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Enantioselective Addition of Diethylzinc to Aldehydes Using γ-Aminoalcohols Derived from α-D-Xylose as New Chiral Catalysts+

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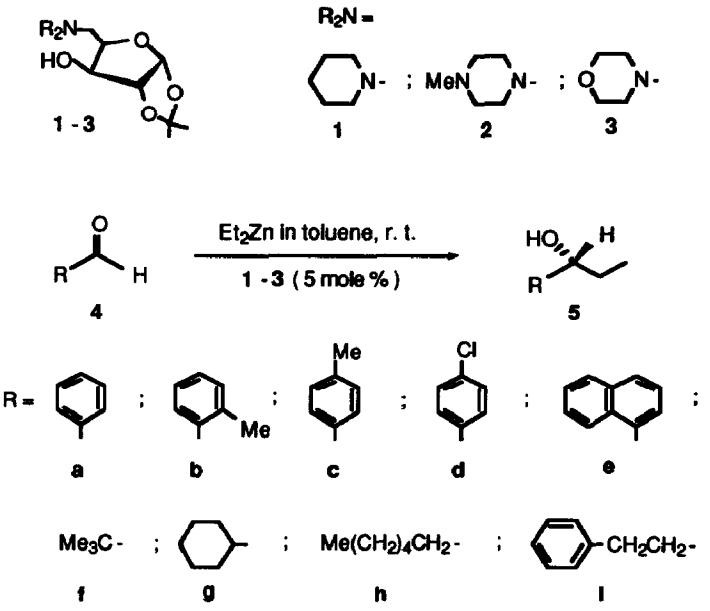
Abstract: The enantioselective addition of diethylzinc to aldehydes using 1,2-isopropylidene-5-deoxy-5-dialkylamino-α-D-xylofuranoses derived from α-D-xylose as new catalysts provided the corresponding alcohlos with 75-96 % ee.

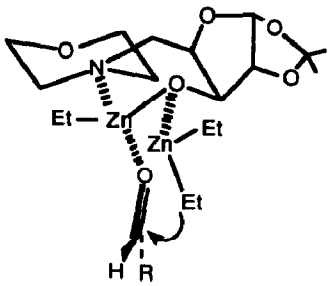
Enantioselective addition of diethylzinc to aldehydes by chiral ligands is a convenient method for the preparation of optically active secondary alcohols.[1] Accordingly, a wide variety of chiral catalysts for the enantioselective addition reaction has been extensively developed.[1a] Among them, most of highly effective chiral catalysts for the reaction are β-aminoalcohols derived from natural products, such as camphor, α-amino acids, norephedrine and cinchona alkaloids. And also several kinds of unnatural chiral aminoalcohol derivatives proved to be potentially chiral catalysts to afford high optical induction for such reaction. However, no report using chiral catalysts derived from carbohydrates in this reaction has not appeared in literatures, although carbohydrates are widely used chiral auxiliaries for asymmetric syntheses.[2] We wish hereby to report the enantioselective addition reaction of diethylzinc to aldehydes using γ-aminoalcohols, 1,2-isopropylidene-5-deoxy-5-dialkylamino-α-D-xylofuranoses **1-3** as new chiral catalysts, which were prepared from 1,2-isopropylidene-5-*O*-*p*-toluenesulphonyl-α-D-xylofuranose[3] and the corresponding amines.[4]

First, we compared the asymmetric inductions of the chiral catalysts for benzadehyde **4a** chosen as a representative aldehyde. Thus, **4a** was reacted with diethylzinc in the presence of 5 mole % of each of **1-3** in toluene at room temperature (*ca.* 25 °C). The reaction with the exception of **2** proceeded smoothly to afford 1-phenylpropanol **5a** in high yields. The addition reaction with **2** was very slow at room temperature (20 % yield, 24 h), but was complete in 2 h at 70 °C. The optical yields of product alcohol **5a** obtained are 87 % ee with **1**, 78 % ee with **2** and 96 % ee with **3**. The results led us to investigate the catalytic enantioselective

addition of diethylzinc to other aldehydes **4** using **3** at room temperature. Both aromatic and aliphatic aldehydes examined were reacted smoothly to provide the corresponding alcohols **5** in good yields. For aromatic aldehydes, consistently high optical yields, such as 89 % ee for *o*-tolualdehyde **4b**, 88 % ee for *p*-tolualdehyde **4c**, 88 % ee for *p*-chlorbenzaldehyde **4d**, and 86 % ee for 1-naphthaldehyde **4e** were



obtained. The catalyst **3** also is highly effective for the enantioselective addition of aliphatic aldehydes, such as 93 % ee for trimethylactaldehyde **4f**, 96 % ee for cyclohexanecarboxaldehyde **4g**, 76 % ee for heptanal **4h**, and 79 % ee for hydrocinnamaldehyde **4i**. The results are summarized in Table 1. The absolute configurations



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of all the products alcohols **5** obtained are consistently enriched in R enantiomers. The stereochemical course of the enantioselective addition can be explained by the mechanism involving structure **6**, similar to those for tertiary aminoalcohols proposed by Corey[7], where the aldehydes are attacked on their *Re* faces to give (R)-alcohols. The study for improvement of their enantioselectivities by varing dialkylamino groups at C-5 position in the catalysts is in progress.

