Keywords: enantioselective; diamine; amino alcohol; alkylation; diethylzinc; benzaldehyde

The highest selectivity was observed when benzaldehyde was alkylated in the presence of the benzylic diamine, giving (R)-1-phenylpropanol with an ee of 42%. Copyright © 2008 John Wiley & Sons, Ltd.

Introduction

Catalytic enantioselective reactions constitute important tools in the synthesis of chiral molecules. In particular, the alkylation of aldehydes with diethylzinc allows for the synthesis of chiral secondary alcohols of great importance in the preparation of pharmaceuticals, agrochemicals and perfumes, among others.[1 – 4]

In these catalytic processes a variety of ligands have been used successfully, namely, amino alcohols, diols, diamines and their derivatives.

Herein we describe the synthesis of a range of δ-diamines and their analogous δ-amino alcohols derived from naturally occurring (R,R)-tartaric acid. Although other procedures have been described for this acid-catalyzed reaction of (R,R)-1 with acetone to give acetone (R,R)-2, although other procedures have been described for this reaction,[18 – 22] our conditions are milder and the product is obtained with good yield.

Following a modified literature procedure, reduction of the ester functions of (R,R)-2 with LiAlH₄ in THF to give diol (S,S)-3,[19,23] which was treated with tosyl chloride in pyridine at 0 °C, originating the corresponding ditosylate (S,S)-4,[8,20]

(S,S)-4 was transformed into the diamine using an adapted literature procedure[24]: reflux in isopropanol with excess of a primary or secondary amine, namely, cyclohexylamine, benzylamine

These compounds seemed particularly appealing due to the fact that some chiral ligands such as diphosphines, diols and amino alcohols with the same backbone structure have been described and show great efficiency in many enantioselective processes. Very good examples are DIOP, its derivatives, the TADDOLs and aminoTADDOLs (Fig. 1).[15 – 17]

Results and Discussion

Synthesis of chiral ligands

A series of δ-diamines was prepared using diethyl-(R,R)-tartarate, (R,R)-1, through a four-step synthetic sequence, Scheme 1.

The protection of the hydroxyl groups was carried out by the acid-catalyzed reaction of (R,R)-1 with acetone to give acetone (R,R)-2. Although other procedures have been described for this protection,[18 – 22] our conditions are milder and the product is obtained with good yield.

Following a modified literature procedure, reduction of the ester functions of (R,R)-2 with LiAlH₄ in THF to give diol (S,S)-3,[19,23] which was treated with tosyl chloride in pyridine at 0 °C, originating the corresponding ditosylate (S,S)-4,[8,20]

(S,S)-4 was transformed into the diamine using an adapted literature procedure[24]: reflux in isopropanol with excess of a primary or secondary amine, namely, cyclohexylamine, benzylamine

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Reactivity and selectivity of chiral diamines

Figure 1. General structure of (L)-tartaric acid derived chiral δ-diamines (a) and δ-amino alcohols (b).

(R)-1-phenylethylamine, (S)-1-phenylethylamine and morpholine. Chiral δ-diamines (S,S)-5a–e were thus obtained in moderate yields.

The synthesis of several δ-amino alcohols, analogues of (S,S)-5, prepared from the common precursor, diol (R,R)-3, was carried out according to Scheme 2. The selective tosylation of one of the hydroxyl functions in the presence of butyllithium originated (S,S)-6 which was purified by column chromatography to remove some of the corresponding ditosylated compound (S,S)-4 which was also formed.

Treatment of (S,S)-6 with sodium azide to give (S,S)-7, followed by hydrogenation originated amino alcohol (S,S)-8. Alternatively, reaction of (S,S)-6 with cyclohexylamine, (S)-1-phenylethylamine, benzylamine and morpholine gave the δ-amino alcohols (S,S)-9–12, respectively.

Enantioselective alkylation reactions

The efficiency of the chiral ligands synthesized was tested in the enantioselective alkylation of benzaldehyde 13 with diethylzinc, under optimized reaction conditions (Scheme 3).

