Synthesis of New Chiral β-Amino Alcohols Derived from Isomannide and Their Application to the Catalytic Enantioselective Addition of Diethylzinc to Aldehydes

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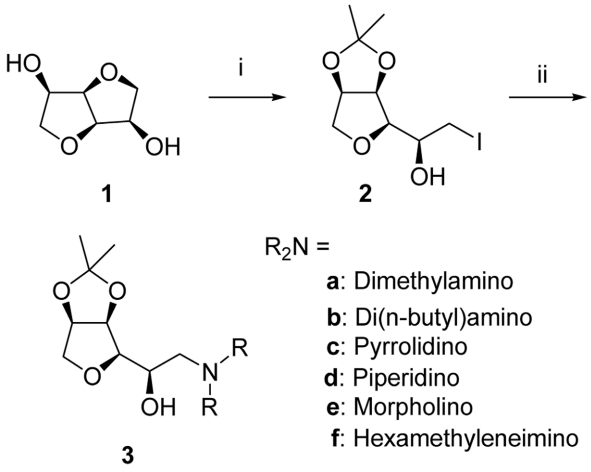
Enantioselective carbon-carbon bond formation is one of the most interesting challenges in organic synthesis. In recent years, the catalytic enantioselective addition of dialkylzincs to aldehydes has attracted much attention because of its potentials in the preparation of optically active secondary alcohols.[1] Over the past decade, various types of chiral ligands using as catalysts for this reaction have been developed. Among the diverse chiral lignads, chiral amino alcohols are predominant. As other type of ligands, chiral amino thiols,[2] amino thiocyanate,[3a] amino thioacetate,[3b] iminyl alcohols,[4] oxazolinyl alcohols,[5] amino amides,[6] sulfonamides,[7] phosphoramides,[8] α-hydroxy carboxylic acid[9] and diols such as TADDOLs[10] and BINOLs[11] have been published. Recently we reported the synthesis of various chiral β- or γ-amino alcohols derived from inexpensive chiral pools, such as α-D-xylose,[12] α-D-glucose[13] and L-tartaric acid,[14] and D-mannitol.[15] As a continuation of our ongoing project on the development of new chiral ligands from an easy and inexpensive starting materials, we hereby report the synthesis of new β-amino alcohols **3a-f** starting from isomannide **1** and their application for the catalytic ethylation to aldehydes.

The ligands **3a-f** were prepared in 87-98% yield by the treatment of **2**[16] with 2.5 equiv. of dialkylamines under solvent-free conditions for 2-3 h at 45 °C (Scheme 1).



Scheme 1

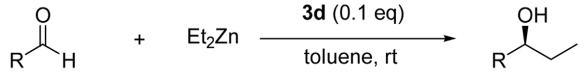
Table 1. Catalytic Enantioselective Addition of Diethylzinc to Benzaldehyde in the Presence of 10 mol% of **3** in Toluene at Room Temperature[a]

Run No.	Cat	Time (h)	1-Phenyl-1-propanol		
			Yield (%)[b]	% ee[c]	Config.[d]
1	**3a**	36	51	37	*S*
2	**3b**	18	53	64	*S*
3	**3c**	12	84	77	*S*
4	**3d**	12	93	86	*S*
5	**3e**	12	91	84	*S*
6	**3f**	12	88	75	*S*

[a][PhCHO] : {Et_2Zn} : [Cat] = 1 : 2 : 0.1, [Cpd] = 0.5 M. [b]Isolated yield. [c]Determined by capillary GC analysis using a β-Dex 120 chiral column. [d]Determined by comparison with the sign of optical rotation value and the elution order of GC analysis of the known compound.

Subsequently we compared the enantioselectivities of these chiral ligands as catalyst for the enantioselctive addition of diethylzinc to benzaldehyde. Thus, the reaction was carried out by addition of 2 equiv. of diethylzinc in toluene to

Table 2. Catalytic Enantioselective Addition of Diethylzinc to Aldehydes in the Presence of 10 mol% of **3d** at Room Temperature[a]



