Convenient Procedures for the Asymmetric Reduction of 1,4-Diphenylbutane-1,4-dione and Synthesis of 2,5-Diphenylpyrrolidine Derivatives

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Abstract: Asymmetric reduction of 1,4-diphenylbutane-1,4-dione (1) was carried out using the reducing agents NaBH4, BH3·THF, and PhNEt2·BH3 in combination with the chiral reagents (S)-(–)-α,α-diphenyl-2-pyrrolidinemethanol (4) or (S)-proline (5), in the presence of TMSCl or B(OMe)3 under various conditions to obtain the corresponding 1,4-diol 2 in 52% to 97% ee. The chiral 1,4-diol 2 was converted to various C2-symmetric (2S,5S)-2,5-diphenylpyrrolidine derivatives 3a–e (45 to 75% yield) via the corresponding dimesylate prepared using MsCl and EtN.

Key words: asymmetric reduction, chiral 1,4-diols, chiral pyrrolidine derivatives, 1,4-dione

Asymmetric synthesis is one of the major expanding areas of research in organic chemistry. The use of C2-symmetric chiral auxiliaries has gained considerable importance in current asymmetric syntheses. Among the various chiral auxiliaries, the 2,5-disubstituted pyrrolidine system is an important class of reagents. The trans-2,5-dimethylpyrrolidine was first developed as a useful chiral auxiliary for enantioselective alkylation of enamines derived from it. In this case, the recovery and recycling of chiral auxiliary are somewhat difficult. Therefore, several groups pursued the synthesis of the corresponding diphenyl analogue, a nonvolatile, stable, crystalline compound. The preparation of this system involves the enantioselective reduction of 1,4-diphenylbutane-1,4-dione (1) and cyclisation of the resultant diol derivative 2 (Scheme 1).

Scheme 1 Synthesis of 2,5-Diphenylpyrrolidine derivatives

The asymmetric reduction of the diferrocenyl-1,4-diketone to obtain the corresponding diol samples of >98% ee has been reported using the CBS oxazaborolidine catalyst, which requires considerable care for preparation to achieve good selectivities. In these reductions, the borane reagents such as BH3·THF, and BH3·SMe2 have been used. In recent years, several simplified procedures have appeared for the oxazaborolidine catalysed asymmetric reduction. For example, an extremely effective oxazaborolidine catalyst can be easily and rapidly prepared in situ from the amino alcohol 4 and trimethyl borate (1 h at r.t.). Also, it has been reported that (S)-proline (5) (Figure 1) and BH3·THF reagent combination was effective in enantioselective reduction of acetophenone at 110 °C in 10 minutes. Accordingly, it is desirable to develop simplified, convenient procedures for the asymmetric reduction of the 1,4-diphenylbutane-1,4-dione (1). We wish to report here the results of detailed studies on the preparation and use of the chiral 1,4-diol 2 for the synthesis of several chiral 2,5-diphenylpyrrolidine derivatives.

Figure 1 Structures of chiral alcohols 4 and 5

The required diphenylbutane-1,4-dione (1) is easily prepared by following an established protocol via the Friedel–Craft acylation of benzene with fumaryl chloride and subsequent reduction with SnCl2/HCl.

The borane reagents like BH3·SMe2, BH3·THF, diborane, and catecholborane suffer from drawbacks such as thermal decomposition, low concentration, noxious odor or expense. Accordingly, we have examined the asymmetric reduction of 1,4-dione 1 using borane reagents generated in situ using NaBH4 and amine-boranes in combination with (S)-(–)-α,α-diphenyl-2-pyrrolidinemethanol (4) and (S)-proline (5). The results are summarised in Tables 1 and 2. When (S)-(–)-α,α-diphenyl-2-pyrrolidinemethanol (4) (10 mol%) was used in combination with NaBH4/Me3SiCl reagent, the 1,4-diol 2 was obtained in 70% yield, with dlmeso ratio 75:25 and in 52% ee (Table 1, entry 1). The results were better when B(OMe)3 was used in combination with NaBH4/Me3SiCl, BH3·THF and PhNEt2·BH3 as hydride sources, (Table 1, entries 2, 3 and 4) (Scheme 2). The chiral (S)-(–)-α,α-diphenyl-2-pyrrolidinemethanol (4) was prepared from (S)-proline (5) in several steps. Although good enantioselectivities (Table 1) were achieved using this reagent, we have examined the development of a practical method for the reduction using (S)-proline (5) itself. Buono et al. have reported that (S)-proline (5) gives good results in the asymmetric reduction of
Scheme 2  Asymmetric reduction using (S)-(-)-α,α-diphenyl-2-pyrrolidinemethanol (4) in combination with borane reagent and B(OMe)₃ (dllmeso = 75:25 to 93:7; 52–97% ee, 70–85% yield)

