Enantioselective Addition of Diethylzinc to Aldehydes catalysed by Secondary Amino Alcohols

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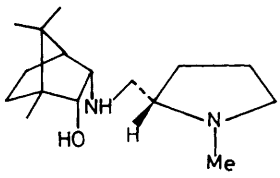
Secondary amino alcohols serve as efficient catalysts in the enantioselective addition of diethylzinc to aldehydes with predictable stereochemistry.

There has been considerable interest in the enantioselective addition of diethylzinc to aldehydes using chiral catalysts such as amino alcohols and natural cinchona alkaloids.[1—13] The use of tertiary amino alcohols is essential for high chemical yields and high enantioselectivities. Of particular interest is a recent report by Corey and Hannon in which they show that in the reaction of aromatic aldehydes, the absolute stereochemistry of product correlates with the chirality of the benzylic alcohol stereocentre of the tertiary amino alcohols used in zinc(II) complexes.[8,9] In contrast, with secondary amino alcohols, the enantiomeric excess of the alcohols is very low and hitherto no mechanistic model which predicts the stereochemical course of the addition of diethylzinc[1,2,4] has been presented.

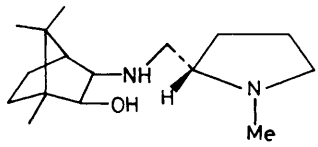
In the course of our studies of 3-amino-2-hydroxybornanes as chiral auxiliaries in the cyclopropanation reaction, we reported that *exo*-3-amino-*exo*-2-hydroxybornane is an efficient amine for the asymmetric cyclopropanation of 3-(phenylthio)-2-[(phenylthio)methyl]propanamides.[14] We have now found that when these amines are employed as catalysts for the enantioselective addition of diethylzinc to aldehydes, both chemical yields and enantioselectivities in this reaction are high and the stereochemistry of the products can be predicted correctly.

Thus, *endo*-amine(**1a**)[15] catalysed the addition of diethylzinc to benzaldehyde to give (*R*)-1-phenyl-propan-1-ol in high enantiomeric excess (e.e.) as shown in Table 1. In the presence of *exo*-amine (**1b**),[16] the stereoselectivity is reversed. A similar control of the stereoselectivity is realized by using the catalyst *endo*-(**2a**) and *exo*-(**2b**), or *endo*-(**3a**) and *exo*-(**3b**).

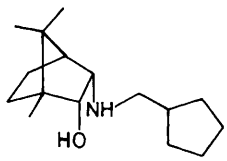
The reaction of diethylzinc with (**2a**) (1 : 1) in toluene at room temperature was very slow and only half of the



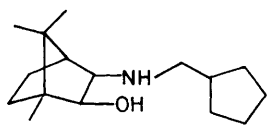
(**1a**)



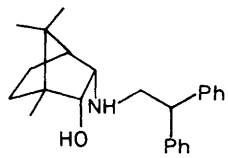
(**1b**)



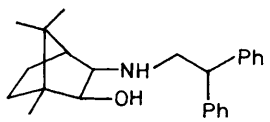
(**2a**)



(**2b**)



(**3a**)

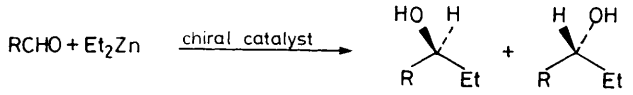


(**3b**)

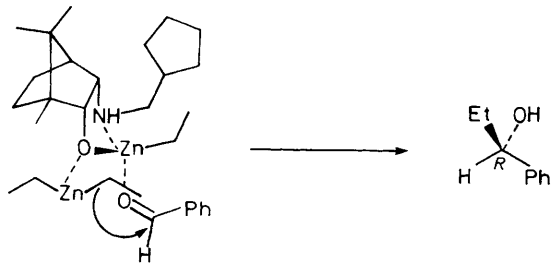
Table 1. Enantioselective addition of Et_2Zn to aldehydes (Scheme 1).

