Asymmetric autocatalytic reaction of 3-quinolylalkanol with amplification of enantiomeric excess

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The enantiomeric excess of a chiral 3-quinolylalkanol increases from 8.9 to 88.1% by a series of asymmetric autocatalytic alkylations of quinoline-3-carbaldehyde using diisopropylzinc.

The homochirality of biomolecules,[1] *i.e.* L-amino acids in protein and D-sugars in DNA and RNA, and the ability of automultiplication,[2] *i.e.* self-replication at molecular, cellular and individual levels, are the most characteristic features of living organisms. Symmetry breakings by physical mechanisms are proposed[3] but their degrees of imbalance in chirality are usually very small. Thus an increase of enantiomeric enrichment would be necessary to explain the process leading to the homochirality.[1] The development of the asymmetric automultiplication reaction, in which a chiral molecule with low enantiomeric excess (ee) amplifies both its amount and ee without the assistance of any other chiral catalysts, may provide an experimental model for the chemical evolution.[4]

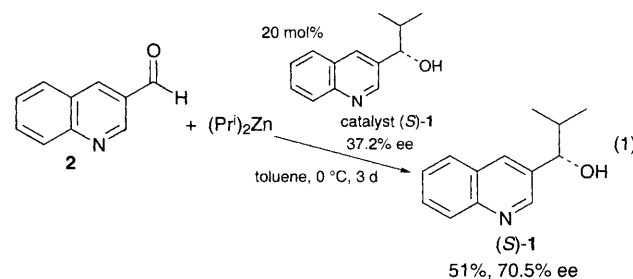**Table 1** Asymmetric autocatalytic amplification of the enantiomeric excess of (*R*)-1
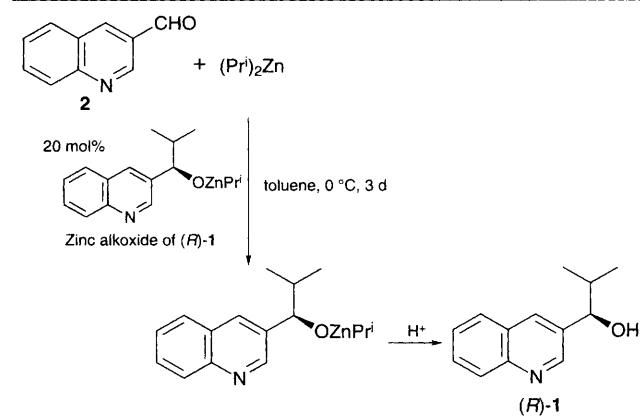
	Ee of autocatalyst 1 (%)	Yield of newly formed 1[b] (%)	Ee of obtained 1[c] (%)	Factor by which (*R*) and (*S*)-1 increased	
Entry[a]				(*R*)-1	(*S*)-1
	initial catalyst		8.9	1.0	0.83
1	8.9	56	43.3	5.0	2.0
2	43.3	67	67.0	25.3	5.0
3	67.0	52	81.6	99.5	9.8
4	81.6	72	85.5	467	35.1
5	85.5	78	86.2	1828	138
6	86.2	63	88.1	7628	486

[a] Molar ratio. Quinoline-3-carbaldehyde:(*R*)-1:(Pr^i)$_2$Zn = 1:0.2:1.2. [b] The yield of alkanol 1 after substracting that of 1 used as a catalyst from that of the total alkanol 1 obtained. [c] The ee of 1 obtained which includes both newly formed 1 and 1 used as a catalyst.

We recently reported that a chiral quinolylalkanol automultiplies in the alkylation of quinoline-3-carbaldehyde with almost no loss of optical purity.[5] This result prompted us to treat 2-methyl-1-(3-quinolyl)propan-1-ol 1 with low ee as an asymmetric autocatalyst; a catalytic amount (20 mol%) of the zinc alkoxide of (*R*)-3-quinolylalkanol 1 with only 8.9% ee [*R*-isomer:*S*-isomer = 54.5:45.5] was used as an asymmetric autocatalyst in the alkylation of quinoline-3-carbaldehyde 2 by diisopropylzinc.[6] As a result, (*R*)-3-quinolylalkanol 1 was obtained after acidic work-up in 76% yield and 43.3% ee [*R*-isomer:*S*-isomer = 71.6:28.4] as a mixture of the newly formed product 1 and the catalyst 1, which means that (*R*)-3-quinolylalkanol 1 with 8.9% ee generates itself with higher ee of 55.8% (Table 1 entry 1).† The asymmetric autocatalytic reaction was performed successively using the zinc alkoxide of the 3-quinolylalkanol 1, which was obtained by the last entry, as a catalyst for the next entry (entries 2–6). This series proved that the asymmetric alkylation using the zinc alkoxide of 3-quinolylalkanol 1 as an autocatalyst meaningfully enhances the small initial imbalance in chirality (from 8.9 up to 88.1% ee).

