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Kinetic Resolution of Racemic Aldehydes by Enantioselective Alkylation

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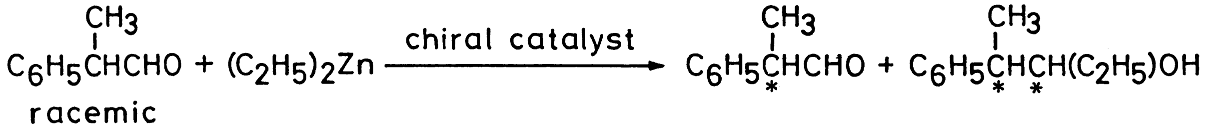
Kinetic resolution of racemic aldehydes proceeds by enantioselective ethylation catalyzed by chiral β-aminoalcohols, thus providing a convenient method for the preparation of chiral aldehydes.

Chemical kinetic resolution of racemic compounds is now recognized as one of indispensable methods for obtaining optically active compounds, and several successful reactions have been reported.$^{1)}$

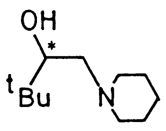
The catalytic asymmetric alkylation of various aldehydes with dialkylzinc has been intensively investigated by many researchers these years.$^{2)}$

Here we want to report the first example of kinetic resolution of racemic aldehydes based on enantioselective ethylation catalyzed by small amount of chiral β-aminoalcohols. We examined the reaction of racemic 2-phenylpropanal with diethylzinc in the presence of various chiral β-aminoalcohols, and the results are summarized in Table 1. It can be seen from the table that the k_f/k_s value (= k_{rel}) was highly dependent on catalysts, where k_f and k_s represent the fast and slow ethylation rate of two enantiomers, respectively. Efficient kinetic resolution was realized by using the catalysts with *t*-butyl group at carbon atom bonded to hydroxy group. The catalyst 2 bearing phenyl group instead of *t*-butyl group showed low k_f/k_s value (entry 4). The kinds of *N*-substituents were also very important factor to obtain high k_f/k_s. For example, the reaction using 2 mol% of (*R*)-(-)-1-diisopropylamino-3,3-dimethyl-2-butanol (3) gave (*S*)-2-phenylpropanal of 85.7% ee as unreacted aldehyde at 69.8% conversion (k_f/k_s = 5.4) (entry 5). The outcome of stereochemistry was very interesting. When we used the catalysts possessing *R* absolute configuration, faster reacting enantiomer was always *R* (i.e. recovered aldehyde possessed predominantly *S* configuration), and the carbon atom produced by the addition of ethyl group had also *R* con-



$$\underset{\text{racemic}}{C_6H_5\overset{CH_3}{\overset{|}{C}}HCHO} + (C_2H_5)_2Zn \xrightarrow{\text{chiral catalyst}} C_6H_5\overset{CH_3}{\overset{|}{\underset{*}{C}}}HCHO + C_6H_5\overset{CH_3}{\overset{|}{\underset{*}{C}}}H\underset{*}{C}H(C_2H_5)OH$$

chiral catalyst



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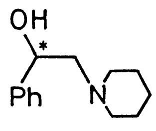

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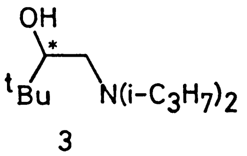

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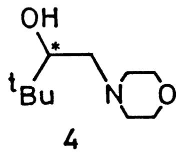

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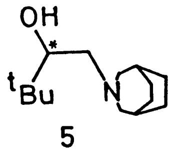

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Table 1. Kinetic Resolution of Racemic 2-Phenylpropanal by Enantioselective Ethylation Catalyzed by Chiral β-Aminoalcohols

		Conditions			Unreacted substrate			
Entry	catalyst[a)]	solvent	temp/°C	time/h	% conversion[b)]	% ee[c)]	confign[d)]	k_f/k_s[e)]
1	(*R*)-(-)-**1**	hexane	-20	16	71.0	77.3	*S*	4.1
2	(*R*)-(-)-**1**	toluene	-20	52	58.0	47.1	*S*	3.1
3	(*R*)-(-)-**1**	ether	-10	69	56.8	37.4	*S*	2.5
4	(*S*)-(+)-**2**[f)]	hexane	-20	48	60.0	11.2	*R*	1.3
5	(*R*)-(-)-**3**	hexane	-20	16	69.8	85.7	*S*	5.4
6	(*R*)-(-)-**4**	hexane	-20	40	72.6	30.7	*S*	1.6
7	(*R*)-(-)-**5**	hexane	-20	40	69.5	23.4	*S*	1.5

a) These catalysts (>99% ee) were prepared by the reaction of (*R*)-(-)-*t*-butylethylene oxide with secondary amines. Ref.3 b) Determined by GLC analysis using naphthalene as an internal standard. c) HPLC analysis. d) "Dictionary of Organic Compounds", ed by J. Buckingham, Chapman and Hall (1982), Vol. 5, p. 4661. e) Calculated by Kagan's equation. G. Balavoine, A. Moradpour, and H. B. Kagan, J. Am. Chem. Soc., 96, 5152 (1974). f) Y. Matsuda, T. Tokumitsu, and N. Oguni, 34th Symposium on Organometallic Chemistry, Japan, Abstracts p.355 (1987).

figuration mainly. The ratio of the product, (2*R*,3*R*)-2-phenyl-3-pentanol:(2*S*,3*R*)-:(2*S*,3*S*)-:(2*R*,3*S*)- was determined as 69:25:6:0 by HPLC analysis (entry 5).

A typical experimental procedure is illustrated as follows: In a flame dried Schlenk tube were placed (*R*)-(-)-1-diisopropylamino-3,3-dimethyl-2-butanol (**3**) (30 mg, 0.15 mmol), naphthalene (100 mg), and dry hexane (15 mL). The mixture was degassed and covered with argon. To this solution was added diethylzinc (0.84 mL, 8.2 mmol), and the resulting solution was stirred at 17 °C for 1 h. After cooling to -20 °C, 2-phenylpropanal (1.0 g, 7.45 mmol) was added and the mixture was stirred at this temperature under monitoring by GLC. After 16-h stirring (69.8% conversion), the solution was quenched by 1 mol m^{-3} HCl (60 mL). Usual extraction with diethyl ether (50 mL x 3), followed by separation of ethylated product and unreacted aldehyde by silica-gel column chromatography. Unreacted aldehyde was further purified by distillation (240 mg, 24%). $[\alpha]_D^{24}$ +197.4°(c 1.5, $CHCl_3$). The ee of unreacted aldehyde was determined as 85.7% ee by HPLC analysis using Sumipax OA 4000 after reduction by $LiAlH_4$ in ether.

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