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Enantioselective synthesis induced by chiral epoxides in conjunction with asymmetric autocatalysis

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Abstract—5-Pyrimidyl alkanol with an enantiomeric excess of up to 96% was formed using chiral epoxides as a chiral initiator in the enantioselective addition of diisopropylzinc to pyrimidine-5-carbaldehyde, in conjunction with asymmetric autocatalysis.

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1. Introduction

Chiral epoxides are useful chiral building blocks for the synthesis of biologically important compounds.[1] In recent years, various methods have been developed for the preparation of chiral epoxides.[2] However, to the best of our knowledge, chiral epoxides have rarely been used successfully as chiral ligands or catalysts in asymmetric synthesis.

Recently, high Miller index metal surfaces, which are chiral in nature, have attracted much attention, because of their possible use as heterogeneous asymmetric catalysts.[3] Their enantiospecific properties have been reported in, for example, the chiral adsorption or desorption of organic compounds.[3,4]

We have been studying asymmetric autocatalysis with the amplification of enantiomeric excess, in which a chiral product acts as the chiral catalyst for its own production.[5,6] We thought that asymmetric autocatalysis initiated by propylene oxide with very low ee correlates the chirality of a metal surface and that of an organic compound with very high ee: The discrimination of chiral propylene oxide has been reported in the desorption from a chiral metal surface.[7]

2. Results and discussion

Herein, we report on the use of chiral propylene oxide and styrene oxide, which are readily available, as chiral inducers in the highly enantioselective synthesis of a pyrimidyl alkanol by the enantioselective addition of diisopropylzinc (i-Pr_2Zn) to 2-alkynylpyrimidine-5-carbaldehyde (Scheme 1).

The enantioselective addition of i-Pr_2Zn to 2-(2-*tert*-butylethynyl)pyrimidine-5-carbaldehyde **1** was examined in the presence of chiral propylene oxide. As shown in Table 1, (*S*)-5-pyrimidyl alkanol **2** with 96% ee was obtained in 86% yield in the presence of (*R*)-(+)-propylene oxide **3** with 97% ee (entry 1). On the other hand, in the presence of (*S*)-(−)-**3** with 97% ee, the opposite enantiomer, (*R*)-**2** with 94% ee was formed in 78% yield (entry 2). Thus, the absolute configurations of the resulting 5-pyrimidyl alkanols **2** depended on that of epoxide **3** used. Using **3** with a moderate ee as an inducer yielded 5-pyrimidyl alkanol **2** with high ee (89–92% ee) (entries 3 and 4). Even epoxide **3** with only 3% and 2% ee were found to serve as chiral initiators in the asymmetric autocatalysis, producing (*S*)-**2** and (*R*)-**2** with 79% and 74% ee, respectively (entries 9 and 10).

Next, the enantioselective addition of i-Pr_2Zn to 2-alkynylpyrimidine-5-carbaldehyde **1** in the presence of chiral styrene oxide **4** was examined. The results are summarized in Table 2. (*R*)-(+)-Styrene oxide **4** with >99.5% ee, used as a chiral initiator, gave (*S*)-**2** with 91% ee (entry 1) and (*S*)-(−)-**4** gave (*R*)-**2** with 92% ee (entry 2) (molar ratio. **4**: aldehyde **1**: i-Pr_2Zn = 0.35: 1.05: 2.15). Even when a half amount of (*S*)-**4** with >99.5% ee was used, (*R*)-**2** with 90% ee was formed (entry 3). When epoxide **4** with moderate ee (58% and 59% ee) was used as inducer, (*S*)-**2** and (*R*)-**2** with 95% and 92% ee were obtained in 84% and 83% yields, respectively (entries 4 and 5). (*R*)- and (*S*)-**4** with only 2% ee

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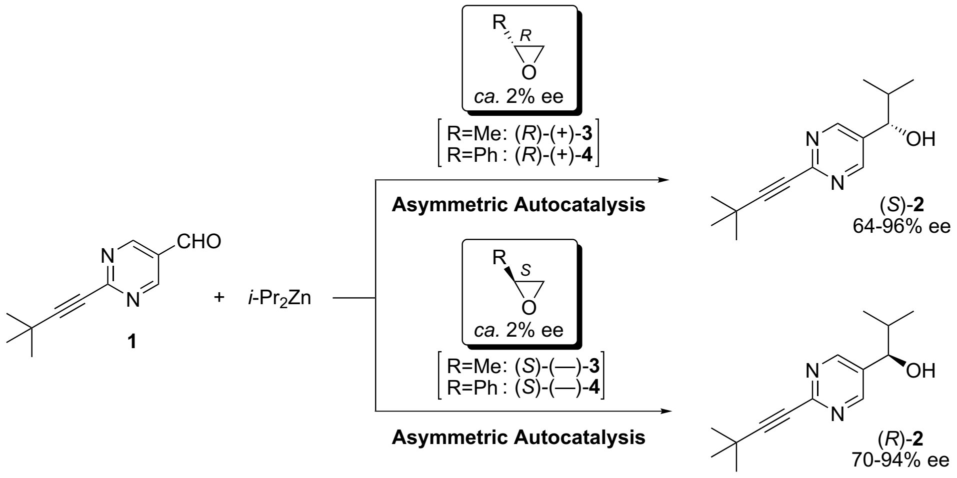

Scheme 1. Highly enantioselective asymmetric autocatalysis using chiral epoxide.