Reactions were carried out at 0°C for 24 h in cyclohexane using 2 equivalents of diethylzinc and 15 mol% of the ligand. The results of the alkylations in the presence of δ-diamines (S,S)-5a–e are summarized in Table 1. Under the described reaction conditions, the ligands catalyzed the alkylations with moderate conversions and enantiomeric excesses which varied from 6 to 42%. With the exception of (S,S)-5e, all ligands originated (R)-1-phenylpropanol 14 as the major reaction product. The formation of benzyl alcohol as a secondary reaction product was observed. The most efficient ligand with respect to both activity and selectivity was the benzylic diamine (S,S)-5b, which originated (R)-14 with an ee of 42%.

The influence of additional chiral centers on the selectivity of this type of ligand was studied using (S,S)-5c and (S,S)-5d. There are two new chiral centers on each of these ligands, directly bonded to the nitrogen atoms. The use of (S,S)-5c and (S,S)-5d originated quite different results. With (S,S)-5c in which the additional chiral centers have (R) absolute configuration, the conversion and percentage of chiral alcohol 14 as well as the ee were low. With (S,S)-5d, in which the additional chiral centers have (S) absolute configuration, the conversion and percentage of 14 were slightly higher and the

Scheme 1. Synthetic sequence for δ-diamines (S,S)-5.

Scheme 2. Synthesis of δ-amino alcohols (S,S)-8–12.
The use of structurally similar ligands, namely the TADDOLs which (5a–e) have significantly decreased steric factors which contribute to the more selective catalytic species. Nonetheless, ligands are not as active as their diamine counterparts and the δ-aldehydes with diethylzinc, the chiral ligands were used in the enantioselective alkylation of alcohols with lower ee than benzaldehyde itself. Conversions and percentages of chiral alcohol were slightly lower for the p-substituted aldehydes, while they were highest when the electron-attracting chlorine substituent was present. Under our reaction conditions and with the substrates studied, we found that the alkylation with (S,S)-5b mostly gave (R) alcohol as the major enantiomer, resulting from coordination of the Re face of the aldehyde. However, the ortho substituted aldehydes originated (S) alcohols. This may be due to some additional steric hindrance in these cases, which forces the aldehydes to coordinate with the Si face.

Conclusions

Synthetic procedures for the preparation of tartaric acid-derived chiral δ-diamines (S,S)-5a–e and their structurally analogous δ-amino alcohols (S,S)-8–12 have been established. When these chiral ligands were used in the enantioselective alkylation of aldehydes with diethylzinc, the δ-diamines demonstrated greater activity and selectivity than their δ-amino alcohol counterparts. The ligand showing greatest efficiency was the benzylic diamine (S,S)-5b, which showed the highest selectivity in the reaction transition state so that a product with high selectivity results. Although (S,S)-5a–e have two bulky groups, their position does not seem to be the most suitable for high discrimination of the enantiotopic aldehyde faces in the transition state. Using (S,S)-5b, which showed the highest selectivity in the alkylation of benzaldehyde 13, we carried out the alkylation of a variety of other aromatic aldehydes (Table 3).

All of the substituted aldehydes gave the corresponding chiral alcohols with lower ee than benzaldehyde 13 itself. Conversions and percentages of chiral alcohol were slightly lower for the p-substituted aldehydes, while they were highest when the electron-attracting chlorine substituent was present. Under our reaction conditions and with the substrates studied, we found that the alkylation with (S,S)-5b mostly gave (R) alcohol as the major enantiomer, resulting from coordination of the Re face of the aldehyde. However, the ortho substituted aldehydes originated (S) alcohols. This may be due to some additional steric hindrance in these cases, which forces the aldehydes to coordinate with the Si face.

