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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Key Words: Diethylzinc, Isomannide, Enantioselective addition, Chiral β-amino alcohol

Enantioselective carbon-carbon bond formation is one of the most interesting challenges in organic synthesis. In recent years, the catalytic enantioselective addition of dialkydzincs to aldehydes has attracted much attention because of its potentials in the preparation of optically active secondary alcohols. Over the past decade, various types of chiral ligands using as catalysts for this reaction have been developed. Among the diverse chiral ligands, chiral amino alcohols are predominant. As other type of ligands, chiral amino thiols, amino thiocyanate, amino thioacetate, iminyl alcohols, oxazolinyl alcohols, amino amides, sulfonamides, α-hydroxy carboxylic acid and diols such as TADDOLs and BINOLs have been published. Recently we reported the synthesis of various chiral β- or γ-amino alcohols derived from inexpensive chiral pool, such as α-D-xylose, α-D-glucose and L-tartaric acid, and D-mannitol. 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 1 with 2.5 equiv. of dialkylamines under solvent-free conditions for 2-3 h at 45 °C (Scheme 1).

![Scheme 1](image)

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

<table>
<thead>
<tr>
<th>Run No.</th>
<th>Cat</th>
<th>Time (h)</th>
<th>1-Phenyl-1-propanol</th>
<th>Yield (%)</th>
<th>% ee</th>
<th>Config.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3a</td>
<td>36</td>
<td>51</td>
<td>37</td>
<td>S</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>3b</td>
<td>18</td>
<td>53</td>
<td>64</td>
<td>S</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>3c</td>
<td>12</td>
<td>84</td>
<td>77</td>
<td>S</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>3d</td>
<td>12</td>
<td>93</td>
<td>86</td>
<td>S</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>3e</td>
<td>12</td>
<td>91</td>
<td>84</td>
<td>S</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>3f</td>
<td>12</td>
<td>88</td>
<td>75</td>
<td>S</td>
<td></td>
</tr>
</tbody>
</table>

[a] [PhCHO] : [Et2Zn] : [Cat] = 1 : 2 : 0.1, [Cat] = 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 enantioselctivities of these chiral ligands as catalyst for the enantioselective 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

<table>
<thead>
<tr>
<th>Run No.</th>
<th>Aldehyde</th>
<th>Time (h)</th>
<th>Product alcohols</th>
<th>Yield (%)</th>
<th>% ee</th>
<th>Config.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4- Tolualdehyde</td>
<td>15</td>
<td>88</td>
<td>85°</td>
<td>S</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>4-Chlorobenzaldehyde</td>
<td>15</td>
<td>85</td>
<td>82°</td>
<td>S</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>1-Naphthaldehyde</td>
<td>24</td>
<td>67</td>
<td>65°</td>
<td>S</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>2-Naphthaldehyde</td>
<td>12</td>
<td>86</td>
<td>78°</td>
<td>S</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>(E)-Cinnamaldehyde</td>
<td>12</td>
<td>82</td>
<td>45°</td>
<td>S</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Hydrocinnamaldehyde</td>
<td>12</td>
<td>83</td>
<td>70°</td>
<td>S</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Cyclohexanecarboxaldehyde</td>
<td>24</td>
<td>90</td>
<td>80°</td>
<td>S</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Caproxyaldehyde</td>
<td>24</td>
<td>84</td>
<td>70°</td>
<td>S</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>Isovaleraldehyde</td>
<td>24</td>
<td>90</td>
<td>65°</td>
<td>S</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Furfural</td>
<td>8</td>
<td>87</td>
<td>28°</td>
<td>S</td>
<td></td>
</tr>
</tbody>
</table>

[a] See the corresponding footnotes in Table 1. [b] Determined by HPLC analysis using a Chiralcel OD-H chiral column. [c] Determined by HPLC analysis of the corresponding 3,5-dinitrobenzoates using a Chiralcel OD-H chiral column. [d] Determined by comparison with the sign of optical rotation value and the elution order of GC or HPLC analysis of the known compound.
These ligands can be synthesized in two to three steps by the addition of diethylzinc to aromatic and aliphatic aldehydes. The reactions were monitored by TLC using glassware. Liquid materials were transferred with a double-ended needle. The reactions were complete within 1.5 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 aldehyde, furfural, the reaction provided low enantiomeric selectivities (runs 5 and 10). The absolute configurations of all the alcohols obtained are consistently in the case of 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.  

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 x 15 mL). The combined ether extracts were dried over anhydrous MgSO₄ 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; Rf 0.42; oil; [α]D⁰ 

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

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1-Deoxy-1-(N,N-dialkylamino)-4,5-O-isopropylidene-3,6-anhydro-D-mannitol 3b: 92% yield; Rf 0.46; oil; [α]D⁰ 

Preparation of 1-deoxy-1-(N,N-dialkylamino)-4,5-O-isopropylidene-3,6-anhydro-D-mannitol 3c: 95% yield; Rf 0.32; oil; [α]D⁰ 

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1-Deoxy-1-piperidino-4,5-O-isopropylidene-3,6-anhydro-D-mannitol 3d: 93% yield; R$_f$ 0.28; oil; [a]$_D$$^{20}$ = -19.26 (c 1.35, MeOH); IR (film cm$^{-1}$) 3439, 2934, 2850, 1455, 1379, 1208, 1123, 1083, 987, 863; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 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, 4H), 3.46 (dd, 1H, $J$ = 3.58, 6.05 Hz), 4.82 (dd, 1H, $J$ = 3.58, 6.05 Hz); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 24.87, 26.73, 54.06, 62.94, 64.02, 73.44, 80.68, 81.01, 85.06, 112.55; Anal. Calc'd for C$_{14}$H$_{27}$NO$_3$: 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 mixture, the reaction 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 x 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.

Acknowledgment. This study was supported by the Research Grant from Hallym University, Korea.

References


