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# Chiral secondary alcohol-induced asymmetric autocatalysis: correlation between the absolute configuration of the chiral initiators and the product

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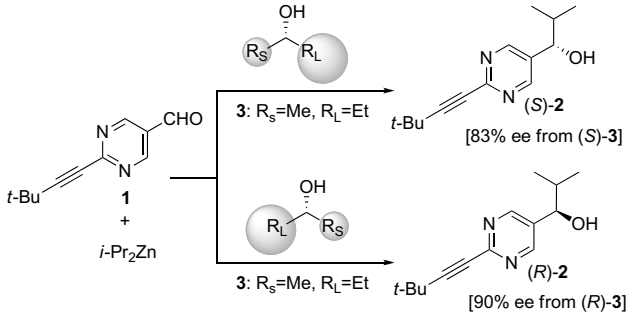
**Abstract**—In the presence of various chiral secondary alcohols as chiral initiators, an enantioselective alkylation of a pyrimidine-5-carbaldehyde using diisopropylzinc was examined: a pyrimidyl alkanol was obtained in high yield and enantiomeric excess. The correlation between the absolute configuration of the chiral secondary alcohols and the pyrimidyl alkanol is discussed.


## 1. Introduction

When the alkylation of a prochiral carbonyl compound is examined in the presence of a small amount of a chiral substance, an enantiomeric imbalance most certainly appears in the alkylated product. In most cases, however, the enantiomeric imbalance (enantiomeric excess) is very slight and a commonly used apparatus, such as HPLC using chiral stationary phase, cannot detect it. We have comprehensively studied an asymmetric autocatalysis with the amplification of the enantiomeric excess in the enantioselective alkylation of pyrimidine-5-carbaldehyde using diisopropylzinc (*i*-$Pr_2Zn$), in which a slight enantiomeric imbalance is drastically amplified by the consecutive asymmetric autocatalytic reaction,[1–3] its mechanism study using physical models has been reported by several groups including us.[4] When the asymmetric autocatalytic reaction is examined in the presence of a chiral substance (we named it as a 'chiral initiator'), a slight enantiomeric imbalance could be induced, then it is amplified by the consecutive asymmetric autocatalysis, finally highly enantiomerically enriched pyrimidyl alkanol is obtained. The absolute configuration of the product is dependent upon that of the chiral initiator.[5,6]

In fact, when the isopropylation of 2-(*tert*-butylethynyl) pyrimidine-5-carbaldehyde **1** was examined in the presence of (*S*)-2-butanol **3** with ca. 0.1% ee, (*S*)-pyrimidyl alkanol **2** with 83% ee was obtained. (*R*)-2-Butanol **3** surely induced (*R*)-pyrimidyl alkanol **2** (Scheme 1). These correlations between the absolute configuration of the chiral secondary alcohol and pyrimidyl alkanol **2** are derived from the chirality in 2-butanol **3**, that is, discrimination of the bulkiness of the ethyl and methyl groups (Et > Me).

In other words, the correlation of the absolute configurations of chiral secondary alcohols and product **2** elucidates the steric discrimination of the substituents ($R_L > R_S$) of a




**Scheme 1.** The concept of steric discrimination in the enantioselective alkylation of **1** using chiral secondary alcohols as chiral initiators.

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chiral secondary alcohol in the present enantioselective alkylation (Scheme 1). We here examined the enantioselective isopropylation of pyrimidine-5-carbaldehyde **1** using various chiral secondary alcohols as chiral initiators. The correlation of the absolute configurations is comprehensively studied and the discrimination on the basis of the bulkiness of various substituents is discussed.

## 2. Results and discussion

We prepared chiral secondary alcohols of ca. 10% ee and used them as chiral initiators of asymmetric autocatalysis. First, alkyl-substituted benzyl alcohols were submitted to the asymmetric autocatalysis as the chiral initiator[7] (Table 1). When the alkylation was examined in the presence of (*S*)-methyl phenyl carbinol **4**, (*S*)-pyrimidyl alkanol **2** was obtained in high ee and yield (entry 1) and vice versa (entry 2).[8] The correlation [(*S*)-secondary alcohol induces (*S*)-**2**] was the same as 2-butanol **3**. On the contrary, in the case of isopropyl phenyl carbinol **5**,[9] the correlation was opposite: (*S*)-secondary alcohol **5** induced (*R*)-**2** (entries 3 and 4). When the isopropyl group was replaced by a more bulky *tert*-butyl group, that is, *tert*-butyl phenyl carbinol **6**[10] was subjected to the asymmetric autocatalysis, the correlation was the same as the results of **5** (entries 5 and 6). When alcohol **7**[11] with a cyclopropyl group instead of isopropyl substitution was used, the correlation was the opposite (entries 7 and 8), which means that the correlation was the same as the case of methyl phenyl carbinol **4**.