Table 1  Asymmetric Reduction of 1,4-Dione 1 to 1,4-Diol 2 Using (S)-(-)-α,α-Diphenyl-2-pyrrolidinemethanol (4)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Borane Reagent</th>
<th>Yield (%)</th>
<th>dllmeso Ratio</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>NaBH₄/TMSCl</td>
<td>70</td>
<td>75:25</td>
<td>52 (1R,4R)</td>
</tr>
<tr>
<td>2a</td>
<td>NaBH₄/TMSCl</td>
<td>70</td>
<td>93.7</td>
<td>93 (1R,4R)</td>
</tr>
<tr>
<td>3a</td>
<td>BH₃·THF</td>
<td>85</td>
<td>88:12</td>
<td>97 (1R,4R)</td>
</tr>
<tr>
<td>4a</td>
<td>PhNEt₂·BH₃</td>
<td>70</td>
<td>90:10</td>
<td>97 (1R,4R)</td>
</tr>
</tbody>
</table>

a All the reactions were carried out using 10 mol% of catalyst 4 and 5 mmol of 1,4-dione 1.

b Yields are of 1,4-diol 2 isolated by column chromatography on silica gel using hexane–EtOAc as eluent.

c The dllmeso ratios were calculated from 1H NMR data.

d All ee values reported here are based on maximum [α]D²¹ -58.5 (c = 1.01, CHCl₃, >98% ee) for (S)-1,4-diol (i.e. R,R- and S,S-isomers) present in the mixture.

e Reaction was performed without using B(OMe)₃.

Scheme 3  Synthesis of (2S,5S)-N-alkyl and N-aryldihydroxyproline derivatives

In conclusion, the enantioselective reduction of 1,4-diphenylbutane-1,4-dione (1) to the corresponding 1,4-diol 2 is conveniently carried out using (S)-(-)-α,α-diphenyl-2-pyrrolidinemethanol (4) and (S)-proline (5) and easy to handle borane reagents. The convenient synthetic procedures described here for the preparation of the chiral 2,5-diphenylpyrrolidine system 3 should facilitate the syntheses and application of these derivatives.

Table 2  Asymmetric Reduction of 1,4-Dione 1 to 1,4-Diol 2 Using (S)-Proline (5)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Borane Reagent</th>
<th>Yield (%)</th>
<th>dllmeso Ratio</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>NaBH₄</td>
<td>60</td>
<td>22:78</td>
<td>64 (1S,4S)</td>
</tr>
<tr>
<td>2b</td>
<td>BH₃·THF</td>
<td>60</td>
<td>62:38</td>
<td>81 (1R,4R)</td>
</tr>
<tr>
<td>3c</td>
<td>BH₃·THF</td>
<td>60</td>
<td>76:24</td>
<td>53 (1R,4R)</td>
</tr>
<tr>
<td>4d</td>
<td>PhNEt₂·BH₃</td>
<td>75</td>
<td>73:27</td>
<td>85 (1R,4R)</td>
</tr>
</tbody>
</table>

a Yields are of 1,4-diol 2 isolated by column chromatography on silica gel using hexane–EtOAc as eluent.

b The dllmeso ratios were calculated from 1H NMR data.

c All ee values reported here are based on maximum [α]D²¹ -58.5 (c = 1.01, CHCl₃, >98% ee) for (S)-1,4-diol (i.e. R,R- and S,S-isomers) present in the mixture.

d 100 mol% of 5 was used.

e 2.5 mmol of the 1,4-dione 1 was used.

f 2 mmol of the 1,4-diene 1 was used.

g (S)-proline (5) was added to BH₃·THF prepared in situ using NaBH₄/I₂.

h 20 mol% of 5 was used.

i BH₃·THF prepared in situ using NaBH₄/I₂ was added to (S)-proline (5).

Reduction of 1,4-Diphenylbutane-1,4-dione (1) Using BH₃·THF Complex/(S)-(-)-α,α-Diphenyl-2-pyrrolidinemethanol (4)/B(OMe)₃ (10 mol %) Reagent Combination (Entry 3, Table 1) NaBH₄ (0.76 g, 20 mmol) was suspended in anhyd THF (40 mL) under N₂. The reaction mixture was cooled to 0 °C and a solution of I₂ (2.1 g, 8.3 mmol) in THF (25 mL) was added dropwise during 2.5 h at 0 °C using a pressure equalizing dropping funnel. A solution of 4 (0.8 mmol) and B(OH)₃, (1 mmol) in THF (10 mL) was added and the mixture was stirred for 10 min. To this mixture, was added slowly 1,2-dibenzoyl methane (1 g, 4.6 mmol) dissolved in THF (15 mL) with a pressure equalizing dropping funnel during 1 h at 10 °C and the mixture was further stirred at 25 °C for 1 h. The mixture was hydrolysed using 2 N HCl (15 mL) and the organic layer was separated. The aqueous layer was extracted with EtO. The combined organic extracts were washed with brine (10 mL) and dried (MgSO₄). After evaporation, the crude product was purified on a silica gel column using hexane–EtOAc (80:20) as eluent to obtain the (+)-1,4-diol 2 in 97% ee; yield: 1.02 g (85%); mp 63–65 °C; [α]D²¹ = 49.8 (c = 0.542, CHCl₃), [α]D²¹ = 35.1 (c = 1.01, CHCl₃, >98% ee) for (1R,4S) and (1S,4R).

