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Asymmetric autocatalysis of 5-carbamoyl-3-pyridyl alkanols with amplification of enantiomeric excess

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Abstract

5-Carbamoyl-3-pyridyl alkanols with low e.e. act as asymmetric autocatalysts in the consecutive asymmetric autocatalytic addition of diisopropylzinc to 5-carbamoyl-3-pyridinecarbaldehydes. The e.e. of pyridyl alkanol amplified up to 88% e.e. without the need for any other chiral auxiliary.

Asymmetric autocatalysis[1] has received a growing interest as a new method for asymmetric synthesis in which a chiral product acts as a chiral catalyst for its own production.[2] In asymmetric autocatalysis, a chiral compound automultiplies without the need for any other chiral auxiliary. On the other hand, asymmetric synthesis with amplification of enantiomeric excess (e.e.) affords a product with higher e.e. than that of the catalyst.[3] If the asymmetric autocatalytic reaction amplifies the e.e. of the product, it may become a unique synthetic method for non-racemic chiral compounds.[1] It would also be important with regard to the problem of the origin(s) of chirality and the chemical process of homochirality of organic compounds.[4] However, the compounds which display asymmetric autocatalysis with amplification of e.e. are limited to only pyrimidyl[5a,c] and quinolyl alkanols.[5b]

We report herein that chiral 5-carbamoyl-3-pyridyl alkanols **2a**,**b** with low e.e.s automultiply with dramatic amplification of e.e. without using any other chiral auxiliary in the enantioselective alkylation of 5-carbamoylpyridine-3-carbaldehydes **1a**,**b** with diisopropylzinc (i-Pr_2Zn) (Scheme 1). The results are summarized in Table 1. When (*S*)-1-(5-*N*,*N*-diisopropylcarbamoyl-3-pyridyl)-2-methyl-1-propanol **2a** with 4% e.e. was used as an asymmetric autocatalyst (20 mol%)

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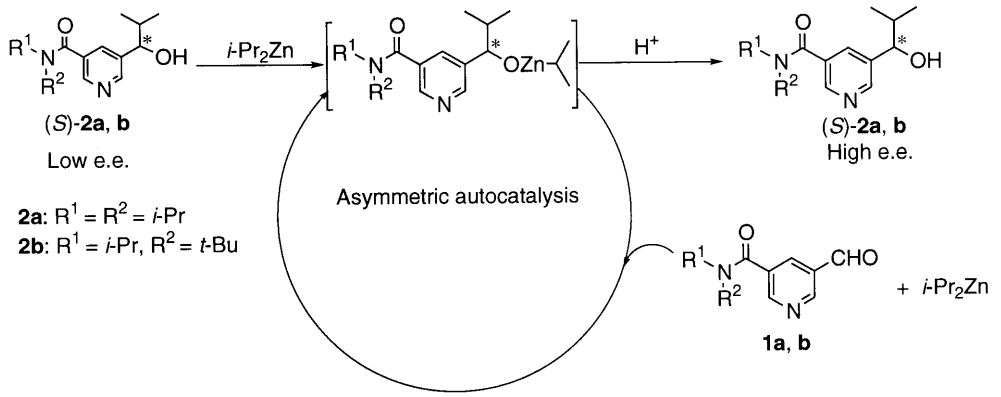

Scheme 1.

in the enantioselective addition of i-Pr_2Zn to 5-*N*,*N*-diisopropylcarbamoylpyridine-3-carbaldehyde **1a**, (*S*)-3-pyridyl alkanol **2a** with 14% e.e. was obtained as a mixture of the initial asymmetric autocatalyst **2a** and the newly formed product **2a** (entry 1). Thus, (*S*)-3-pyridyl alkanol **2a** with higher e.e. than that of the catalyst initially used was generated without the assistance of any other chiral auxiliary. This is the first report on the asymmetric autocatalytic reaction with amplification of e.e. using chiral pyridyl alkanols functionalized by amide groups.

