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Enantioselective Addition of Diethylzinc to Aldehydes Catalized by Chiral Diamino-diols Derived from Ephedrine

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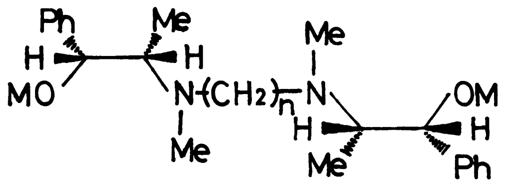
Dilithium salts of chiral diamino-diols possessing $\underline{C}_2$ axis derived from ephedrine catalyzed the enantioselective addition of diethylzinc to aldehydes to afford optically active sec-alcohols in up to 85% enantiomeric excess(e.e.).

Increasing interest has been centered on catalytic asymmetric induction in carbon-carbon bond forming reaction.¹⁾ Some chiral aminoalcohols have been utilized in the enantioselective addition of dialkylzincs to aldehydes.²⁾ Very recently, asymmetric induction of 80% was reported in the addition of diethylzinc (Et_2Zn) to benzaldehyde using N-alkyl derivatives of ephedrine,³⁾ however the catalyst failed to cause any asymmetric induction in the addition to aliphatic aldehyde. Although the effectiveness of chiral auxiliary with $\underline{C}_2$ axis has been recognized in the catalytic asymmetric induction, no chiral aminoalcohol with $\underline{C}_2$ axis has been utilized in the above catalytic carbon-carbon bond forming reaction.

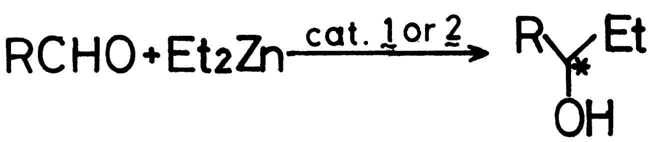
We report a synthesis of new chiral diamino-diols(**1** and **2**) with $\underline{C}_2$ axis from ephedrine and their use as catalysts in the enantioselective addition of Et_2Zn to aldehydes. One step reaction of (1R, 2S)-(-)-ephedrine(**3**) with 1, 3-diiodopropane in the presence of sodium carbonate (EtOH, reflux) afforded 79% yield of **1**, $[\alpha]^{26}_{D}$ -11.5° (c 1.06, $CHCl_3$). On the other hand, reaction of **3** with oxalyl chloride in the presence of 4-dimethylaminopyridine afforded the corresponding diamide(**4**) in 65% yield. Subsequent reduction of **4** with lithium aluminum hydride (THF, reflux) afforded 72% yield of diamino-diol **2**, $[\alpha]^{25}_{D}$ +16.9° (c 0.97, $CHCl_3$).

As catalysts, **1**, chiral propane-1, 3-diamine derivative, was found to be superior to **2**, ethane-1, 2-diamine derivative. The results are shown in Table 1. Thus, when benzaldehyde was treated with Et_2Zn in the presence of a catalytic amount (4 mol%) of **1**, which had been deprotonated by the reaction with



1; n = 3, M = H, Li

2; n = 2, M = H, Li



up to 85%e.e.

Table 1. Enantioselective addition of diethylzinc to aldehydes using **1** and **2**

Entry	Aldehyde	Catalyst	Solvent[a)]	Yield/%	$[\alpha]_D$/°(*c*, solvent)	e.e./%[b)]	Config.
1	C_6H_5CHO	**1**	TH	59	+38.8 (3.82,$CHCl_3$)	85	R
2	C_6H_5CHO	**1**	H	63	+32.5 (4.35,$CHCl_3$)	72	R
3	C_6H_5CHO[c)]	**1**	TH	79	+28.4 (4.78,$CHCl_3$)	63	R
4	*o*-$CH_3OC_6H_4CHO$	**1**	TH	93	+37.6 (3.02,$C_6H_5CH_3$)	73	-
5	*n*-$C_8H_{17}CHO$	**1**	TH	43	-2.6 (2.06,C_2H_5OH)	42	R
6	1-naphthaldehyde	**1**	TH	51	+36.3 (2.14,$CHCl_3$)	62[d)]	-
7	C_6H_5CHO	**2**	H	95	+14.3 (4.12,$CHCl_3$)	32	R
8	C_6H_5CHO	**2**[e)]	H	47	-6.3 (1.83,$CHCl_3$)	14	S

a)TH = toluene-hexane(≈1 : 1), H = hexane. b) Reported values for (*S*)-1-phenyl-1-propanol, see the text and Ref. 4; for (+)-1-(2-methoxyphenyl)-1-propanol in 87% e.e., $[\alpha]_D$ +47.0° (*c* 1.2, $C_6H_5CH_3$), A. Smaardijk and H. Wynberg, J. Org. Chem., 52, 135(1987); for (*R*)-3-undecanol, $[\alpha]_D$ -6.22° (C_2H_5OH), "Dictionary of Organic Compounds," ed by J. Backingham, Chapman and Hall, New York (1982). c) Room temperature. d) Determined by HPLC analysis using chiral column (Bakerbond DNBPG). e) Cat. **2** was used without lithiation.

butyllithium, (*R*)-(+)-1-phenylpropanol [$[\alpha]^{23}_D$ +38.8° (*c* 3.8, $CHCl_3$), lit. $[\alpha]_D$ -45.45° (*c* 5.15, $CHCl_3$)[4)]] was obtained in 85% e.e.(entry 1).

As to the effect of solvent, better e.e.'s were observed in toluene-hexane(≈1 : 1) than in hexane(entries 1, 2). When the catalyst(**2**) was not lithiated, the sence of the asymmetric induction was reversed and much lower enantioselectivity was observed (entries 7, 8). Thus, the lithiation of the catalyst was essential for the high enantioselection. Ethylation of *o*-methoxybenzaldehyde afforded the corresponding *sec*-alcohol in good e.e.(entry 4). Even aliphatic aldehyde (1-nonanal) was ethylated in moderate e.e.(entry 5).

Typical procedure is as follows. Butyllithium(0.09 mmol, 1.5 M hexane solution, 0.06 ml) was added to a toluene(2.6 ml) solution of the catalyst(**1**) (0.015 g, 0.04 mmol), and the mixture was stirred for 10 min. Benzaldehyde (0.1 ml, 1 mmol) was added and stirred for 10 min. Then the mixture was cooled to 0 °C and Et_2Zn in hexane (1 M solution, 2.2 ml) was added and stirred for 2 days. The reaction was quenched by 1 M HCl(5 ml). Extraction with dichloromethane, drying over anhydrous Na_2SO_4, evaporation under reduced pressure, and the subsequent purification on silica gel TLC($CHCl_3$ as eluent) afforded (*R*)-(+)-1-phenyl-1-propanol (0.089 g, 59%).

Further investigation is in progress.

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