Table 1. Enantioselective addition of diethylzinc to benzaldehyde in the presence of (S,S)-5a

<table>
<thead>
<tr>
<th>Ligand</th>
<th>Conversion (%)</th>
<th>1-Phenylpropanol (%)</th>
<th>ee(%)d/abs. config.</th>
</tr>
</thead>
<tbody>
<tr>
<td>(S,S)-5a</td>
<td>68</td>
<td>84</td>
<td>8 (R)</td>
</tr>
<tr>
<td>(S,S)-5b</td>
<td>69</td>
<td>100</td>
<td>42 (R)</td>
</tr>
<tr>
<td>(S,S)-5c</td>
<td>42</td>
<td>57</td>
<td>8 (R)</td>
</tr>
<tr>
<td>(S,S)-5d</td>
<td>59</td>
<td>81</td>
<td>27 (R)</td>
</tr>
<tr>
<td>(S,S)-5e</td>
<td>57</td>
<td>69</td>
<td>6 (S)</td>
</tr>
</tbody>
</table>

Table 2. Enantioselective addition of diethylzinc to benzaldehyde in the presence of (S,S)-8–12

<table>
<thead>
<tr>
<th>Ligand</th>
<th>Conversion (%)</th>
<th>1-Phenylpropanol (%)</th>
<th>ee(%)d/abs. config.</th>
</tr>
</thead>
<tbody>
<tr>
<td>(S,S)-8</td>
<td>57</td>
<td>74</td>
<td>3 (S)</td>
</tr>
<tr>
<td>(S,S)-9</td>
<td>55</td>
<td>71</td>
<td>8 (S)</td>
</tr>
<tr>
<td>(S,S)-10</td>
<td>55</td>
<td>36</td>
<td>8 (R)</td>
</tr>
<tr>
<td>(S,S)-11</td>
<td>83</td>
<td>70</td>
<td>&lt;1</td>
</tr>
<tr>
<td>(S,S)-12</td>
<td>56</td>
<td>61</td>
<td>9 (R)</td>
</tr>
</tbody>
</table>

Table 3. Enantioselective addition of diethylzinc to aromatic aldehydes in the presence of (S,S)-5b

<table>
<thead>
<tr>
<th>Aldehyde</th>
<th>Conversion (%)</th>
<th>Chiral alcohol (%)</th>
<th>ee(%)d/abs. config.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzaldehyde</td>
<td>69</td>
<td>100</td>
<td>42 (R)</td>
</tr>
<tr>
<td>1-Naphthaldehyde</td>
<td>62</td>
<td>81</td>
<td>6 (R)</td>
</tr>
<tr>
<td>o-Methoxybenzaldehyde</td>
<td>74</td>
<td>91</td>
<td>20 (S)</td>
</tr>
<tr>
<td>m-Methoxybenzaldehyde</td>
<td>66</td>
<td>77</td>
<td>20 (R)</td>
</tr>
<tr>
<td>p-Methoxybenzaldehyde</td>
<td>30</td>
<td>64</td>
<td>13 (R)</td>
</tr>
<tr>
<td>o-Chlorobenzaldehyde</td>
<td>80</td>
<td>93</td>
<td>15 (S)</td>
</tr>
<tr>
<td>p-Chlorobenzaldehyde</td>
<td>73</td>
<td>83</td>
<td>31 (R)</td>
</tr>
</tbody>
</table>

Reactions were carried out at 0 °C for 24 h after the addition of a 1 M hexane solution of diethylzinc (2 mmol) to (S,S)-5b (0.15 mmol) and aldehyde (1 mmol) in cyclohexane. Determined by GC. Relative to converted aldehyde. Determined by chiral GC analysis.

This difference is most probably due to the presence of substituents on C1 and C2. The steric crowding caused by these substituents, usually bulky phenyl, strongly favors the predominant coordination by one of the aldehyde faces in the reaction transition state so that a product with high selectivity results. Although (S,S)-5a–e have two bulky groups, their position does not seem to be the most suitable for high discrimination of the enantiotopic aldehyde faces in the transition state. Using (S,S)-5b, which showed the highest selectivity in the alkylation of benzaldehyde 13, we carried out the alkylation of a variety of other aromatic aldehydes (Table 3).

