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Enantioselective addition of diethylzinc to aldehydes catalyzed by a new chiral β-amino alcohol derived from D-mannitol †

Byung Tae Cho * and Yu Sung Chun

Department of Chemistry, Hallym University, Chunchon 200-702, South Korea

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Abstract

A new chiral β-dialkylamino alcohol **1** prepared from D-mannitol has been used as a highly effective chiral catalyst for the enantioselective addition of diethylzinc to unhindered aliphatic aldehydes to afford the product alcohols in up to 94% ee. © 1998 Elsevier Science Ltd. All rights reserved.

Enantioselective carbon–carbon bond formation is one of the most interesting challenges in organic synthesis. In recent years the catalytic enantioselective addition of diethylzinc to aldehydes has attracted much attention because of its potential in the preparation of optically active secondary alcohols.[1] Previously most of the studies have focused on the use of β-amino alcohols as chiral catalysts derived from natural products, such as camphor, α-amino acids and norephedrine.[1,2] Also, several kinds of synthetic chiral amino alcohol derivatives have proved to be effective chiral catalysts and may afford high asymmetric induction in such reactions.[1,2] Recently, we reported the enantioselective addition of diethylzinc to aldehydes catalyzed by chiral β- or γ-dialkylamino alcohols derived from α-D-xylose,[3] α-D-glucose[4] and L-tartaric acid.[5] On the other hand, it has been realized that most of the catalysts reported so far are highly effective for aromatic and relatively hindered aliphatic aldehydes, leading to the corresponding optically active secondary alcohols with high enantioselectivity. For unhindered aliphatic aldehydes, only limited success has been achieved.[3e,6] In the course of developing new chiral catalysts for the addition reaction from inexpensive chiral pools, we found that 3-deoxy-3-*N*,*N*-di-*n*-octylamino-1,2;5,6-di-*O*-isopropylidene-D-altritol **1** obtained from D-mannitol served as a highly effective chiral catalyst for the ethylation to both aromatic and unhindered aliphatic aldehydes. In this communication, we report the preliminary results for the reaction.

The β-amino alcohol **1**[7] was prepared by refluxing 3-amino-3-deoxy-1,2;5,6-di-*O*-isopropylidene-D-altritol **2**[8] with 2 equiv. of *n*-octyl iodide in the presence of excess potassium carbonate in acetonitrile (Scheme 1).

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* Corresponding author. E-mail: btcho@sun.hallym.ac.kr

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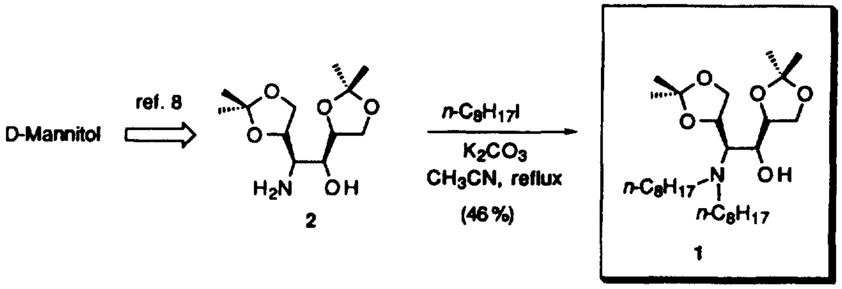

Scheme 1.

The enantioselective reaction was carried out by the addition of 2 equiv. of diethylzinc to aldehydes in the presence of 0.1 equiv. of the catalyst in toluene at 0°C. As shown in Table 1, all the reactions proceeded smoothly to give the corresponding product alcohols in good yields. In particular, the catalyst **1** is highly effective for the enantioselective addition to relatively unhindered aliphatic aldehydes, such as butanal, hexanal, heptanal, undecanal and 3-phenylpropanal, to provide the corresponding alcohols with enantiomeric excesses of a range between 82 and 94% ee (entries 1–4). To the best of our knowledge, the values of % ee are one of the best results reported for such aldehydes. Also, the catalyst was found to be useful for the ethylation of aromatic aldehydes to afford good enantioselectivity (88–92% ee). In this reaction, it is observed that the steric effect of the *O*-substituent on the benzene ring on asymmetric induction is not significant (entries 9 and 10).

