Highly enantioselective synthesis of a chiral 3-quinolylalkanol by an asymmetric autocatalytic reaction

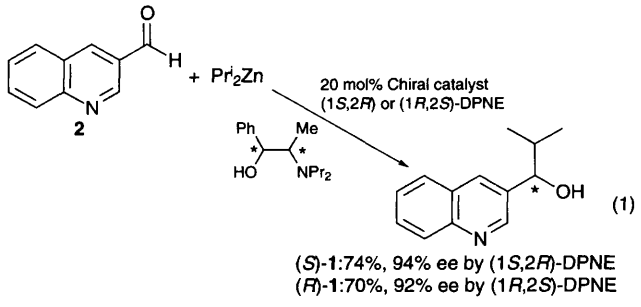
Takanori Shibata, Kaori Choji, Hiroshi Morioka, Tadakatsu Hayase and Kenso Soai*

Department of Applied Chemistry, Faculty of Science, Science University of Tokyo, Kagurazaka, Shinjuku-ku, Tokyo, 162, Japan

A catalytic amount of a chiral zinc alkoxide of 2-methyl-1-(3-quinolyl)propan-1-ol catalyses the enantioselective alkylation of quinoline-3-carbaldehyde by diisopropylzinc to afford 2-methyl-1-(3-quinolyl)propan-1-ol with the same configuration in high ee (up to 94%).

The quinoline alkaloid skeleton is fundamental in many natural products and their derivatives often have physiological or pharmacological assays.[1,2] For example, 3-quinolylalkanols are already known to have antimalarial activity[3] and remedial activity for Alzheimer's disease.[4] Therefore, the development of a synthesis for chiral 3-quinolylalkanol may provide a convenient tool for research into the screening of quinoline derivatives. We have studied the enantioselective alkylation of aldehydes using a catalytic amount of various chiral amino alcohols.[5]

Here we report that quinoline-3-carbaldehyde **2** is enantiomerically isopropylated in the presence of a catalytic amount of 2-methyl-1-(3-quinolyl)propan-1-ol **1**, which is also the product, without the use of a chiral catalyst with a different structure from that of the product. At first, this asymmetric autocatalytic reaction between aldehyde **2** and Pr^i_2Zn was examined using (*S*)-enriched 3-quinolylalkanol **1** [(*S*)-**1**][6],† [eqn. (1)], with 94% ee as a chiral catalyst (molar ratio of **1**:**2**:Pr^i_2Zn = 0.2:1.0:2.0, concentration of chiral catalyst was 3.0×10^{-2} mol dm^{-3}, toluene was used as solvent) (Table 1, run 1). As a result, 3-quinolylalkanol **1** was obtained as a mixture of the newly formed **1** and catalyst **1** which had an 83% (*S*)-isomer excess. This means that 3-quinolylalkanol **1** was formed in an (*S*)-isomer excess of 80%; in other words the chiral alcohol (*S*)-**1** regenerates itself with the same configuration (Scheme 1).



(1)

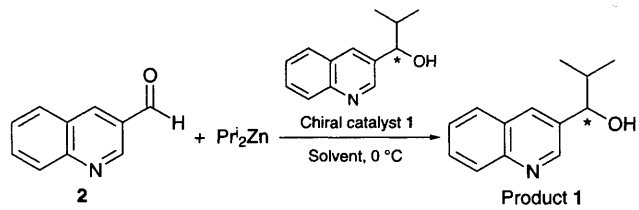
(*S*)-**1**:74%, 94% ee by (1*S*,2*R*)-DPNE
(*R*)-**1**:70%, 92% ee by (1*R*,2*S*)-DPNE

When the reaction was carried out in dilute solution {[(*S*)-**1**] = 0.4×10^{-2} mol dm^{-3}}, a remarkable increase in the optical purity of the product was observed (run 2). Moreover, a decrease in the amount of diisopropylzinc used (from 2.0 to 1.2 equiv.) increased the optical purity of the newly formed alcohol **1** to up to 90% ee (run 3).‡ Several different solvents (runs 3–6) were tried with cumene and the asymmetric autocatalytic reaction was found to proceed without any loss of optical purity to afford (*S*)-**1** with 94% ee (run 4).