All of the substituted aldehydes gave the corresponding chiral alcohols with lower ee than benzaldehyde 13 itself. Conversions and percentages of chiral alcohol were slightly lower for the p-substituted aldehydes, while they were highest when the electron-attracting chlorine substituent was present. Under our reaction conditions and with the substrates studied, we found that the alkylation with (S,S)-5b mostly gave (R) alcohol as the major enantiomer, resulting from coordination of the Re face of the aldehyde. However, the ortho substituted aldehydes originated (S) alcohols. This may be due to some additional steric hindrance in these cases, which forces the aldehydes to coordinate with the Si face.

Conclusions

Synthetic procedures for the preparation of tartaric acid-derived chiral δ-diamines (S,S)-5a–e and their structurally analogous δ-amino alcohols (S,S)-8–12 have been established. When these chiral ligands were used in the enantioselective alkylation of aldehydes with diethylzinc, the δ-diamines demonstrated greater activity and selectivity than their δ-amino alcohol counterparts. The ligand showing greatest efficiency was the benzylic diamine (S,S)-5b, originating alkylation products with ee up to 42%.

Further studies on the application of these ligands in other enantioselective transformations are underway.

Experimental

General

All solvents were dried prior to use following standard procedures. Reactions were carried out in an inert atmosphere using standard conditions.
Schlenk-type techniques. Diethylzinc (Aldrich) was used as a 1 M solution in hexane. Benzaldehyde was distilled prior to use and stored over 4 Å molecular sieves. Commercially acquired cyclohexylamine, (R)-1-phenylethylamine, (S)-1-phenylethylamine, benzylamine and morpholine were stored over KOH.

Melting points were determined using a Leitz–Wetzler 799 microscope with a heated plate (values are uncorrected). Optical rotations were measured with an Optical Activity AA-5 polarimeter. NMR spectra were recorded on a Bruker AMX 300 (300 and 75.5 MHz for 1H and 13C, respectively). The solvent was CDC13. TMS was used as the internal standard and chemical shifts are given in δ. Elemental analyses were carried out on a Fisons Instruments EA 1108 CHNS-O elemental analyzer. GC analyses were recorded on an HP 5890A instrument coupled to an HP 3396A integrator using a capillary column (Supelcowax 10, 30 m, 0.25 i.d., 0.25 μm). Infrared spectra were recorded on a Perkin Elmer 1720X FTIR (liquids were measured with a capillary column (Supelcowax 10, 30 m, 0.25 i.d., 0.25 mm) or on a Fisons Instruments-Platform with an APCI probe coupled to a ThermoSeparation SpectraSeries P200 chromatograph.

Alkylation reaction products were identified by comparison with authentic commercially acquired samples and by GC/MS analysis. Catalytic experiments were repeated in order to confirm results. Enantiomeric excesses were determined by using a chiral γ cyclodextrin capillary column (FS-Lipodex-E, 25 m, 0.25 μm) from Machery-Nagel using hydrogen as carrier gas, on an HP 5890A instrument coupled to an HP 3396A integrator. The detailed procedure of the enantiomeric纯化 was provided in the reference.[8,20] using ([R,R]-3) (0.17 mol, 27.2 g) to give 80% of a white solid, m.p. 90–92 °C. [α]D 20 = −12.0 (c 8.8, CHCl3). 1H NMR: 1.30 (s, 6H, CH3); 2.46 (s, 6H, PhCH3); 4.00–4.10 (m, 6H, CH2CH2); 7.37 (d, 4H, J = 8 Hz, CH2Ar); 7.78 (d, 4H, J = 8 Hz, CH2Ar). 13C NMR: 21.60 (PhC2H); 26.70 (CH3); 66.40 (CH3); 75.00 (CH); 110.80 (CH2); 128.00 (arom.); 129.90 (arom.); 132.40 (arom.); 145.20 (arom.). C9H12O2S2: calculated: C, 53.6; H, 5.57; S, 13.63; found: C, 53.49; H, 5.57; S, 14.22. LC-MS (m/z): 471 ([M + 1]), 457, 456, 455, 285, 227, 155, 126, 113, 91, 69.