R	Catalyst[a]	Yield,%	$[\alpha]_D^{23}$/° (*c*)	%E.e.	Config.
Ph	(**1a**)	90	+44.6 (5.06)	92[b]	*R*
Ph	(**1b**)	87	−43.1 (5.01)	88	*S*
Ph	(**2a**)	92	+45.2 (5.05)	93	*R*
Ph	(**2b**)	89	−25.7 (5.03)	53	*S*
Ph	(**3a**)	83	+46.9 (5.08)	97	*R*
Ph	(**3b**)	95	−23.7 (5.04)	49	*S*
p-$MeOC_6H_4$	(**1a**)	90	+31.8 (5.02)	94	*R*
C_6H_{13}	(**1a**)	82	−7.25 (8.06)	75	*R*
C_6H_{13}	(**1b**)	86	+7.10 (8.04)	74	*S*
$PhCH_2CH_2$	(**1a**)	47	−22.0 (4.80)	82	*R*
$PhCH_2CH_2$	(**1b**)	60	+19.5 (5.25)	73	*S*

[a] The reaction was carried out in toluene at room temperature using 5 mol% of the catalyst. [b] Reported value for (*S*)-1-phenylpropan-1-ol in 98% e.e. is $[\alpha]_D$ −47.6° (*c* 6.11, $CHCl_3$).[5]



Scheme 1



(**4**)

diethylzinc was consumed to afford the zinc alkoxide.† Since the secondary amine hydrogen of the catalysts is intact under these conditions,‡ the amine group co-ordinates with the zinc atom to form a rigid transition state. The stereochemical course of the enantioselective addition can be explained by a mechanism involving structure (**4**), similar to that for tertiary amino alcohols advanced by Corey and Hannon[8] where the aldehyde is attacked on its *Re* face to give (*R*)-1-phenylpropan-1-ol.

The present method provides either enantiomer in high optical purity by appropriate choice of 3-amino-2-hydroxybornanes which are readily prepared from D-camphor.

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† Quantitative evolution of ethane was observed when water was added to this mixture. This indicates that 0.5 equiv. of diethylzinc remains in the mixture.

‡ No ethane evolution was observed when diethylzinc was mixed with a sterically hindered amine such as di-isopropylamine in toluene at room temperature for 24 h.

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14 K. Tanaka, I. Funaki, A. Kaji, K. Minami, M. Sawada, and T. Tanaka, *J. Am. Chem. Soc.*, 1988, **110**, 7185.
15 For the preparation of *endo*-3-amino-*endo*-2-hydroxybornane from D-camphor, see: H. Pauling, *Helv. Chim. Acta*, 1975, **58**, 1781. The amine (**1a**) was prepared by reduction of the corresponding amide, (1*R*,2*R*,3*S*,4*S*)-3-*N*-[(*S*)-*N*-(benzyloxycarbonyl)prolyl]-amino-2-hydroxy-1,7,7-trimethylbicyclo[2.2.1]heptane, with lithium aluminium hydride in 54% yield; $[\alpha]_D^{22}$ +44.6° (*c* 1.68, $CHCl_3$). This amide was prepared from *endo*-3-amino-endo-2-hydroxybornane and (*S*)-*N*-(benzyloxycarbonyl)proline by using 2-chloro-1-methylpyridinium tosylate as a condensing agent in 71% yield; m.p. 130 °C, $[\alpha]_D^{25}$ −43.5° (*c* 2.07, $CHCl_3$). The amines (**2a**) and (**3a**) were prepared by a similar method.
16 For preparations of *exo*-3-amino-*exo*-2-hydroxybornane from D-camphor, see: R. A. Chittenden and G. H. Cooper, *J. Chem. Soc. (C)*, 1970, 1; A. H. Beckett, N. T. Lan, and G. R. McDonough, *Tetrahedron*, 1969, **25**, 5689. The amine (**1b**) was prepared from *exo*-3-amino-*exo*-2-hydroxybornane by a procedure similar to that for the preparation of (**1a**); (**1b**): $[\alpha]_D^{24}$ −26.4° (*c* 2.10, $CHCl_3$).