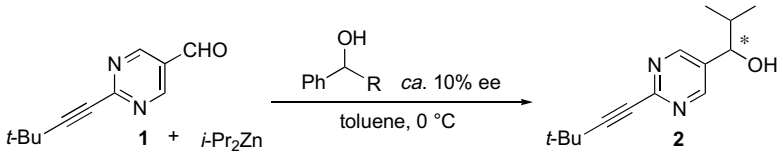
To ensure the absolute configuration of alcohol **7**, X-ray single crystal analysis was performed to the crystalline derivative. (−)-Alcohol **7** obtained from the resolution, was transformed into the ferrocene carboxylate. The X-ray crystal structure shown in Figure 1 clearly indicated the absolute configuration of (−)-**7** to be (*R*) (CCDC 618865).

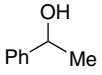
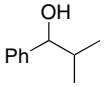
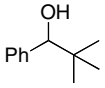
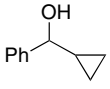
Based on the concept depicted in Scheme 1, these results in Table 1 could be explained as follows: in the alkylation of pyrimidine-5-carbaldehyde **1** using *i*-$Pr_2Zn$, phenyl was distinguished as a more bulky group than methyl and cyclopropyl, and as a less bulky one than isopropyl and *tert*-butyl (Scheme 2).[13] Therefore, isopropyl is surely more bulky than cyclopropyl, as expected.

Next, the unsaturated group-substituted benzyl alcohols were used (Table 2): in the case of phenyl isopropenyl carbinol **8**,[14] the correlation was the same as phenyl isopropyl carbinol **5** (entries 1 and 2). Conversely, phenyl vinyl carbinol **9**[15] brought about the opposite correlation (entries 3 and 4). These results imply that branched substituents play a pivotal role for the bulkiness (Scheme 3).

Finally, β-branched alkyl group-substituted benzyl alcohols were examined (Table 3): when isobutyl phenyl carbinol **10**[16] was used as a chiral initiator, (*S*)-alcohol **10** induced (*S*)-pyrimidyl alkanol **2** and the correlation was the same as methyl phenyl carbinol **4** (entries 1 and 2). Even if the isobutyl group was replaced with a more bulky

**Table 1.** Alkyl-substituted benzyl alcohols as chiral initiators




| Entry[a] | Chiral initiator[b] | | | Pyrimidyl alkanol **2** | |
|---|---|---|---|---|---|
| | | | ee (%) | ee[c,d] (%) | Yield[e] (%) |
| 1 |  | **4**[f] | 10 (*S*) | 93 (*S*) | 88 |
| 2 | | | 8 (*R*) | 96 (*R*) | 97 |
| 3 |  | **5** | 9 (*S*) | 94 (*R*) | 91 |
| 4 | | | 12 (*R*) | 92 (*S*) | 91 |
| 5 |  | **6** | 11 (*S*) | 80 (*R*) | 90 |
| 6 | | | 10 (*R*) | 87 (*S*) | 89 |
| 7 |  | **7** | 10 (*S*) | 88 (*S*) | 98 |
| 8 | | | 10 (*R*) | 96 (*R*) | 93 |

[a] The molar ratio of *sec*-alcohol–aldehyde **1**–*i*-$Pr_2Zn$ = 0.02:2.1:5.
[b] *sec*-Alcohol with ca. 10% ee was prepared by thorough mixing of optically active and racemic ones. Ee was determined by HPLC on a chiral stationary phase.
[c] The ee value was determined by HPLC on a chiral stationary phase (Daicel Chiralcel OD).
[d] See Ref. 12.
[e] Isolated yield.
[f] Enantiomerically pure and racemic **4** are commercially available.