**General procedure for the synthesis of** (S,S)-2,3-O-isopropylidene-butane-1,4-diylditosylate ([S,S]-4)

The compound was prepared according to a previously described procedure, using ([R,R]-3) (0.17 mol, 27.2 g) to give 80% of a white solid, m.p. 90–92 °C. [α]D 20 = −12.0 (c 8.8, CHCl3). 1H NMR: 1.30 (s, 6H, CH3); 2.46 (s, 6H, PhCH3); 4.00–4.10 (m, 6H, CH2CH2); 7.37 (d, 4H, J = 8 Hz, CH2Ar); 7.78 (d, 4H, J = 8 Hz, CH2Ar). 13C NMR: 21.60 (PhC2H); 26.70 (CH3); 66.40 (CH3); 75.00 (CH); 110.80 (CH2); 128.00 (arom.); 129.90 (arom.); 132.40 (arom.); 145.20 (arom.). C9H12O2S2: calculated: C, 53.6; H, 5.57; S, 13.63; found: C, 53.49; H, 5.57; S, 14.22. LC-MS (m/z): 471 ([M + 1]), 457, 456, 455, 285, 227, 155, 126, 113, 91, 69.

**Synthesis of** (S,S)-2,3-O-isopropylidene-butane-1,4-diylditosylate ([S,S]-4)

To a solution of the amine (80 mmol) in 40 ml of dry isopropanol, solid sodium hydride (60% dispersion in oil) was slowly added so that the temperature was maintained below 25 °C. The reaction was stirred overnight at room temperature. At 0 °C, ethyl acetate was slowly added to destroy excess hydride, followed sequentially by water (10.8 ml), NaOH, 15% (10.8 ml) and water (32.4 ml). The resulting mixture was stirred for 1 h, filtered over celite and dried over anhydrous MgSO4. Evaporation of the solvent under reduced pressure originated the product in 75% yield, a pale yellow oil, which was used directly without further purification.

By further stirring the solvent salts residue in ethyl acetate for 2–3 h, an additional batch of product could be obtained. [α]D 20 = +3.9 (c 5, CHCl3). 1H NMR: 1.42 (s, 6H, CH3); 3.70–3.74 (m, 6H, CH2CH2); 4.95 (bs, 2H, OH). 13C NMR: 26.80 (CH3), 62.10 (CH2), 78.40 (CH), 109.20 (CMe2). IR (cm⁻¹): 3407, 2950, 2936, 2884, 1570, 1454, 1412, 1377, 1252, 1219. GC-MS (m/z): 147 ([M − CH3]+), 131, 87, 69, 59.

**Synthesis of** (S,S)-2,3-O-isopropylidene-butane-1,4-diylditosylate ([S,S]-4)

The resulting oil was chromatographed on silica gel using hexane–ethyl acetate (9:1) to give 46% of the product, m.p. 90–92 °C. [α]D 20 = −15.6 (c 22, CH2Cl2). 1H NMR: 1.38 (s, 6H, CH3); 1.99 (bs, 2H, NH); 2.72–2.80 (m, 4H, CH2); 3.79 (s, 4H, CH2); 3.93–3.98 (m, 2H, CH); 7.17–7.34 (m, 10H, Ph). 13C NMR: 27.21 (CH3), 51.19 (CH2); 54.03 (CH2Ph); 78.75 (CH), 108.76 (CMe2); 126.94 (arom.); 128.07 (arom.); 128.37 (arom.). IR (cm⁻¹): 3350, 3027, 2930, 1602, 1494, 1454, 1374, 1248, 1216, 1166, 850, 820, 739, 699. LC-MS (m/z): 341 ([M + 1]), 194, 148.
The resulting oil was chromatographed on silica gel using AcOEt–MeOH (95:5) to give the product as an oil (27%). \[ \text{[S,S]} \] 1H NMR: 1.33 (d, 6H, J = 6.6 Hz, CH\(_3\)); 1.36 (6, s, CH\(_3\)); 2.51 (dd, 2H, J = 4.2, 12.3 Hz, CH\(_2\)); 2.60 (dd, 2H, J = 3.4, 12.3 Hz, CH\(_2\)); 3.73 (q, 2H, J = 6.6 Hz, CHMe); 3.90 (approx. 1, 2H, J = 2.9 Hz, CH\(_2\)); 7.21 – 7.31 (10H, aromatic). 13C NMR: 24.41 (CH\(_3\)), 27.20 (CH\(_3\)), 49.47 (CH\(_3\)), 58.28 (CHMe), 78.51 (CH), 108.63 (CMe), 126.54 (C\(_{arom}\)), 128.41 (C\(_{arom}\)), 145.41 (C\(_{arom}\)). IR (cm\(^{-1}\)): 3400, 3025, 2930, 1640, 1492, 1451, 1370, 1248, 1212, 1169, 845, 761, 701. LC-MS (m/z): 369 ([M + 1]), 312, 265, 248, 208, 188, 162, 144.

