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Enantioselective Addition of Diethylzinc to Aldehydes Catalyzed by Chiral Hydroxy Aminal

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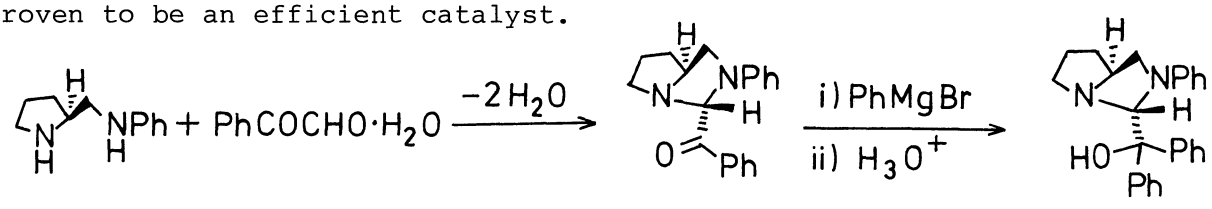
Chiral secondary alcohols are obtained in high enantiomeric excesses (ee's) by the enantioselective addition of diethylzinc to aldehydes in the presence of a chiral hydroxy aminal derived from (S)-2-(anilinomethyl)-pyrrolidine.

Enantioselective alkylation of aldehydes is a useful method for the preparation of chiral secondary alcohols.[1] The reaction has been extended to catalytic system since Oguni and Omi reported the reaction of diethylzinc and benzaldehyde in the presence of a catalytic amount of chiral alcohol, amine or amino alcohol.[2] A number of chiral catalysts have been reported for the last five years, and β-amino alcohols having rigid structure are usually found to be effective.[3]

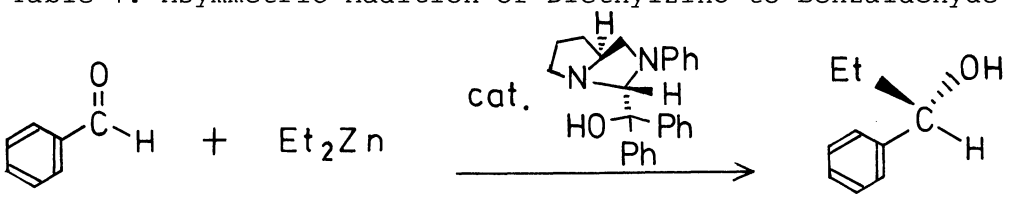
Previously we reported several highly stereoselective asymmetric reactions employing chiral aminals derived from (S)-2-(anilinomethyl)-pyrrolidine (1).[4] In those reactions, the high selectivity was attributed to rigid cis-fused five-membered bicyclic ring structure of the aminal. Thus we attempted to apply the aminal structure to the enantioselective addition of diethylzinc to aldehydes, and chiral hydroxy aminal, (2R,5S)-2-(diphenylhydroxymethyl)-3-phenyl-1,3-diazabicyclo[3.3.0]octane (2), has proven to be an efficient catalyst.



1 3 2

Scheme 1.

Table 1. Asymmetric Addition of Diethylzinc to Benzaldehyde[a)]



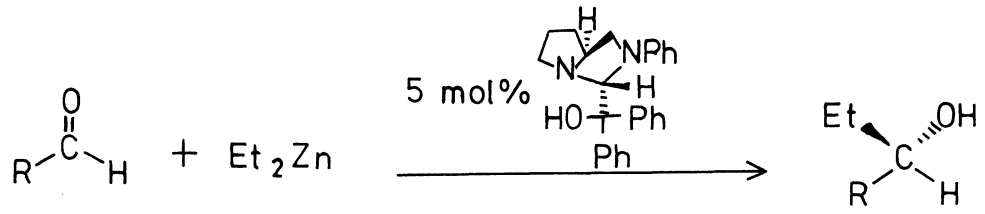
Ent.	Solvent	Amount of 2	Reaction temperature	Yield/%[b)]	ee/%[c)]
1	Hexane	5 mol%	rt	84	96
2	Cyclohexane	5 mol%	rt	93	96
3	Toluene	5 mol%	rt	79	94
4	Ether	5 mol%	rt	77	95
5	Cyclohexane[d)]	2.5 mol%	rt	72	88
6	Cyclohexane	7.5 mol%	rt	94	96
7	Cyclohexane[e,f)]	5 mol%	3 °C	82	95
8	Cyclohexane[e,g)]	5 mol%	reflux	74	87
9	Cyclohexane[h)]	5 mol%	rt	92	96

a) Reaction was carried out for 15-18 h using 2.0 equivalents of diethylzinc unless otherwise specified. b) Isolated yield. c) The ee was determined by HPLC using a Daicel Chiralcel OB column.[3j)] The absolute configuration was S in every case. d) Reaction time was 40 h. e) 1.5 Equivalents of diethylzinc was used. f) Reaction time was 24 h. g) Reaction time was 1 h. h) 1.8 Equivalents of diethylzinc was used.