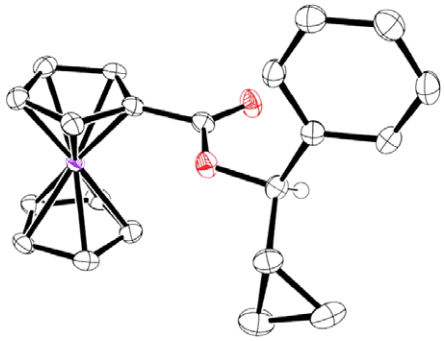
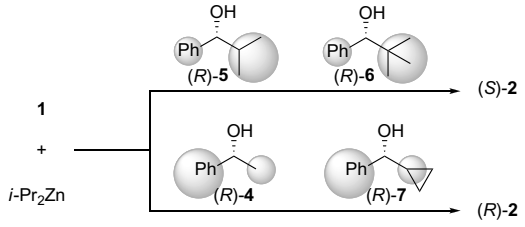
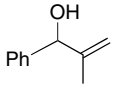
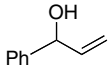


**Figure 1.** X-ray crystal structure of ferrocenyl derivative of (−)-cyclopropyl(phenyl)methanol **7**.

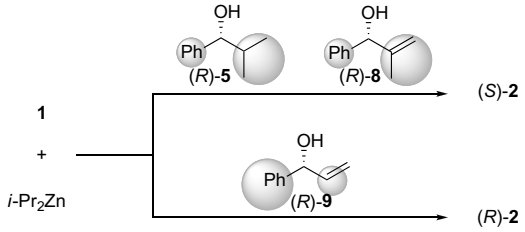



**Scheme 2.** The steric discrimination of Me, *i*-Pr, *t*-Bu, *c*-Pr versus Ph group.

**Table 2.** Unsaturated group-substituted benzyl alcohols as chiral initiators

| Entry[a] | Chiral initiator[b] | | Pyrimidyl alkanol **2**[c] | | |
|---|---|---|---|---|---|
| | | | ee (%) | ee[d] (%) | Yield (%) |
| 1 |  | **8** | 10 (*S*) | 94 (*R*) | 87 |
| 2 | | | 11 (*R*) | 86 (*S*) | 92 |
| 3 |  | **9** | 12 (*S*) | 97 (*S*) | 94 |
| 4 | | | 13 (*R*) | 96 (*R*) | 96 |

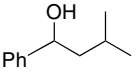
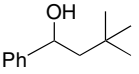
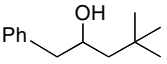
[a] See Table 1, footnote a.
[b] See Table 1, footnote b.
[c] See Table 1, footnote c and d.
[d] See Ref. 12.



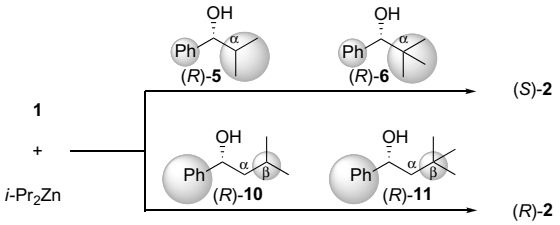

**Scheme 3.** The steric discrimination of isopropenyl and vinyl groups versus a Ph group.

neopentyl one using **11**,[17] the correlation did not change (entries 3 and 4). In order to keep the phenyl group at a distance, benzyl neopentyl carbinol **12**[18] was used but the correlation was retained (entries 5 and 6). These results imply that the branching at the α-position of the stereogenic center causes steric bulkiness while the influence of the branch at β-position is relatively small. (Scheme 4).

**Table 3.** β-Branched alkyl-substituted benzyl alcohols as chiral initiators

| Entry[a] | Chiral initiator[b] | | Pyrimidyl alkanol **2**[c] | | |
|---|---|---|---|---|---|
| | | | ee (%) | ee[d] (%) | Yield (%) |
| 1 |  | **10** | 10 (*S*) | 96 (*S*) | 92 |
| 2 | | | 10 (*R*) | 96 (*R*) | 96 |
| 3 |  | **11** | 12 (*S*) | 95 (*S*) | 90 |
| 4 | | | 8 (*R*) | 93 (*R*) | 97 |
| 5 |  | **12** | 12 (*S*) | 91 (*S*) | 89 |
| 6 | | | 13 (*R*) | 87 (*R*) | 87 |

[a] See Table 1, footnote a.
[b] See Table 1, footnote b.
[c] See Table 1, footnote c and d.
[d] See Ref. 12.




**Scheme 4.** The steric discrimination of isobutyl and neopentyl groups versus Ph group.

## 3. Conclusion

We have studied the asymmetric induction using various chiral secondary alcohols as chiral initiators in the alkylation of pyridine-5-carbaldehyde **1** by *i*-$Pr_2Zn$. Based on the correlation of the absolute configurations of 2-butanol **3** and pyrimidyl alkanol **2**, the bulkiness of various substituents was determined in comparison with the phenyl group. In conclusion, it can be ascertained that branching of the substituent and its position determines the bulkiness.

