entries 5 and 6), whereas the reaction in the presence of (1*S*,2*R*)-**2b** gave (*S*)-5-pyrimidyl alkanol **3** with 93% ee (Entries 7 and 8). As shown in Table 1, the reproducibility of the reaction is confirmed by 4 pairs of experiments carried out under the same conditions (Entries 1, 2 and 3, 4 and 5, 6 and 7, 8). Hybrid silica is recoverable and can be used without any loss of enantioselectivity (Entries 8 and 9).

In summary, we demonstrated a highly enantioselective asymmetric autocatalysis in the presence of chiral inorganic–organic hybrid materials. 5-Pyrimidyl alkanol with up to 97% ee was obtained with the absolute configuration corresponding to that of the hybrid silica used as a chiral initiator.

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Experimental

Silica gel 60 (0.063–0.210 mm) (70–230 mesh ASTM) was purchased from Kanto. Chiral hybrid silica **2a** was synthesized according to the literature.[3,8]

Preparation of (5-Bromopentyl)trimethoxysilane: 2-Propanol solution (0.6 mL) of hydrogen hexachloroplatinate hexahydrate (0.06 g, 0.12 mmol) was added to the mixture of trimethoxysilane and 5-bromo-1-pentene at 0 °C. The mixture was refluxed at 140 °C for 7 d, and was cooled to r.t. (5-Bromopentyl)trimethoxysilane was obtained by distillation. A colorless oil; 13.34 g, yield 30%; bp 110 °C (2 mmHg). ^{1}H NMR (CDCl$_3$) δ 0.65 (2H, m), 1.45 (4H, m), 1.84 (2H, m), 3.40 (2H, t, $J = 6.8$ Hz), 3.57 (9H, s); ^{13}C NMR (75 MHz, CDCl$_3$) δ 9.0, 21.9, 31.5, 32.4, 33.8, 50.5; IR (neat) 2949, 1458, 1192, 1091 cm^{-1}; Anal. Found: C, 35.60; H, 7.02%. Calcd for $C_8H_{19}BrO_3Si$: C, 35.43; H, 7.06%.

Preparation of (5-Bromopentyl)silyl-Functionalized Silica Gel: (5-Bromopentyl)trimethoxysilane immobilized on silica gel was prepared from silica gel (silica gel was activated by refluxing in concd. hydrochloric acid for 4 h)[9] and (5-bromopentyl)trimethoxysilane according to a literature procedure.[8] Anal. Found: C, 7.64; H, 1.64%.

Preparation of (1*R*,2*S*)- or (1*S*,2*R*)-Ephedrine Immobilized on Silica Gel 2b: The chiral hybrid silica **2b** was prepared by the reaction of (5-bromopentyl)silyl-functionalized silica gel (2 g) and (1*R*,2*S*)- or (1*S*,2*R*)-ephedrine (0.582 g, 3.5 mmol), respectively, in refluxing toluene for 20 h in the presence of triethylamine (0.49 mL, 3.5 mmol). After cooling the reaction mixture, **2b** was collected by filtration, washed with ether and methanol, and dried in vacuo at 40 °C for 3 h. Chiral hybrid silica **2b** was obtained (1.65 g). Elemental analysis showed that 0.60–0.63 mmol of ephedrine was immobilized on 1 g of **2b**. Anal. Found: C, 17.06; H, 2.73; N, 0.88%.

Representative Procedure for the Enantioselective Addition of Diisopropylzinc to Pyrimidine-5-carbaldehyde in the Presence of Chiral Hybrid Silica (1*S*,2*R*)-2b (Table 1, Entry 7): To an ice cooled mixture of hybrid silica (1*S*,2*R*)-**2b** (60 mg, ephedrine content: 0.63 mmol/g) and a toluene solution (1.0 M) of *i*-Pr_2Zn (0.12 mmol) was added a toluene (0.1 mL) solution of aldehyde **1** (4.7 mg, 0.025 mmol) over a period of 30 min. The mixture was stirred for 16 h at 0 °C. Toluene (1.9 mL), *i*-Pr_2Zn (0.2 mmol, 0.2 mL of 1.0 M toluene solution) and a toluene (1.0 mL) solution of aldehyde **1** (18.8 mg, 0.10 mmol) were added successively, and the reaction mixture was stirred for 4 h. Toluene (7.5 mL), *i*-Pr_2Zn (0.8 mmol, 0.8 mL of 1.0 M toluene solution) and a toluene (2.0 mL) solution of aldehyde **1** (75.3 mg, 0.40 mmol) were then added successively, and the mixture was stirred at 0 °C for an additional 3 h. The reaction was quenched by adding 1 M hydrochloric acid (2.2 mL), and the mixture was neutralized by adding satd. aq. sodium hydrogencarbonate (6.6 mL). The mixture was filtered using 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 (*S*)-pyrimidyl alkanol **3** with 93% ee in an isolated yield of 84% (0.103 g).

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