The catalyst 2 was synthesized from 1 in two steps. A mixture of an equimolar amount of 1 and phenylglyoxal monohydrate in benzene was heated to reflux with azeotropic removal of water. After removal of benzene resulting keto aminal 3[5)] was treated sequentially with 4 equivalents phenylmagnesium bromide (THF, rt, 2 h) and saturated NH_4Cl to give crude hydroxy aminal 2. After alumina column chromatography and recrystallization (cyclohexane) 2[5,6)] was obtained as colorless crystals (59% from 1) (Scheme 1).

The reaction of diethylzinc and benzaldehyde was examined in the presence of 2 under a variety of reaction conditions. The results are summarized in Table 1. High chemical yield as well as asymmetric induction was achieved by using 5 mol% 2 in cyclohexane at room temperature (Entries 1-4). The selectivity decreased when the reaction was carried out at higher reaction temperature (Entry 8) or less amount of catalyst (2.5 mol%) was used (Entry 5). 1.8 Equivalents of diethylzinc was enough to obtain high chemical yield and selectivity (Entry 9).

Table 2. Asymmetric Addition of Diethylzinc to Aldehyde[a)]



R	Yield/%[b)]	[α] (c, solvent)	ee/%[c,d)]
C_6H_5-	92	$[\alpha]_D^{26}$ -46.1° (5.15, $CHCl_3$)	96
p-ClC_6H_4-	87	$[\alpha]_D^{28}$ -26.8° (5.06, benzene)	95[e)]
p-$CH_3OC_6H_4$-	90	$[\alpha]_D^{27}$ -34.8° (5.02, benzene)	93
(E)-C_6H_5CH=CH-	90	$[\alpha]_D^{31}$ -5.27° (3.00, $CHCl_3$)	73
$C_6H_5CH_2CH_2$-	73	$[\alpha]_D^{26}$ +21.9° (5.02, C_2H_5OH)	81
n-C_6H_{13}-	82	$[\alpha]_D^{24}$ +7.25° (8.33, $CHCl_3$)	75[f)]

a) Reaction was carried out in cyclohexane at room temperature for 15 h by using 5 mol% 2 and 1.8 equivalents of diethylzinc per aldehyde. b) Isolated yield. c) Determined by HPLC using a Daicel Chiralcel OB column unless otherwise specified. d) All products are of S-configuration based on the optical rotation.[3a)] e) Determined by ^{1}H-NMR spectrometry after esterification with (-)-MTPACl.[3m)] f) Determined by ^{13}C-NMR spectrometry after esterification with (-)-MTPACl.[3m)]

The reaction was then applied to several aldehydes and chiral secondary alcohol with S-configuration was obtained from every aldehyde examined. As shown in Table 2 high selectivity was achieved for aryl aldehydes and good selectivity was obtained even for aliphatic aldehydes and α,β-unsaturated aldehyde.

A typical procedure is as follows: Under a nitrogen atmosphere, to a cyclohexane (3.0 ml) solution of benzaldehyde (106 mg, 1.0 mmol) and 2 (18.5 mg, 0.05 mmol) was added a hexane (1.8 ml) solution of diethylzinc (1.8 mmol) at 0 °C. After the reaction mixture was stirred at room temperature for 15 h, saturated NH_4Cl solution (2.0 ml) and 2 M HCl solution (2.0 ml) was added to quench the reaction. The mixture was extracted with ether, and the organic layer was dried over anhyd Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by silica-gel TLC to afford 1-phenylpropanol (126 mg, 92%) $[\alpha]_D^{26}$ -46.1° (c 5.15, $CHCl_3$). The ee was determined by HPLC after bulb-to-bulb distillation.

Thus, chiral hydroxy aminal 2 was found to be one of the most

effective catalysts reported to date for enantioselective addition of dialkylzinc to aldehyde. Further application of chiral catalyst 2 to other asymmetric reactions are now under investigation.

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5) ^{1}H-NMR (270 MHz) spectra of 2 and 3 show only one peak at δ=5.21 and 5.66 ppm respectively assigned to the methine proton (-N-CH-N-). Therefore single diastereomers, (2R,5S)-2 and (2R,5S)-3, are supposed to be formed because of the structural feature of the aminals.

6) 2: mp 139-140 °C; $[\alpha]_D^{26}$ -84.8° (c 1.20, $CHCl_3$); IR (KBr) 3550 cm^{-1} (O-H); NMR ($CDCl_3$) δ=1.4-1.6 (m, 1H), 1.6-2.0 (m, 3H), 2.58 (q, 1H, J=9 Hz), 2.7-2.9 (m, 1H), 2.93 (t, 1H, J=9 Hz), 3.2-3.4 (m, 2H), 4.80 (brs, 1H), 5.21 (s, 1H), 6.28 (d, 2H, J=8 Hz), 6.59 (t, 1H, J=7 Hz), 6.9-7.1 (m, 2H), 7.1-7.4 (m, 6H), 7.5-7.8 (m, 4H). Found: C, 80.94, H, 7.13, N, 7.63%. Calcd for $C_{25}H_{26}N_2O$: C, 81.04, H, 7.07, N, 7.56%.

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