Table1. Catalytic Enantioselective Addition of Diethylzinc to Aldehydes in the Presence of 5 mole % of **1-3** in Toluene at Room Temperature[a]

Aldehydes (4)	Catalysts	Time	Products alcohols **5**		
		h	yield[b]	% ee[c]	abs. config.[d]
4a	**1**	10	92	87	R
4a	**2**	2[e]	96	78	R
4a	**3**	10	90	96	R
4b	**3**	10	88	89[f]	R
4c	**3**	10	84	88	R
4d	**3**	10	91	88[f]	R
4e	**3**	10	90	86[g]	R
4f	**3**	24	86	93[h]	R
4g	**3**	12	88	96[h]	R
4h	**3**	12	95	75	R
4i	**3**	12	96	79	R

[a] [aldehyde] : [catalysts] : [Et_2Zn] = 1 : 0.05 : 2. [b] GC yields. [c] Determined by capillary GC analyses of (+)-MTPA esters, unless otherwise indicated.[5] [d] Based on the sign of optical rotations and elution orders of peaks in GC or HPLC analyses. [e] At 70°C. [f] Determined by capillary GC analyses of (-)-menthylcarbonates.[6] [g] Determined by HPLC analysis using Chiralcel OD column. [h] Determined by capillary GC analyses using a Chiraldex GTA column (Astec Inc.).

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+ Catalytic Enantioselective Reactions. Part 3.

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4. **1** : m.p. 73 - 74 °C; IR (KBr, cm^{-1}), 3055, 2925, 2814, 2693, 1461, 1380; ^1H NMR (300 MHz, $CDCl_3$, TMS) δ 1.32 (s, 3 H, $C\underline{H}_3$), 1.38-1.42 (m, 2 H, $NCH_2CH_2C\underline{H}_2CH_2CH_2$), 1.47 (s, 3 H, $C\underline{H}_3$), 1.52-1.60 (m, 4 H, $NCH_2C\underline{H}_2CH_2C\underline{H}_2CH_2$), 2.37-2.41 (m, 2 H, $NC\underline{Ha}HbCH_2CH_2CH_2C\underline{Ha}Hb$), 2.80 - 2.90 (m, 2 H, $NCHa\underline{Hb}CH_2CH_2CH_2CHa\underline{Hb}$), 2.82 (dd, 1 H, J_{HaH4} = 3.0 Hz, J_{gem} = 14.6 Hz, H-5a), 3.06 (dd, 1 H, J_{HbH4} = 2.8 Hz, J_{gem} = 14.6 Hz, H-5b), 4.10 (dd, 1 H, J = 5.5 Hz and 2.8 Hz, H-4), 4.30 (d, 1 H, J = 2.5 Hz, H-3), 4.40 (d, 1 H, J = 3.8 Hz, H-2), 5.97 (d, 1 H, J = 3.6 Hz, H-1), 8.37 (brs, 1 H, OH); Anal. Calcd. for $C_{13}H_{23}NO_4$: C, 60.71 ; H, 9.22 ; N, 5.80. Found : C, 60.69 ; H, 9.01 ; N, 5.41. **2** : m.p. 152 - 153 °C; IR (KBr, cm^{-1}), 3057, 2908, 2802, 1457, 1373; ^1H NMR (300 MHz, $CDCl_3$, TMS) δ 1.32 (s, 3 H, $C\underline{H}_3$), 1.47 (s, 3 H, $C\underline{H}_3$), 2.26 (s, 3 H, $C\underline{H}_3N$-), 2.26-2.53 (m, 6 H, $MeNC\underline{H}_2C\underline{Ha}HbNC\underline{Ha}HbC\underline{H}_2$), 2.85-3.12 (m, 2 H, $MeNCH_2CHa\underline{Hb}NCHa\underline{Hb}CH_2$), 2.89 (dd, 1 H, J_{HaH4} = 2.75 Hz, J_{gem} = 14.6 Hz, H-5a), 3.10 (dd, 1 H, J_{HbH4} = 2.8 Hz, J_{gem} = 14.6 Hz, H-5b), 4.13 (dd, 1 H, J = 5.0 Hz and 2.75 Hz, H-4), 4.30 (d, 1 H, J = 2.7 Hz, H-3), 4.49 (d, 1 H, J = 3.6 Hz, H-2), 5.97(d, 1 H, J = 3.8 Hz, H-1); Anal. Calcd. for $C_{13}H_{24}N_2O_4$: C, 57.33 ; H, 8.88 ; N, 10.29. Found : C, 57.30 ; H, 8.97 ; N, 10.20. **3** : m.p. 63 - 64 °C; IR (KBr, cm^{-1}), 3140, 2926, 2842, 1462, 1373; ^1H NMR (300 MHz, $CDCl_3$, TMS) δ 1.32 (s, 3 H, $C\underline{H}_3$), 1.47 (s, 3 H, $C\underline{H}_3$), 2.44-2.51 (m, 2 H, $NCHa\underline{Hb}CH_2OCH_2CHa\underline{Hb}$), 2.83-2.91 (m, 2 H, $NC\underline{Ha}HbCH_2OCH_2C\underline{Ha}Hb$), 2.86 (dd, 1 H, J_{HaH4} = 2.75 Hz, J_{gem} = 14.5 Hz, H-5a), 3.11 (dd, 1 H, J_{HbH4} = 3.0 Hz, J_{gem} = 14.5 Hz, H-5b), 3.69 (t, 4 H, J = 4.7 Hz, $NCH_2C\underline{H}_2OC\underline{H}_2CH_2$), 4.15 (dd, 1 H, J = 5.5 Hz and 2.8 Hz, H-4), 4.31 (d, 1 H, J = 2.5 Hz, H-3), 4.50 (d, 1 H, J = 3.7 Hz, H-2), 5.95 (d, 1 H, J = 3.8 Hz, H-1), 7.57 (brs, 1 H, OH); Anal. Calcd. for $C_{12}H_{21}NO_5$: C, 55.59; H, 8.16; N, 5.40. Found: C, 55.62; H, 8.32; N, 5.63.
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