On the other hand, (*S*)-3-quinolylalkanol 1 of low ee (37.2% ee), instead of (*R*)-1, also automultiplied itself with significant amplification of enantiomeric excess of the (*S*)-isomer (70.5% ee) in the same reaction conditions as (*R*)-1 [eqn. (1)]. Thus each

(1)

enantiomer can act as an asymmetric autocatalyst with significant amplification of enantiomeric excess.

For several years, we[7] and others[8] have studied the asymmetric autocatalytic reaction but in each case the ee of the chiral products has always been lower than that of the chiral catalysts. The present study shows a very rare example of asymmetric autocatalysis with amplification of enantiomeric excess. The only other example of such an asymmetric autocatalyst is a 5-pyrimidylalkanol, which has two nitrogens on its aromatic ring.[9] The present paper discloses that only one nitrogen atom on the aromatic ring of the catalyst is required for the asymmetric autocatalyst with amplification of ee[10]
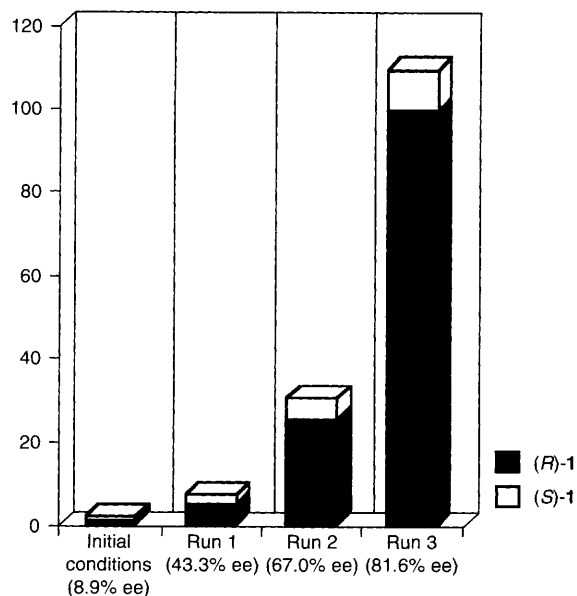
Fig. 1 The degree of amplification of (R)-**1** against that of (S)-**1** (corresponding to entries 1–3 in Table 1)

Footnote

† A typical experimental procedure and the calculation of newly formed alcohol **1** (Table 1, entry 1) are as follows: After a mixture of 3-quinolylalkanol (R)-**1** [40.3 mg (0.20 mmol), 8.9% ee, containing (R)-isomer (21.9 mg), (S)-isomer (18.4 mg)] in toluene (44.8 ml) and $(Pr^i)_2Zn$ (1.2 ml of 1 mol dm^{-3} toluene, 1.2 mmol) was stirred for 30 min at 0 °C, a toluene solution (4.0 ml) of aldehyde **2** (157.2 mg, 1.00 mmol) was added at 0 °C. The reaction mixture was stirred for 72 h at 0 °C, and then quenched by the addition of 1 mol dm^{-3} hydrochloric acid (5 ml) and sat. aq. $NaHCO_3$ (15 ml) at 0 °C. The mixture was filtered using Celite and the filtrate was extracted with ethyl acetate. The extract was dried over anhydrous sodium sulfate and evaporated to dryness under reduced pressure. Purification of the crude on silica gel TLC gave 3-quinolylalkanol **1** (153.3 mg), a mixture of the newly formed alcohol **1** and the catalyst alcohol (40.3 mg). HPLC analysis of the mixture using a chiral column (Daicel Chiralcel OD-H,

eluent: 2% propan-2-ol in hexane; flow rate: 1.0 ml min^{-1}; 254 nm UV detector) showed that it had an enantiomeric purity of 43.3% ee. Therefore the mixture contained (R)-isomer (109.9 mg) and (S)-isomer (43.4 mg). The amount of newly formed alcohol **1** was 113.0 mg (0.56 mmol, 56% yield), consisting of the major (R)-isomer (88.0 mg) and the minor (S)-isomer (25.0 mg). Therefore the newly formed (R)-enriched alcohol **1** had an enantiomeric purity of 55.8% ee.

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