Run No	Aldehyde	Time (h)	Product alcohols		
			Yield (%)[b]	% ee	Config.[f]
1	4-Tolualdehyde	15	88	85[c]	*S*
2	4-Chlorobenzaldehyde	15	85	82[c]	*S*
3	1-Naphthaldehyde	24	67	65[d]	*S*
4	2-Napthaldehyde	12	86	78[d]	*S*
5	(*E*)-Cinnamaldehyde	12	82	45[d]	*S*
6	Hydrocinnamaldehyde	12	83	70[d]	*S*
7	Cyclohexanecarboxaldehyde	24	90	80[e]	*S*
8	Caproaldehyde	24	84	70[e]	*S*
9	Isovaleraldehyde	24	90	65[c]	*S*
10	Furfural	8	87	28[d]	*S*

[a-c]See the corresponding footnotes in Table 1. [d]Determined by HPLC analysis using a Chiralcel OD-H chiral column. [e]Determined by HPLC analysis of the corresponding 3,5-dinitrobenzoates using a Chiralcel OD-H chiral column. [f]Determined by comparison with the sign of optical rotation value and the elution order of GC or HPLC analysis of the known compound.

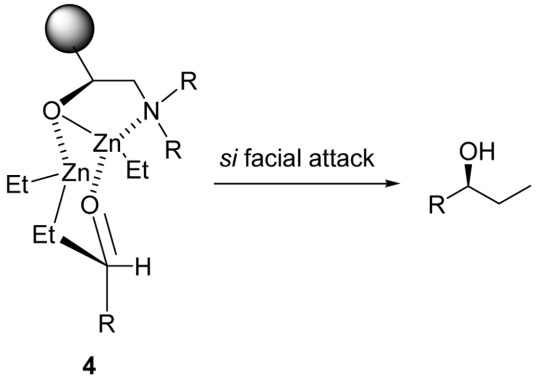


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Figure 1

benzaldehyde in the presence of 0.1 equiv. of each of **3** at 0 °C As shown in Table 1, all the reaction except the cases using **3a** and **3b** proceeded smoothly to give the product alcohol, 1-phenyl-1-propanol, in good yields. With respect to enantioselectivity of the product alcohol, **3d** among ligands examined afforded the best result to provide 86% ee (run 4). Based on this result, we carried out the asymmetric ethylation to other aromatic and aliphatic aldehydes using **3d** as catalyst under the same reaction conditions (Table 2). The reactions of aromatic aldehydes examined were complete within 15 h except the case of 1-naphthaldehyde to give the corresponding alcohols with good enantiomeric excesses in the range of 65-85% ee (runs 1-4). For aliphatic analogues, the reaction proceeded somewhat slowly to produce the desired alcohols with 65-80% ee (runs 6-9). In the case of α,β-unsaturated aldehyde, (*E*)-cinnamaldehyde, and a heterocyclic aldehdyde, furfural, the reaction provided low enantioselectivities (runs 5 and 10). The absolute configurations of all the alcohols obtained are consistently in the *S* enantiomers. The stereochemical course of this reaction can be explained by the proposed mechanism involving six-membered transition state **4**,[16] in which ethyl group in Et_2Zn is transferred to aldehydes on the *si* side to produce (*S*)-alcohols.

In summary, we have developed a new class of chiral ligands, 1-deoxy-1-*N*,*N*-dialkylamino-4,5-*O*-isopropylidene-3,6-anhydro-D-mannitol (**3**), for the enantioselective addition of diethylzinc to aromatic and aliphatic aldehydes. These ligands can be synthesized in two to three steps starting from isomannide which is an easy and inexpensive chiral pool.

Experimental Section

General. All operations with air-sensitive materials were carried out under a nitrogen atmosphere with oven-dried glassware. Liquid materials were transferred with a double-ended needle. The reactions were monitored by TLC using silica gel plates and the products were purified by flash column chromatography on silica gel (Merck; 230-400 mesh). NMR spectra were recorded at 300 MHz for ^{1}H and 75 MHz for ^{13}C using Me_4Si as the internal standard in $CDCl_3$. *J*-Values are given in Hz. Optical rotations were measured with a high resolution digital polarimeter. Enantiomeric excesses (% ees) of the product alcohols were determined by capillary GC analyses using a 30 m β-Dex 120 chiral column or by HPLC analyses using a 25 cm Chiralcel OD-H. Most of organic compounds utilized in this study were commercial products of the highest purity. They were further purified by distillation when necessary. Toluene was distilled over sodium and stored in an ampule under nitrogen atmosphere. 1-Deoxy-1-iodo-4,5-*O*-isopropylidene-3,6-anhydro-D-mannitol **2** using a starting material was prepared from isomannide according to the literature procedure.[16]

Preparation of 1-deoxy-1-*N*,*N*-dialkylamino-4,5-*O*-isopropylidene-3,6-anhydro-D-mannitols (3)

General method: Iodohydrin **2** (2 mmol) was treated with dialkylamine (5 mmol) for 2-3 h at 45 °C until **2** disappeared on TLC. To the reaction mixture was added 1 *N* NaOH (15 mL) and extracted with ether (3 × 15 mL). The combined ether extracts were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was further purified by flash column chromatography on silica gel using methanol/ethyl acetate (4 : 1) to give products **3**.

