Complementary Catalytic Asymmetric Induction in the Enantioselective Addition of Diethylzinc to Aldehydes

Kenso Soai,* Atsuhiro Ookawa, Kazuo Ogawa, and Tatsuya Kaba

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

Both enantiomers of sec-alcohols were obtained in high enantiomeric excess (up to 92%) from the enantioselective addition of diethylzinc to aldehydes using chiral pyrrolidinylmethanol derivatives as catalysts.

There are several reports on the enantioselective addition of organometallic reagents to aldehydes using non-catalytic quantities of chiral ligands.[1] Asymmetric induction in these reactions using a catalytic amount of chiral ligand is a challenging problem.[2] Recently, (−)-3-*exo*-(dimethylamino)isoborneol[3] was reported to be an efficient catalyst for the formation of (*S*)-alcohols in an enantioselective manner by the addition of dialkylzinc compounds to aldehydes.[4]

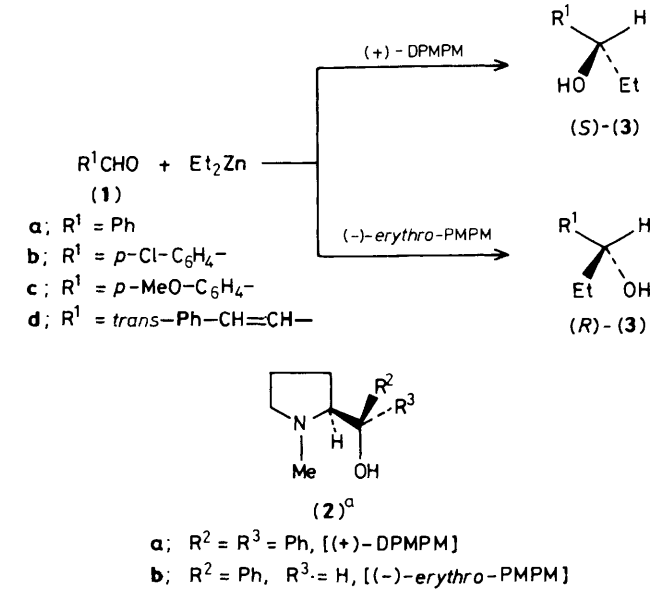
We now report a catalytic asymmetric induction in the enantioselective addition of diethylzinc to aldehydes using pyrrolidinylmethanol derivatives, the synthesis of which we have reported previously.[5] When benzaldehyde (**1a**) was treated with diethylzinc (Et_2Zn) in the presence of a catalytic amount (2 mol%) of (2′*S*)-(+)-diphenyl(1′-methylpyrrolidin-2′-yl)methanol (**2a**) (DPMPM),† (*S*)-(−)-1-phenylpropanol (**3a**), {$[\alpha]_D$ −44.2° (*c* 5.0, $CHCl_3$), lit.[6] $[\alpha]_D$ −45.45° (*c* 5.15, $CHCl_3$)} was obtained in 98% chemical yield and in 92% enantiomeric excess (e.e.) (g.l.c. analysis of the correspond-

† Satisfactory n.m.r. and i.r. spectroscopic data and elemental (and/or high resolution mass spectrometric) analyses were obtained for all new compounds.

Table 1. Enantioselective addition of Et_2Zn to (**1**) using (**2**) as catalyst.[a]

			(3)			
Entry	(1)	(2)		$[\alpha]_D$/° (c, solvent)	Yield/%	% e.e.	Configuration
1[b]	**a**	**a**	**a**	−44.2 (5.0, $CHCl_3$)	98	92[d]	(*S*)
2[b]	**b**	**a**	**b**	−23.5 (5.0, PhH)	100	91[d]	(*S*)
3[b]	**c**	**a**	**c**	−27.4 (5.1, PhH)	100	81[e]	(*S*)
4[b]	**d**	**a**	**d**	−5.74 (2.6, $CHCl_3$)	91	65[f] (97[g])	(*S*)
5[c]	**a**	**b**	**a**	+32.1 (4.6, $CHCl_3$)	100	71[e]	(*R*)
6[c]	**b**	**b**	**b**	+16.83 (5.0, PhH)	92	70[e]	(*R*)
7[c]	**c**	**b**	**c**	+20.8 (5.0, PhH)	97	62[e]	(*R*)