3-quinolylalkanol with the opposite configuration [(*R*)-**1**] with 92% ee also automultiplied itself to afford (*R*)-**1** with 90% ee (run 7). Thus, the present asymmetric autocatalytic reaction system is applicable for the synthesis of each enantiomer of **1**.

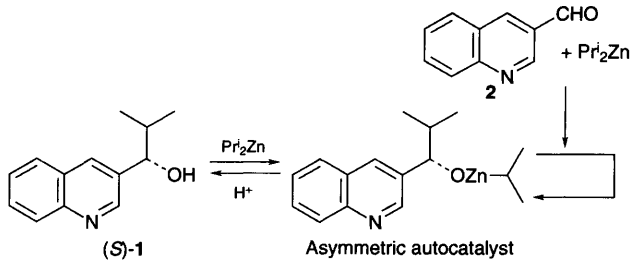
Over the past few years, we[7] and others[8] have studied asymmetric autocatalytic reactions because of their novelty and availability.[9] They are completely different from conventional asymmetric synthesis.[10] The asymmetric autocatalytic reaction possesses the following advantages over the conventional

Table 1 Asymmetric autocatalytic reaction of (*S*)- and (*R*)-**1**



Run[a]	Catalyst [ee (%)]	Solvent	*t*/h	Mol Ratio Pr^i_2Zn:**2**	Mixture of catalyst and product: Yield (%)[b]	Mixture of catalyst and product: ee (%)	Newly formed product: Yield (%)	Newly formed product: ee (%)
1[c]	(*S*)-**1** (94)	toluene	30	2.0	92	83	72	80
2	(*S*)-**1** (94)	toluene	48	2.0	85	88	65	86
3	(*S*)-**1** (94)	toluene	72	1.2	85	91	65	90
4	(*S*)-**1** (94)	toluene + P.E.[d]	72	1.2	68	91	48	90
5	(*S*)-**1** (94)	cumene	72	1.2	75	94	55	94
6	(*S*)-**1** (94)	CH_2Cl_2	72	1.2	<20	93	—	—
7	(*R*)-**1** (92)	toluene	72	1.2	80	89	60	90

[a] Unless otherwise noted, catalyst concentration 0.4×10^{-2} mol dm^{-3}. Molar ratio of chiral catalyst **1** against aldehyde **2** is 20 mol%. [b] The recovered chiral catalyst (20 mol%) is included. [c] Catalyst concentration 3.0×10^{-2} mol dm^{-3}. P.E. = petroleum ether.



Scheme 1 Asymmetric autocatalytic reaction of (*S*)-**1**

asymmetric reaction: (i) The chiral product does not need to be separated from the chiral catalyst and (ii) no other chiral catalyst than the product itself is required.

We thank Y. Aizu for his assistance with experiments. Financial support by a Grant-in-Aid for Scientific Research from the Ministry and Education, Science and Culture, the New Energy and Industrial Technology Development Organization (NEDO), and a SUT Special Grant for Research Promotion are gratefully acknowledged.

Footnotes

† *Preparation of chiral alcohol* (*S*)- *and* (*R*)-**1**. Enantioselective isopropylation[11] of quinoline-3-carbaldehyde **2** using a catalytic amount of a chiral amino alcohol, (1*S*, 2*R*)-*N*,*N*-dipropylnorephedrine (DPNE) gave (*S*)-2-methyl-1-(3-quinolyl)propan-1-ol **1** with high ee (93.6%) in 74% yield. Similarly, by using (1*R*, 2*S*)-DPNE instead of (1*S*, 2*R*)-DPNE, (*R*)-**1** with 91.5% ee was obtained in 70% yield. Compounds (*S*)- and (*R*)-**1** showed ^{1}H NMR, FTIR, and high resolution mass spectra consistent with the structure shown.