1-Deoxy-1-*N*,*N*-dimethylamino-4,5-*O*-isopropylidene-3,6-anhydro-D-mannitol 3a: 87% yield; R_f 0.42; oil; $[\alpha]_D^{26}$ –22.95 (*c* 0.61, MeOH); IR (film)/cm^{-1}) 3478, 3460, 2826, 1462, 1380, 1208, 1103, 1083, 1029, 862, 733; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.36 (s, 3H), 1.51 (s, 3H), 2.31 (s, 6H), 2.49-2.52 (m, 2H), 3.26 (m, 1H), 3.48 (m, 1H), 3.96-4.04 (m, 3H), 4.77-4.82 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.82, 26.28, 45.90, 63.46, 65.14, 73.36, 80.72, 80.93, 84.68, 112.28; Anal. Calcd for $C_{11}H_{21}NO_4$: C, 57.12; H, 9.15; N, 6.06. Found: C, 57.21; H, 9.13; N, 6.08.

1-Deoxy-1-*N*,*N*-di(*n*-butyl)amino-4,5-*O*-isopropylidene-3,6-anhydro-D-mannitol 3b: 92% yield; R_f 0.46; oil; $[\alpha]_D^{26}$ –1.62 (*c* 1.34, MeOH); IR (film)/cm^{-1}) 3456, 2956, 2933, 2870, 1239, 1208, 1100, 1085, 1051; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.83 (t, 3H, *J* = 7.15 Hz), 1.29 (s, 3H), 1.44 (s, 3H), 1.17-1.42 (m, 8H), 2.31-2.38 (m, 2H), 2.41-2.51 (m, 3H), 2.65 (dd, 1H, *J* = 3.58, 12.65 Hz), 3.17 (dd, 1H, *J* = 3.58, 8.12 Hz), 3.40 (dd, 1H, *J* = 3.58, 10.73 Hz), 3.76 (m, 1H), 3.95 (d, *J* = 10.73 Hz), 4.67-4.76 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.47, 20.93, 24.82, 26.29, 29.62, 54.17, 58.73, 64.44, 73.44, 80.73, 81.00, 85.24, 112.29; Anal. Calcd for $C_{17}H_{33}NO_4$: C, 64.73; H, 10.54; N, 4.44. Found: C, 64.75; H, 10.57; N, 4.41.

1-Deoxy-1-pyrrolidino-4,5-*O*-isopropylidene-3,6-anhydro-D-mannitol 3c: 95% yield; R_f 0.32; oil; $[\alpha]_D^{26}$ –28.35 (*c* 1.25, MeOH); IR (film)/cm^{-1}) 3414, 2932, 1272, 1215, 1078, 1051, 990, 861; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.35 (s, 3H), 1.51 (s, 3H), 1.75-1.79 (m, 4H), 2.48-2.52 (m, 2H), 2.61-2.78 (m, 4H), 3.27 (dd, 1H, *J* = 3.58, 8.11 Hz), 3.48 (dd, 1H, *J* = 3.58, 10.59 Hz), 3.97-4.05 (m, 2H), 4.75-4.84 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.96, 24.86, 26.32, 54.48, 59.92, 66.43, 73.38, 80.79, 80.99, 84.73, 112.34; Anal. Calcd for $C_{13}H_{23}NO_4$: C, 60.68; H, 9.01; N, 5.44. Found: C, 60.72; H, 9.18; N, 5.41.