The resulting oil was chromatographed on silica gel using AcOEt–MeOH (95:5) to give the product as an oil (27%). \[ \text{[S,S]} \] 1H NMR: 1.33 (d, 6H, J = 6.6 Hz, CH\(_3\)); 1.36 (6, s, CH\(_3\)); 2.51 (dd, 2H, J = 4.2, 12.3 Hz, CH\(_2\)); 2.60 (dd, 2H, J = 3.4, 12.3 Hz, CH\(_2\)); 3.73 (q, 2H, J = 6.6 Hz, CHMe); 3.90 (approx. 1, 2H, J = 2.9 Hz, CH\(_2\)); 7.21 – 7.31 (10H, aromatic). 13C NMR: 24.41 (CH\(_3\)), 27.20 (CH\(_3\)), 49.47 (CH\(_3\)), 58.28 (CHMe), 78.51 (CH), 108.63 (CMe), 126.54 (C\(_{arom}\)), 128.41 (C\(_{arom}\)), 145.41 (C\(_{arom}\)). IR (cm\(^{-1}\)): 3400, 3026, 2928, 1643, 1492, 1452, 1373, 1248, 1214, 1169, 848, 762, 701. LC-MS (m/z): 369 ([M + 1]), 312, 265, 248, 208, 188, 162, 144.

The resulting oil was chromatographed on silica gel using AcOEt–MeOH (95:5) to give the product as an oil (27%). \[ \text{[S,S]} \] 1H NMR: 1.33 (d, 6H, J = 6.6 Hz, CH\(_3\)); 1.36 (6, s, CH\(_3\)); 2.51 (dd, 2H, J = 4.2, 12.3 Hz, CH\(_2\)); 2.60 (dd, 2H, J = 3.4, 12.3 Hz, CH\(_2\)); 3.73 (q, 2H, J = 6.6 Hz, CHMe); 3.90 (approx. 1, 2H, J = 2.9 Hz, CH\(_2\)); 7.21 – 7.31 (10H, aromatic). 13C NMR: 24.41 (CH\(_3\)), 27.20 (CH\(_3\)), 49.47 (CH\(_3\)), 58.28 (CHMe), 78.51 (CH), 108.63 (CMe), 126.54 (C\(_{arom}\)), 128.41 (C\(_{arom}\)), 145.41 (C\(_{arom}\)). IR (cm\(^{-1}\)): 3240, 3467, 3422, 3414, 3399, 3362, 2988, 1654, 1384, 1218, 1166, 1075.

General procedure for the synthesis of \(\text{[S,S]}\) 2,3-O-isopropylidene-4-amino-butan-1-ol from \(\text{[S,S]}\) 6

A solution of \(\text{[S,S]}\) 6 (2.7 g, 6.4 mmol) in 25 ml dry isopropanol was refluxed for 24 h. The solvent was evaporated and ethyl acetate and water were added. The aqueous phase was extracted three times with ethyl acetate and the joint organic phases dried over MgSO\(_4\). After evaporating the solvent, the product was purified as described below.