[a] Reactions were carried out in hexane at 0 °C for 4—15 h. [b] Molar ratio (**1**):(**2**):Et_2Zn 1:2 mol%:2.2. [c] Molar ratio (**1**):(**2**):Et_2Zn 1:5 mol%:2.2. [d] Determined as the corresponding (−)-α-methoxy-α-(trifluoromethyl)phenylacetic acid esters[7] by g.l.c. analysis [silicone OV-1701, 25 m capillary column, flame ionisation detector]; (**3a**) column temperature 168 °C, retention time 44 and 45 min; (**3b**) column temperature 178 °C, retention time 58 and 60 min for the diastereoisomeric esters. [e] Based on the reported values of $[\alpha]_D$ +45.45° (*c* 5.15, $CHCl_3$) for (*S*)-(**3a**);[8] $[\alpha]_D$ −10.4° (*c* 5, PhH) for (*S*)-(**3b**) in 43% e.e.;[9] $[\alpha]_D$ −17.2° (*c* 5, PhH) for (*S*)-(**3c**) in 51% e.e.[9] [f] Based on the reported value of $[\alpha]_D^{23}$ −6.6° (*c* 3.2, $CHCl_3$) for (*S*)-(**3d**) in 75% e.e.[10] [g] Based on the reported value of $[\alpha]_D^{22}$ −5.7° ($CHCl_3$) for (*S*)- (**3d**) in 96% e.e. which is confirmed by Noyori *et al.* by using a chiral h.p.l.c. column (Bakerbond DNBPG).[4]



Scheme 1. [a] (**2a**); $[\alpha]_D^{23}$ +57.0° (*c* 1.0, $CHCl_3$). Prepared by the reaction of (*S*)-*N*-benzyloxycarbonylproline methyl ester with PhMgBr followed by $LiAlH_4$ in 83% yield. (**2b**); $[\alpha]_D^{24}$ −59.0° (*c* 0.73, $CHCl_3$). Prepared by *N*-methylation (95%) with HCHO–HCO_2H of (1*R*,2′S)-phenyl(2′-pyrrolidinyl)methanol.[5]

ing MTPA ester[7]) (Scheme 1).‡ In a similar manner, other (*S*)-alcohols, (**3b—d**), were obtained in high e.e.s from the corresponding aldehydes (Table 1). One of the possible reasons for the high asymmetric induction may be co-ordination of the alkoxide of (**2a**) with the zinc atom of Et_2Zn, thus inducing chirality in the ethylating reagent.

However (1*R*,2′*S*)-(−)-phenyl(1′-methylpyrrolidin-2′-yl)-methanol (**2b**) (*erythro*-PMPM) afforded (*R*)-alcohols (**3**) and was found to be a complementary catalyst to (+)-DPMPM. Thus, the structure of the alcohol moiety in (**2**) plays an essential role in controlling the asymmetric induction.

This method is useful because (i) it requires only a catalytic amount of chiral source, (ii) both enantiomers of the sec-alcohols are obtained respectively by using either (+)-DPMPM or (−)-*erythro*-PMPM. Both catalysts can be synthesized from (*S*)-proline.

Received, 20th November 1986; Com. 1655

‡ Typical procedure for asymmetric induction. A mixture containing (+)-DPMPM (**2a**) (0.0053 g, 0.02 mmol), benzaldehyde (0.10 ml, 1.0 mmol), and hexane (2.5 ml) was refluxed for 20 min then cooled to 0 °C. Diethylzinc in hexane (1 M solution, 2.2 ml) was added to the ice-cooled mixture over a period of 5 min and stirred for a further 4 h. 1 M HCl was added to quench the reaction. The mixture was extracted with dichloromethane and the extract was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The residue was purified by silica gel t.l.c. ($CHCl_3$ as developing solvent) followed by distillation (bulb-to-bulb method, 150 °C/26 mmHg). 1-Phenylpropanol (0.132 g) was obtained in 97% yield, $[\alpha]_D^{23}$ −44.2° (*c* 5.0, $CHCl_3$). G.l.c. analysis of the corresponding (−)-α-methoxy-α-(trifluoromethyl)phenylacetic acid ester (MTPA ester)[7] showed the e.e. of (**3a**) was 92%.

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