One of the advantages of asymmetric autocatalysis is that the structures of the catalyst and the product are the same. Thus, a series of asymmetric autocatalytic reactions was examined successively using the chiral alkanol (*S*)-**2a** obtained from the reaction of one cycle as an asymmetric autocatalyst for the next cycle (entries 2–8). The e.e.s of the obtained (*S*)-**2a**, containing asymmetric autocatalyst **2a** and the newly formed **2a**, were increased stepwise by the consecutive asymmetric autocatalysis. During the first five consecutive asymmetric autocatalyses of **2a**, the e.e. of **2a** reached 84% and the major component (*S*)-**2a** in the initial asymmetric autocatalyst automultiplied by a factor of 587 times, whereas the minor component (*R*)-**2a** in the initial catalyst was only increased by a factor of 50 (Fig. 1). Further consecutive asymmetric autocatalysis enabled the e.e. of the (*S*)-3-pyridyl alkanol **2a** to reach 87–88% e.e. (entries 7 and 8). When (*S*)-3-pyridyl alkanol **2a** with 88% e.e. was employed as an asymmetric autocatalyst, the e.e. of the obtained alkanol was kept constant (entry 8). On the other hand, when (*R*)-3-pyridyl alkanol **2a** with 4% e.e. instead of (*S*)-**2a** was employed as an initial catalyst, the e.e. of the obtained (*R*)-alkanol **2a** after the consecutive asymmetric autocatalysis reached 86% e.e. (entries 9–17). These results show that 3-pyridyl alkanol **2a** with low 4% e.e. automultiplied with an amplification of e.e. (up to 86–88% e.e.) during the consecutive asymmetric autocatalysis.

The asymmetric autocatalytic reaction of **2b**, which has *t*-butyl and isopropyl substituents on the nitrogen atom of the carbamoyl group, also proceeded with amplification of e.e. Thus, the reaction of 5-(*N*-*t*-butyl-*N*-isopropylcarbamoyl)pyridine-3-carbaldehyde **1b** and i-Pr_2Zn using chiral (*S*)-pyridyl alkanol **2b** with 4% e.e. as an asymmetric autocatalyst gave (*S*)-pyridyl alkanol **2b** with 13% e.e. (entry 18). The e.e. of (*S*)-**2b** increased to 78% during the subsequent consecutive asymmetric autocatalytic reactions (entries 19–26).

A typical experimental procedure is as follows (Table 1, entry 3): After a mixture of (*S*)-**2a**[2d] (27.8 mg, 0.10 mmol) with 56% e.e., consisting of the (*S*)-isomer (21.7 mg, 0.078 mmol), the

Table 1
Consecutive asymmetric autocatalysis of chiral pyridylalkanol **2** with amplification of e.e.

Entry[a]	Asymmetric autocatalyst **2**	Asymmetric autocat. And newly formed **2**	Newly formed alkanol **2**	
	E.e. (%)	E.e. (%)[b]	Yield (%)[c]	E.e. (%)[c]
1	**2a** 4 (*S*)	14	**2a** 25	22 (*S*)
2	**2a** 14 (*S*)	56	**2a** 49	74 (*S*)
3	**2a** 56 (*S*)	77	**2a** 48	85 (*S*)
4	**2a** 77 (*S*)	82	**2a** 42	85 (*S*)
5	**2a** 82 (*S*)	84	**2a** 60	85 (*S*)
6	**2a** 84 (*S*)	86	**2a** 39	86 (*S*)
7	**2a** 86 (*S*)	88	**2a** 48	89 (*S*)
8	**2a** 88 (*S*)	87	**2a** 42	87 (*S*)
9	**2a** 4 (*R*)	11	**2a** 33	16 (*R*)
10	**2a** 11 (*R*)	25	**2a** 34	33 (*R*)
11	**2a** 25 (*R*)	52	**2a** 34	67 (*R*)
12	**2a** 52 (*R*)	66	**2a** 32	76 (*R*)
13	**2a** 66 (*R*)	76	**2a** 63	79 (*R*)
14	**2a** 76 (*R*)	83	**2a** 58	86 (*R*)
15	**2a** 83 (*R*)	84	**2a** 57	85 (*R*)
16	**2a** 84 (*R*)	86	**2a** 53	87 (*R*)
17	**2a** 86 (*R*)	86	**2a** 64	86 (*R*)
18[d]	**2b** 4 (*S*)	13	**2b** 54	16 (*S*)
19[d]	**2b** 13 (*S*)	22	**2b** 45	26 (*S*)
20[d]	**2b** 22 (*S*)	44	**2b** 68	50 (*S*)
21[d]	**2b** 44 (*S*)	51	**2b** 60	54 (*S*)
22[d]	**2b** 51 (*S*)	60	**2b** 78	62 (*S*)
23[d]	**2b** 60 (*S*)	73	**2b** 71	77 (*S*)
24[d]	**2b** 73 (*S*)	74	**2b** 66	74 (*S*)
25[d,e]	**2b** 74 (*S*)	77	**2b** 58	78 (*S*)
26[d,e]	**2b** 77 (*S*)	78	**2b** 75	78 (*S*)