The following procedure is representative. Under a nitrogen atmosphere, a toluene solution (2 ml) of diethylzinc (2 mmol) was added to **1** (48.6 mg, 0.1 mmol) in toluene (1 ml) and stirred at 0°C for 30 min. After undecanal (170 mg, 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 (10 ml) and then extracted with ether (3×10 ml). The ether extract was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The alcohol product was purified by flash column chromatography on silica gel (230–400 mesh) using ethyl acetate:hexane (1:9) as eluent to give 3-tridecanol (R_f 0.43, 184 mg, 92% yield). Enantiomeric excess was measured by capillary GC analysis of trifluoromethyl acetate of the product alcohol using a Chiraldex B-PH capillary column (AStec Inc.). GC analysis showed a composition of 97 (R) and 3 (S) (*i.e.*, 94% ee, R).

In conclusion, we found that a new chiral β-amino alcohol **1** derived from D-mannitol serves as an effective catalyst for enantioselective addition of diethylzinc to aldehydes. Especially, it is noteworthy that this catalyst is highly effective for relatively unhindered aliphatic aldehydes to give high enantioselectivity with a range of 81–94% ee. Further applications using this catalyst are now under investigation.

Acknowledgements

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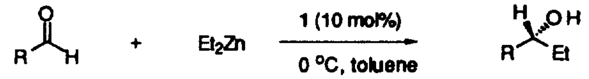
Table 1
Enantioselective addition of diethylzinc to aldehydes catalyzed by 10 mol% of **1** in toluene at 0°C[a]



Entry	Aldehydes	Product alcohols			
		Time (h)	Yield[b] (%)	% ee	Config[c]
1	Butanal	10	88	82[d]	*R*
2	Hexanal	10	90	84[d]	*R*
3	Heptanal	10	83	85[d]	*R*
4	Undecanal	12	92	94[e]	*R*
5	3-Phenylpropanal	12	81	90[f]	*R*
6	3-Methylbutanal	8	92	81[d]	*R*
7	Cyclohexanecarboxaldehyde	9	78	86[d]	*R*
8	Benzaldehyde	12	87	92[g]	*R*
9	*o*-Tolualdehyde	12	85	88[f]	*R*
10	*p*-Tolualdehyde	12	83	90[d]	*R*
11	*p*-Chlorobenzaldehyde	12	93	89[f]	*R*
12	1-Naphthaldehyde	18	82	88[h]	*R*

[a] [aldehyde] : [Et_2Zn] : [**1**] = 1 : 2 : 0.1. [aldehyde] = 0.3 M. [b] Isolated yield. [c] Determined by the sign of optical rotation and the elution order of GC or HPLC analysis. [d] Determined by capillary GC analysis of (*R*)-MTPA ester of the corresponding alcohol.[9] [e] Determined by capillary GC analysis of trifluoromethyl acetate of 3-tridecanol using Chiraldex B-PH column (Astec Inc.). [f] Determined by capillary GC analysis of (-)-menthyl carbonate of the corresponding alcohol.[10] [g] Determined by capillary GC analysis using a Chiraldex B-PH column (Astec Inc.). [h] Determined by HPLC analysis using a Chiralel OD column (eluent: hexane/*i*-PrOH = 9/1).

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7. **1**: Colorless viscous oil; $[\alpha]_D^{20}$ +41.4 (*c* 1.13, $CHCl_3$); IR (neat, cm^{-1}) ν 3482, 2985, 2859, 1466, 1378, 1255, 1214, 1160, 1056, 857; ^1H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, 6H, J=7.0 Hz), 1.26–1.48 (m, 24H), 1.34 (s, 3H), 1.36 (s, 3H), 1.40 (s, 6H), 2.56–2.63 (m, 2H), 2.71–2.80 (m, 3H), 3.30 (br s, 1H), 3.48 (t, 1H, J=6.0 Hz), 3.73 (t, 1H, J=7.8 Hz), 3.84–3.89 (m, 1H), 4.09–4.14 (m, 3H), 4.53–4.59 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 109.22, 108.41, 76.23, 75.89, 70.93, 68.14, 67.31, 65.15, 53.05, 31.86, 29.69, 29.63, 29.37, 27.42, 26.74, 26.45, 25.58, 25.10, 22.67, 14.11; anal. calcd for $C_{28}H_{55}NO_5$: C, 69.23; H, 11.41; N, 2.88. Found: C, 69.11; H, 11.59; N,2.64.

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