1H NMR (200 MHz, CDCl₃); δ = 1.17–1.9 (m, 4 H), 2.8 (s, 2 H), 4.6–4.7 (m, 2 H), 7.2–7.4 (m, 10 H).

1C NMR (50 MHz, CDCl₃); δ = 35.1 (meso), 36.0 (dl), 73.9 (meso), 74.4 (dl), 126.0, 127.4, 128.4, 144.8.

acetophenone at refluxing conditions. Accordingly, we have examined the asymmetric reduction of the 1,4-dione 1 using (S)-proline 5 along with various hydride sources. The results are summarised in Table 2.

Unfortunately, the 1,4-diol 2 was obtained only with lower selectivities using (S)-proline (5). However, the mixture of nonracemic and meso diastereomers of 2 has been readily purified to obtain the samples of >95% ee using (S)-proline (5) and B(OH)₃. The resultant 1,4-diol 2 (>95% ee) was readily cyclised using primary amines to obtain the corresponding 2,5-diphenylpyrrolidine derivatives 3a–e via the dimesylate 6 (Scheme 3).
Reduction of 1,4-Diphenylbutane-1,4-dione (1) with NaBH₄/(S)-Proline (5) Complex (Entry 1, Table 2)
NaBH₄ (0.19 g, 5 mmol) and (S)-proline (5; 0.58 g, 5 mmol) were taken in THF (10 mL) and stirred for 2 h at r.t. 1,2-Dibenzoylethane (0.59 g, 2.5 mmol) was added to this suspension of sodium L-prolinate borane complex and the mixture was stirred at 40 °C for 4 d. The excess reagent was decomposed with H₂O and the mixture was concentrated under reduced pressure and extracted with Et₂O. The organic extracts were washed with 10% HCl (10 mL), aq sat. NaHCO₃ solution (10 mL), brine (10 mL), and dried (MgSO₄). The solvent was evaporated and the crude product was purified on a silica gel column using hexane–EtOAc (80:20) as eluent to obtain the (–)-1,4-diol (–)–1,4-diphenylpyrrolidine (3a); yield: 0.186 g (70%); [α]D₂¹ –123 (c = 0.155, CHCl₃).

(25,5S)-N-Phenyl-2,5-diphenylpyrrolidine (3b)
Yield: 0.148 (45%); [α]D₂¹ –15 (c = 0.100, CHCl₃).

(IR (KBr): 3052, 2965, 1596, 740, 700 cm⁻¹.

1H NMR (200 MHz, CDCl₃): δ = 1.8–2.1 (m, 2 H), 2.3–2.5 (m, 2 H), 3.4 (s, 3 H), 4.8–4.9 (t, 2 H, J = 2.7 Hz), 6.6–6.7 (m, 4 H), 7.2–7.6 (m, 10 H).

13C NMR (50 MHz, CDCl₃): δ = 35.0, 55.2, 67.8, 112.6, 120.8, 121.8, 122.0, 126.1, 126.8, 128.6, 144.0, 145.1.

MS (EI): m/z = 299 (M⁺).

(25,5S)-N-(2-Methoxyphenyl)-2,5-diphenylpyrrolidine (3c)
Yield: 0.186 g (70%); [α]D₂¹ –123 (c = 0.155, CHCl₃).

(IR (KBr): 3375, 1602 cm⁻¹.

1H NMR (200 MHz, CDCl₃): δ = 1.8–2.1 (m, 2 H), 2.3–2.8 (m, 5 H), 3.0–3.3 (m, 1 H), 3.35–3.6 (m, 1 H), 4.2–4.5 (m, 2 H), 7.1–7.6 (m, 10 H).

13C NMR (50 MHz, CDCl₃): δ = 33.5, 49.1, 59.4, 66.5, 127.2, 127.8, 128.6, 144.1.

Anal. Calcd for C₁₉H₁₅NO: C, 83.63; H, 6.76; N, 5.61. Found: C, 83.5; H, 6.7; N, 5.6.

(25,5S)-N-Butyl-2,5-diphenylpyrrolidine (3e)
Yield: 0.153 g (55%); [α]D₂¹ –90 (c = 0.140, CHCl₃).

(IR (KBr): 3063, 2959, 1602 cm⁻¹.

1H NMR (200 MHz, CDCl₃): δ = 0.5–0.7 (t, 3 H), 0.8–1.2 (m, 4 H), 1.7–2.0 (m, 2 H), 2.1–2.3 (m, 2 H), 2.4–2.6 (t, 2 H, J = ? Hz), 3.7–3.9 (t, 2 H, J = 7 Hz), 7.2–7.6 (m, 10 H).

13C NMR (50 MHz, CDCl₃): δ = 13.7, 20.5, 29.3, 34.9, 53.0, 69.4, 126.6, 127.2, 128.2, 146.2.

MS (EI): m/z = 279 (M⁺).

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