[a] Unless otherwise noted molar ratio is as follows: asymmetric autocatalyst **2a**:aldehyde **1a**:*i*-Pr_2Zn = 0.2:1.0:1.2.
[b] Determined by HPLC analyses using a chiral column (Chiralcel OD).
[c] The amounts of the initial (*S*)- and (*R*)-enantiomers of the alkanol used as an initial asymmetric autocatalyst were subtracted from the obtained alkanol by calculation.
[d] Molar ratio: (*S*)-**2b**:**1b**:*i*-Pr_2Zn = 0.2:1.0:2.2.
[e] Cumene was used as a solvent.

(*R*)-isomer (6.1 mg, 0.022 mmol), and *i*-Pr_2Zn (0.6 ml of 1 M toluene solution, 0.6 mmol) in toluene (21.4 ml) was stirred for 20 min at 0°C, a toluene solution (3.0 ml) of aldehyde **1a** (117 mg, 0.5 mmol) was added at 0°C. The reaction mixture was stirred for 48 h at 0°C, then the reaction was quenched by the addition of 1 M hydrochloric acid (5 ml). Satd aq. sodium bicarbonate (15 ml) was added, and the mixture was filtered through Celite. The filtrate was extracted with ethyl acetate. The extract was dried over anhydrous sodium sulfate and evaporated under reduced pressure. Purification of the residue on silica gel TLC gave pyridyl alkanol **2a** (94.4 mg, 0.339 mmol), which contained the newly formed alkanol and the alkanol initially used as an asymmetric autocatalyst. HPLC analysis using a chiral column (Chiralcel OD, eluent: 3% 2-propanol in hexane; flow rate: 1.0 ml/min; 254 nm UV detector) showed that

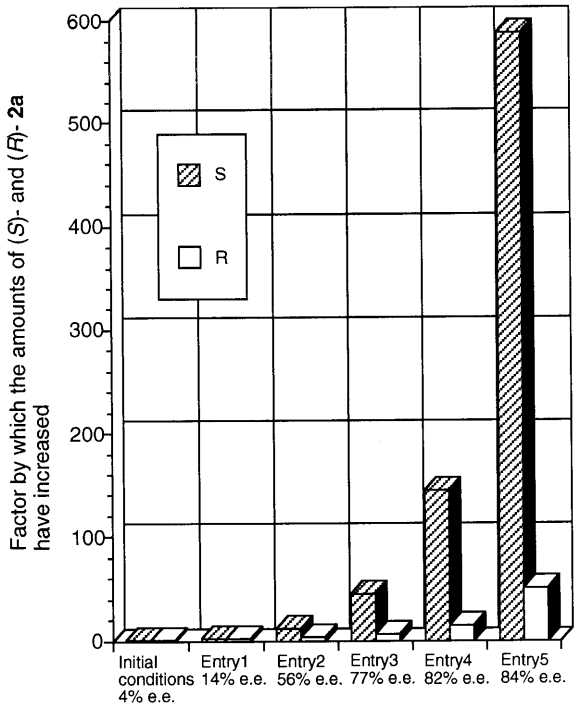

Figure 1. Change of the amounts of (*S*)- and (*R*)-**2a**

the enantiomeric purity of the obtained alkanol **2a** was 77% e.e. Therefore, the obtained alkanol **2a** contained (*S*)-isomer (0.3 mmol) and (*R*)-isomer (0.039 mmol). The amount of the newly formed alkanol **2a** was 0.339–0.1 = 0.239 mmol (48% yield), consisting of the major (*S*)-isomer (0.3–0.078 = 0.222 mmol) and the minor (*R*)-isomer (0.039–0.022 = 0.017 mmol). As a result, an enantiomeric purity of the newly formed alkanol (*S*)-**2a** was calculated as 85% e.e.

In summary, 5-carbamoyl-3-pyridyl alkanols **2a**,**b** with low e.e. automultiplied with amplification of e.e. in the asymmetric autocatalytic addition of *i*-Pr_2Zn to 5-carbamoylpyridine-3-carbaldehydes **1a**,**b**. The results described above enhance the utility of asymmetric autocatalysis because alkanols **2a**,**b** possess amide groups which can be transformed into various functional groups.

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