Table 1. Highly enantioselective synthesis of pyrimidyl alkanol **2** in the presence of propylene oxide **3**

Entry[a]	Propylene oxide **3**		Pyrimidyl alkanol **2**		
	Config.	Ee (%)[b]	Yield (%)[c]	Ee (%)[d]	Config.
1	(*R*)-(+)	97	86	96	*S*
2	(*S*)-(−)	97	78	94	*R*
3	(*R*)-(+)	60	84	89	*S*
4	(*S*)-(−)	57	83	92	*R*
5	(*R*)-(+)	20	81	88	*S*
6	(*S*)-(−)	18	82	89	*R*
7	(*R*)-(+)	6	87	79	*S*
8	(*S*)-(−)	5	87	70	*R*
9	(*R*)-(+)	3	85	79	*S*
10	(*S*)-(−)	2	86	74	*R*

[a] Molar ratio. Propylene oxide **3**:aldehyde **1**:*i*-Pr$_2$Zn = 0.35:1.05:2.15. The reactions were run at 0 °C.

[b] The ee value was determined by chiral HPLC analysis of 1-(naphthalen-2-ylthio)propan-2-ol obtained from the ring opening reaction of **3** with 2-naphthalenethiol.[8]

[c] Isolated yield.

[d] Ee was determined by HPLC analysis using a chiral stationary phase (Chiralcel OD).

induced the generation of (*S*)-**2** with 64% ee and (*R*)-**2** with 74% ee, respectively (entries 11 and 12).

In a typical experiment (Table 2, entry 12), *i*-Pr$_2$Zn (0.15 mL of 1.0 M toluene solution, 0.15 mmol) was added dropwise to a toluene (1.0 mL) solution of (*S*)-styrene oxide **4** (40 μL, 0.35 mmol, 2% ee) and aldehyde **1** (9.4 mg, 0.05 mmol) over a period of 30 min at 0 °C. After the mixture was stirred for 6 h, toluene (3.6 mL) and *i*-Pr$_2$Zn (0.4 mL of 1.0 M toluene solution, 0.4 mmol) were added, and the mixture was stirred for a further 15 min. Then aldehyde **1** (37.6 mg, 0.20 mmol in 1.0 mL toluene) was added dropwise over a period of 30 min at 0 °C. After this mixture was stirred for 2 h, toluene (14.4 mL) and *i*-Pr$_2$Zn (1.60 mL of 1.0 M toluene solution, 1.60 mmol) were added, and the mixture was stirred for 15 min. Then aldehyde **1** (150.6 mg, 0.80 mmol in 1.0 mL toluene) was added dropwise over a period of 30 min at 0 °C, and the mixture was stirred for 2 h. The reaction was quenched by the addition of 1 M hydrochloric acid (4.4 mL), and the solution was made alkaline by the addition of saturated aqueous NaHCO$_3$ (13.2 mL). The mixture was filtrated using Celite, and the filtrate was extracted using ethyl acetate. The combined organic layers were dried over anhydrous sodium sulfate and evaporated in vacuo. Purification of the residue using silica gel thin-layer chromatography (developing solvent, hexane:ethyl acetate = 2:1, v/v) gave (*R*)-5-pyrimidyl alkanol **2** with 74% ee in 83% yield.

Table 2. Highly enantioselective synthesis of pyrimidyl alkanol **2** in the presence of homochiral styrene oxide **4**

Entry[a]	Styrene oxide **4**		Pyrimidyl alkanol **2**		
	Config.	Ee (%)[b]	Yield (%)[c]	Ee (%)[b]	Config.
1[d]	(*R*)-(+)	>99.5	86	91	*S*
2	(*S*)-(−)	>99.5	78	92[e]	*R*
3[f]	(*S*)-(−)	>99.5	89	90	*R*
4	(*R*)-(+)	58	84	95	*S*
5	(*S*)-(−)	59	83	92	*R*
6	(*R*)-(+)	19	88	87	*S*
7	(*S*)-(−)	19	80	90	*R*
8	(*S*)-(−)	11	89	82	*R*
9	(*R*)-(+)	5	89	80	*S*
10	(*S*)-(−)	5	83	80	*R*
11	(*R*)-(+)	2	81	64	*S*
12	(*S*)-(−)	2	83	74	*R*

[a] Unless otherwise noted, molar ratio of styrene oxide **4** : aldehyde **1**:*i*-Pr$_2$Zn = 0.35:1.05:2.15 and the reactions were run at 0 °C.

[b] Ee was determined by HPLC analysis using a chiral stationary phase (Chiralcel OD).

[c] Isolated yield.

[d] To determine the amount of the remaining styrene oxide, the reaction was carried out under the existence of naphthalene as an internal standard under the same conditions. By comparing the ratio of styrene oxide to that of naphthalene before and after the reaction, it was found that 99% of styrene oxide remained. HPLC analysis was performed using chiral column (Chiralcel OD-H, eluent: hexane, 1.0 mL/min).

[e] When this reaction was carried out at room temperature, (*R*)-**2** with 8% ee was obtained.

[f] Molar ratio. **4**:aldehyde **1**:*i*-Pr$_2$Zn = 0.175:1.05:2.15.

3. Conclusion

In summary, we have described a highly enantioselective asymmetric autocatalysis in the presence of chiral propylene oxide and styrene oxide. 5-Pyrimidyl alkanol with an ee up to 96% ee was obtained, with the absolute configuration corresponding to that of the propylene oxide and styrene oxide used as the chiral inducers.

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