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ENANTIOSELECTIVE ADDITION OF DIETHYLZINC TO BENZALDEHYDE CATALYZED BY A SMALL AMOUNT OF CHIRAL 2-AMINO-1-ALCOHOLS

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Summary: The reaction of diethylzinc with benzaldehyde catalyzed by a small amount of chiral 2-amino-1-alcohols in toluene at room temperature gave optically active 1-phenylpropan-1-ol almost quantitatively in ∿ 50% ee.

Asymmetric alkylation of various aldehydes with organometallic reagents in the presence of chiral organic reagents has been recently developed and high ee was attained in some cases[1]. In order to attain high optical yield in the reported systems, the use of a stoichiometric amount of chiral reagents and to run the reaction at very low temperature of -110∼-120°C are essential. Very recently we reported that chiral catalysis by transition metal complexes of d-camphorquinonedioxime in the reaction of diethylzinc with arylaldehydes gave optically active alcohols almost quantitatively in 40∼60% ee at room temperature[2]. The reaction was based upon the no reaction between dialkylzinc and arylaldehydes in nonpolar solvents even at room temperature, although ordinary alkylmetals add to carbonyl groups of organic compounds. In this paper we also describe the asymmetric ethylation of benzaldehyde with diethylzinc catalyzed by chiral 2-amino-1-alcohols. The general procedure for the reaction is given as follows:

$$(C_2H_5)_2Zn \quad + \quad C_6H_5CHO \quad \xrightarrow[\text{2) } H^+]{\text{1) chiral catalyst}} \quad C_6H_5CH(C_2H_5)OH$$

To a stirred solution of benzaldehyde(9 mmol) and chiral 2-amino-1-alcohol(0.18 mmol) in toluene (15 ml) was added diethylzinc(9 mmol) under argon atmosphere, and the whole mixture was stirred at 20°C for 48 h. Then dil HCl was added dropwise to the reaction mixture at 0°C and the organic layer was separated, dried over Na_2SO_4, and concentrated under reduced pressure.
The resulting 1-phenylpropan-1-ol was distilled under reduced pressure. Optical purity of the

product was determined by optical rotations measured with a digital polarimeter, JASCO model DIP.

Various optically active 2-amino-1-alcohols were readily prepared by the reduction of chiral α-amino acids in ether and some of them were commercially available. We examined a equimolar reaction of diethylzinc and benzaldehyde in the presence of a small amount(2 mol % of substrate) of chiral alcohol, amine, and 2-amino-1-alcohols. The results obtained were listed in Table 1.

Table 1. Enantioselective addition of Et_2Zn to C_6H_5CHO catalyzed by chiral catalysts.

Catalyst	Temperature(°C)	Time(h)	Yield(%)	$[\alpha]_D^{27}$	ee(%)
(S)-1-phenylethylamine	20	48	95	+1.5°(R)	3.8
(S)-1-phenylpropan-1-ol	30	48	56	+0.4°	1.6
(S)-alaninol	20	41	97	+10.6°	26.4
(S)-valinol	20	44	95	+18.8°	46.9
(S)-leucinol	20	43	96	+19.5°	48.8
(S)-phenylalaninol	30	41	98	+15.7°	39.2
(S)-prolinol	30	42	100	+11.3°	28.3

The chiral 2-amino-1-alcohols were generally effective and much higher optical yields were achieved in comparison with chiral amine and alcohol. Among the various 2-amino-1-alcohols the best enantioselectivity was observed using S-leucinol bearing a bulky substituent. 1-Phenylpropan-1-ol obtained by the catalysis of various S—2-amino-1-alcohols posessed the R-configration. These chiral 2-amino-1-alcohols reacted with diethylzinc at room temperature in toluene to give ethylzinc monoalkoxide, $[C_2H_5ZnOCH_2CHRNH_2]_n$(n: 2 or 4), which was assumed to be the real active species for the asymmetric addition reaction of diethylzinc to benzaldehyde. Results of a detailed study of the reaction will be published elsewhere.

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