## Acknowledgement

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7. In a typical experiment, a secondary alcohol (0.02 mmol, ca. 10% ee) in a toluene (0.6 mL) and *i*-$Pr_2Zn$ (0.2 mL of 1 M toluene solution, 0.20 mmol) were stirred at 0 °C for 15 min, then aldehyde **1** (0.1 mmol) in toluene (0.4 mL) was added. After the reaction mixture was stirred for 1 h at 0 °C, toluene (1.5 mL) and *i*-$Pr_2Zn$ (1.0 mL of 1 M toluene solution, 1.0 mmol) were added and the combined mixture was stirred for 15 min. Aldehyde **1** (0.4 mmol) in toluene (1.0 mL) was added and the reaction mixture was stirred for additional 1 h at 0 °C. In the same manner, toluene (9.4 mL), *i*-$Pr_2Zn$ (3.8 mL of 1 M toluene solution, 3.8 mmol) and aldehyde **1** (1.60 mmol) in toluene (2.6 mL) were further added and the reaction mixture was stirred for 1 h. The reaction was quenched by the addition of 1 M HCl (5 mL) and *satd* $NaHCO_3$ (15 mL). The mixture was filtered using Celite, and the filtrate was extracted with AcOEt. The extract was dried over $Na_2SO_4$ and evaporated. Purification of the residue on silica gel TLC gave the pure alkanol **2**.
8. When the alkylation of the benzaldehyde was carried out using *i*-$Pr_2Zn$ in the presence of chiral 2-butanol **3**, only a trace amount of isopropylated product could be obtained while asymmetric induction could not be detected. In order to determine the stereochemical correlation between the chiral initiator and alkylated product, asymmetric autocatalysis is necessary for amplification of ee.
9. Compound (*S*)-**5** with 90% ee was prepared by asymmetric isopropylation of benzaldehyde. See: Soai, K.; Hayase, T.; Takai, K.; Sugiyama, T. *J. Org. Chem.* **1994**, *59*, 7908–7909.
10. (*S*)-(−)-**6** of 16% ee was prepared by asymmetric reduction of 2,2-dimethyl-1-phenylpropan-1-one. See: Clark, D. R.; Moscher, H. S. *J. Org. Chem.* **1970**, *35*, 1114–1118.
11. Commercially available DL-**7** was resolved into enantiomers by HPLC on a chiral stationary phase (Daicel Chiralcel OD).
12. The ee was amplified to >99.5% ee by further asymmetric autocatalysis using the obtained pyrimidyl alkanol as a chiral catalyst (Ref. 3c).
13. Both Taft's steric parameter and the *A*-value show that phenyl is bulkier than the isopropyl group. These results imply that the total effect of steric and electronic factors determined 'bulkiness' in the enantioselective alkylation using diisopropylzinc and the estimation of bulkiness discrimination is difficult using conventional steric values but the present system could achieve it.
14. DL-**8** was prepared according to the literature. See: (a) Marco, J. A.; Carda, M.; Rodríguez, S.; Castillo, E.; Kneeteman, M. N. *Tetrahedron* **2003**, *59*, 4085–4101; And it was resolved into two enantiomers by HPLC on a chiral stationary phase (Daicel Chiralcel OD). See also: (b) Dittmer, D. C.; Discordia, R. P.; Zhang, Y.; Murphy, C. K.; Kumar, A.; Petio, A. S.; Wang, Y. *J. Org. Chem.* **1993**, *58*, 718–731.
15. DL-**9** was prepared according to the literature. See: Briot, A.; Baehr, C.; Brouillard, R.; Wagner, A.; Mioskowski, C. *J. Org. Chem.* **2004**, *69*, 1374–1377, Then, it was resolved into two enantiomers by HPLC on a chiral stationary phase (Daicel Chiralcel OD).
16. (*S*)-**10** with 52% ee was synthesized by asymmetric reduction of *iso*-valerophenone according to the literature in Ref. 10. DL-**10** was prepared by $BH_3$-reduction of *iso*-valerophenone.
17. DL-**11** was prepared by $BH_3$-reduction of 3,3-dimethyl-1-phenylbutan-1-one and it was resolved into enantiomers by HPLC using a chiral column (Daicel Chiralcel OD). Compound (−)-**11** was determined to be *S*-isomer using modified Mosher method. See: Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092–4096.
18. DL-Neopentyl(phenylmethyl)methanol **12** was prepared according to the literature in Ref. 14a and DL-**12** was resolved into (−)- and (+)-isomers by HPLC using a chiral column (Daicel Chiralcel OD). (−)-Isomer was determined to be (*S*)-isomer using modified Mosher method. See the literature in Ref. 17.