‡ *A typical experimental procedure and the calculation of newly formed alcohol* **1** (Table 1, run 3) were as follows: A mixture of alcohol (*S*)-**1** [40.4 mg (0.20 mmol), 93.6% ee, containing (*S*)-isomer (39.1 mg), (*R*)-isomer (1.3 mg)] in toluene (44.8 ml) and Pr^i_2Zn (1.2 ml of 1 mol dm^{-3} toluene solution, 1.2 mmol) was stirred for 30 min at 0 °C and then 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 saturated aq. $NaHCO_3$ (15 ml) at 0 °C. The mixture was filtered using Celite and the filtrate extracted with ethyl acetate. The extract was dried over anhydrous sodium sulfate and evaporated to dryness under reduced pressure. Purification by TLC on silica gel gave 3-quinolylalkanol **1** (170.4 mg) as a mixture of the newly formed alcohol **1** and the catalyst alcohol (40.4 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 90.7% ee. Therefore, the mixture contained (*S*)-isomer (162.4 mg) and (*R*)-isomer (8.0 mg). The amount of the newly formed alcohol **1** was 170.4–40.4 = 130.0 mg (0.65 mmol, 65% yield), consisting of the major (*S*)-isomer (162.4–39.1 = 123.3 mg) and the minor (*R*)-isomer (8.0–1.3 = 6.7 mg). Therefore the newly formed (*S*)-enriched alcohol **1** had an enantiomeric purity of 89.7% ee.

References

1 *Comprehensive Heterocyclic Chemistry*, ed. K. T. Potts, vol. 2, 984 Pergamon, Oxford, 1984.
2 Reviews of quinoline alkaloids; M. F. Grundon, *Nat. Prod. Rep.*, 1984, **1**, 195; 1985, **2**, 393; 1987, **4**, 415; 1988, **5**, 293; 1990, **7**, 131; J. P. Michael, *Nat. Prod. Rep.*, 1991, **8**, 53; 1992, **9**, 25.
3 G. Frauke and Z. Felix, *Arch. Pharm.*, 1979, **319**, 767; F. Rainer and S. W. Juergen, *Quant. Struct.-Act. Relat. Pharmcol., Chem. Biol.*, 1985, **4**, 51.
4 E. R. Charles and K. J. Thomas, *Eur. Pat. Appl.*, 258 755 (Chem. Abstr. **92**; 41 724 g).
5 K. Soai and S. Niwa, *Chem. Rev.*, 1992, **92**, 833; K. Soai and T. Hayase, *Yuki Gosei Kagaku Kyokaishi* (*J. Synth. Org. Chem. Jpn.*) 1995, **53**, 138; R. Noyori and M. Kitamura, *Angew. Chem., Int. Ed. Engl.*, 1991, **30**, 49.
6 The absolute configuration of (*S*)-**1** was estimated by the ^{1}H NMR analysis of the corresponding (*S*)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (MTPA) ester: I. Otani, T. Kusumi, Y. Kashman and H. Kakisawa, *J. Am. Chem. Soc.*, 1991, **113**, 4092.
7 K. Soai, S. Niwa and H. Hori, *J. Chem. Soc., Chem. Commun.*, 1990, 982; K. Soai, T. Hayase, C. Shimada and K. Isobe, *Tetrahedron: Asymmetry*, 1994, **5**, 789; K. Soai, T. Hayase and K. Takai, *Tetrahedron: Asymmetry*, 1995, **6**, 637; T. Shibata, H. Morioka, T. Hayase, K. Choji and K. Soai, *J. Am. Chem. Soc.*, 1996, **118**, 471.
8 A. H. Alberts and H. Wynberg, *J. Am. Chem. Soc.*, 1989, **111**, 7265; L. ShengJian, J. Yaozhong, M. Aiqiao and Y. Guishu, *J. Chem. Soc., Perkin Trans. 1*, 1993, 885.
9 For an excellent explanation of the importance of asymmetric automultiplication reaction, see H. Wynberg, *J. Macromol. Sci., Chem.*, 1989, **A26**, 1033.
10 *Catalytic Asymmetric Synthesis*, ed. I. Ojima, VCH, Weinheim, 1993; A. Togni and L. M. Venanzi, *Angew. Chem., Int. Ed. Engl.*, 1994, **33**, 497.
11 K. Soai, T. Hayase, K. Takai and T. Sugiyama, *J. Org. Chem.*, 1994, **59**, 7908.

Received, 20th December 1995; Com. 5/08265J