The product was purified by column chromatography using AcOEt–MeOH (90:5) to give a solid with 33% yield. m.p.: 63 – 65°C. \[ \text{[S,S]} \] 1H NMR: 1.03 – 1.39 (5H, CH\(_2\)); 1.38 (6H, J = 7.7 Hz, CH\(_3\)); 1.41 (s, 3H, CH\(_3\)); 1.60 – 1.73 (3H, CH\(_3\)); 1.90 – 1.96 (m, 2H, CH\(_2\)); 2.41 – 2.49 (m, 1H, CH\(_2\)); 2.61 (dd, 1H, J = 9.8, 11.9 Hz, CH\(_3\)); 3.18 (dd, 1H, J = 3.6, 11.9 Hz, CH\(_2\)); 3.52 (dd, 1H, J = 8.3, 10.2 Hz, CH\(_2\)); 3.67 – 3.86 (3H, 3H, CH\(_2\)O, CH\(_3\)). 13C NMR: 28.64 (CH\(_3\)), 27.01 (CH\(_3\)), 43.03 (CH\(_2\)), 62.39 (CH\(_3\)), 80.95 (CH\(_3\)), 81.06 (CH\(_3\)), 108.66 (CMe). IR (cm\(^{-1}\)): 3467, 3422, 3414, 3399, 3362, 2988, 1654, 1384, 1218, 1166, 1075.

The product was purified by column chromatography using AcOEt–MeOH (90:10) to give the product with 48% yield. \[ \text{[S,S]} \] 1H NMR: 1.38 (s, 3H, CH\(_3\)); 1.40 (s, 3H, CH\(_3\)); 2.70 (dd, 1H, J = 8.2, 12.0 Hz, CH\(_2\)); 3.07 (dd, 1H, J = 3.7, 12.0 Hz, CH\(_2\)); 3.59 (dd, 1H, J = 8.2, 11.9 Hz, CH\(_2\)O); 3.76 – 3.84 (m, 6H).
The residue was purified by column chromatography using AcOEt–MeOH (95:5) to give the product with 43% yield. [δ]D2O = −10 (c 2.0 CH2Cl2). 1H NMR (CDCl3): 1.39 (s, 3H, CH3); 1.40 (s, 3H, CH3); 1.40 (d, 3H, J = 6.6 Hz, CH3); 2.56 (dd, 1H, J = 8.5, 12.0 Hz, CH2N); 2.86 (dd, 1H, J = 4.0, 12.0 Hz, CH2N); 3.53–3.84 (m, 5H, CH2O, CH2); 7.24–7.35 (m, 5H, Ph). 13C NMR: 23.27 (CH3), 26.70 (CH3), 26.89 (CH3), 48.90 (CH3), 58.76 (CH3), 62.24 (CH2), 79.78 (CH), 81.29 (CH), 108.51 (CMe2), 126.34 (Carom), 128.70 (Carom), 129.88 (Carom), 143.98 (Carom). IR (cm−1): 3416, 2984, 2932, 2870, 1737, 1646, 1454, 1375, 1240, 1114, 1066, 860. GC-MS (m/z): 216 [(M – CH3)+], 192, 134, 120, 114, 95, 71, 59.

General procedure for enantiomselective alkylations

To the chiral ligand (0.15 mmol) and the aldehyde (1 mmol) in an inert atmosphere, 4 ml cyclohexane were added. The temperature of the reaction mixture was lowered to 0 °C and diethylzinc (2 ml of a 1 M hexane solution, 2 mmol) was added. The reaction was stirred at the same temperature for 24 h. After this time, a saturated ammonium chloride solution (1 ml) followed by 2 mL HCl (1 M) were added and the reaction mixture was extracted with diethyl ether. The organic phases were washed with water and brine and dried over anhydrous MgSO4. The resulting solution was analyzed by GC in order to determine the conversion and percentage of chiral alcohol. The ee of the chiral alcohol was determined by GC using a chiral γ-cyclodextrin column.

Acknowledgments

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References