1-Deoxy-1-piperidino-4,5-*O*-isopropylidene-3,6-anhydro-D-mannitol 3d: 93% yield; R_f 0.28; oil; $[\alpha]_D^{26}$ –19.26 (*c* 1.35, MeOH); IR (film)/cm^{-1}) 3439, 2934, 2850, 1455, 1379, 1208, 1123, 1101, 1083, 987, 863; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.36 (s, 3H), 1.51 (s, 3H), 1.42-1.47 (m, 2H), 1.54-1.62 (m, 4H), 2.33 (br s, 1H), 2.38 (d, 1H, *J* = 10.45 Hz), 2.42 (d, 1H, *J* = 10.45 Hz), 2.60-2.65 (m, 3H), 3.24 (dd, 1H, *J* = 3.58, 8.25 Hz), 3.48 (dd, 1H, *J* = 3.58, 10.45 Hz), 3.97-4.04 (m, 3H), 4.76 (dd, 1H, *J* = 3.58, 6.05 Hz), 4.82 (dd, 1H, *J* = 3.58, 6.05 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.58, 24.82, 26.30, 26.44, 54.94, 62.74, 64.02, 73.44, 80.68, 81.01, 85.06, 112.55; Anal. Calcd for $C_{14}H_{25}NO_4$: C, 61.97; H, 9.29; N, 5.16. Found: C, 61.98; H, 9.27; N, 5.21.

1-Deoxy-1-morpholino-4,5-*O*-isopropylidene-3,6-anhydro-D-mannitol 3e: 97% yield; R_f 0.35; oil; $[\alpha]_D^{26}$ –16.00 (*c* 1.40, MeOH); IR (film)/cm^{-1}) 3472, 2962, 2849, 1455, 1381, 1208, 1099, 1081, 908, 854; ^{1}H NMR (300 MHz, $CDCl_3$) δ1.35 (s, 3H), 1.50 (s, 3H), 2.40-2.51 (m, 4H), 2.65-2.72 (m, 4H), 3.27 (dd, 1H, *J* = 3.30, 7.98 Hz), 3.48 (dd, 1H, *J* = 3.58, 10.73 Hz), 3.65-3.77 (m, 4H), 4.02 (d, 1H, *J* = 10.73 Hz), 4.75-4.83 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.87, 26.73, 54.06, 62.60, 64.54, 67.33, 73.43, 80.79, 81.00, 84.57, 112.42; Anal. Calcd for $C_{13}H_{23}NO_5$: C, 57.13; H, 8.48; N, 5.12. Found: C, 57.16; H, 8.52; N, 5.15.

1-Deoxy-1-hexamethyleneimino-4,5-*O*-isopropylidene-3,6-anhydro-D-mannitol 3f: 98% yield; R_f0.36; oil; $[\alpha]_D^{26}$ –16.44 (*c* 2.16, MeOH); IR (film)/cm^{-1}) 3443, 2983, 2851, 1455, 1379, 1210, 1099, 1051, 991, 861; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.36 (s, 3H), 1.51 (s, 3H), 1.60-1.68 (m, 8H), 2.44 (dd, 1H, *J* = 10.18, 12.38 Hz), 2.58-2.66 (m, 2H), 2.73-2.80 (m, 2H), 2.90 (dd, 1H, *J* = 3.58, 12.38 Hz), 3.23 (dd, 1H, *J* = 3.58, 7.98 Hz), 3.47 (dd, 1H, *J* = 3.58, 10.59 Hz), 3.87-3.94 (m, 1H), 4.02 (d, 1H, *J* = 11.98 Hz), 4.74-4.83 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.91, 26.31, 69.29, 73.09, 80.57, 81.17, 84.08, 112.73; Anal. Calcd for $C_{15}H_{27}NO_4$: C, 63.13; H, 9.54; N, 4.91. Found: C, 63.24; H, 9.48; N, 4.98.

Catalytic enantioselective addition of diethylzinc to aldehydes. The following procedure is representative. Under a nitrogen atmosphere, a toluene solution (2 mL) of diethylzinc (2 mmol) was added to **3d** (0.1 mmol) in toluene (1 mL) and stirred at 0 °C for 30 min. After benzaldehyde (1 mmol) was added to this, the mixture was stirred at the same temperature for 12 h and then diluted with ether (10 mL). The excess diethylzinc was destroyed by addition of 1 *N* HCl and the reaction mixture was extracted with ether (3 × 10 mL). The ether extract was dried over anhydrous magnesium sulfate and concentrated in *vacuo*. The product alcohols was purified by flash column chromatography on silica gel to give 1-phenyl-1-propanol; 93% yield (86 mg); Capillary GC analysis using a 30 m β-Dex 120 chiral column showed it to be 86% ee.

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