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

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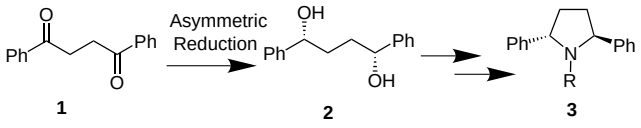
Abstract: Asymmetric reduction of 1,4-diphenylbutane-1,4-dione (**1**) was carried out using the reducing agents $NaBH_4$, BH_3·THF, and $PhNEt_2$·BH_3 in combination with the chiral reagents (*S*)-(–)-α,α-diphenyl-2-pyrrolidinemethanol (**4**) or (*S*)-proline (**5**), in the presence of TMSCl or $B(OMe)_3$ 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 C_2-symmetric (2*S*,5*S*)-2,5-diphenylpyrrolidine derivatives **3a**–**e** (45 to 75% yield) via the corresponding dimesylate prepared using MsCl and Et_3N.

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 C_2-symmetric chiral auxiliaries has gained considerable importance in current asymmetric syntheses.[1] 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.[2–4] In this case, the recovery and recycling of chiral auxiliary are somewhat difficult. Therefore, several groups pursued the synthesis of the corresponding diphenyl anologue, 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-Diphenyl pyrrolidine derivatives

The asymmetric reduction of the diferrocenyl-1,4-diketone to obtain the corresponding diol samples of >98% ee has been reported[5] using the CBS oxazaborolidine catalyst, which requires considerable care for preparation to achieve good selectivities.[6] In these reductions, the borane reagents such as BH_3·THF, and BH_3·SMe_2, have been used. In recent years, several simplified procedures have appeared[7,8] 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.).[9] Also, it has been reported[10] that (*S*)-proline (**5**) (Figure 1) and BH_3·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.

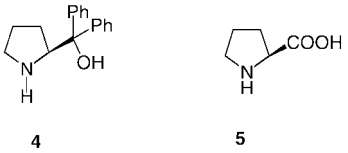


Figure 1 Structures of chiral alcohols **4** and **5**

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 $SnCl_2$/HCl.[11,12]

The borane reagents like BH_3·SMe_2, BH_3·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 $NaBH_4$ 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 $NaBH_4$/Me_3SiCl reagent, the 1,4-diol **2** was obtained in 70% yield, with *dl*/*meso* ratio 75:25 and in 52% ee (Table 1, entry 1). The results were better when $B(OMe)_3$ was used in combination with $NaBH_4$/Me_3SiCl, BH_3·THF and $PhNEt_2$·BH_3 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.[14] 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.[10] have reported that (*S*)-proline (**5**) gives good results in the asymmetric reduction of

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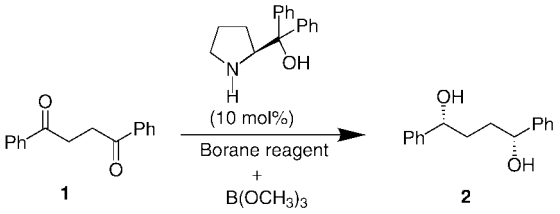


Scheme 2 Asymmetric reduction using (*S*)-(–)-α,α-diphenyl-2-pyrrolidinemethanol (**4**) in combination with borane reagent and $B(OMe)_3$ (*dl*/*meso* = 75:25 to 93:7; 52–97% ee, 70–85% yield)

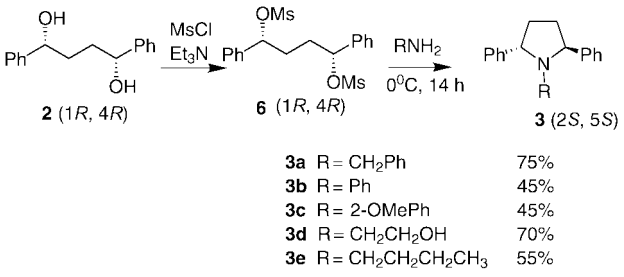
Table 1 Asymmetric Reduction of 1,4-Dione **1** to 1,4-Diol **2** Using (*S*)-(–)-α,α-Diphenyl-2-pyrrolidinemethanol (**4**)

Entry[a]	Borane Reagent	Yield (%)[b]	*dl*/*meso* ratio[c]	ee (%)[d]
1[e]	$NaBH_4$/TMSCl	70	75:25	52 (1*R*,4*R*)
2	$NaBH_4$/TMSCl	70	93:7	93 (1*R*,4*R*)
3	BH_3·THF	85	88:12	97 (1*R*,4*R*)
4	$PhNEt_2$·BH_3	70	90:10	97 (1*R*,4*R*)

[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 *dl*/*meso* ratios were calculated from ^{13}C NMR data.
[d] All ee values reported here are based on maximum $[\alpha]_D^{21}$ –58.5 (*c* = 1.01, $CHCl_3$, >98% ee) for (1*S*,4*S*)-(–)-**2**[13] and the % of ee was calculated based on amount of *dl* (i.e. *R*,*R*- and *S*,*S*-isomers) present in the mixture.
[e] Reaction was performed without using $B(OMe)_3$.

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 $B(OH)_3$.[15] 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).



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

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

Entry	Borane Reagent	Yield (%)[a]	*dl*/*meso* Ratio[b]	ee (%)[c]
1[d,e]	$NaBH_4$	60	22:78	64 (1*S*,4*S*)
2[d,f]	BH_3·THF[g]	60	62:38	81 (1*R*,4*R*)
3[f,h]	BH_3·THF[i]	60	76:24	53 (1*R*,4*R*)
4[f,h]	$PhNEt_2$·BH_3	75	73:27	85 (1*R*,4*R*)

[a] Yields are of 1,4-diol **2** isolated by column chromatography on silica gel using hexane–EtOAc as eluent.
[b] The *dl*/*meso* ratios were calculated from ^{13}C NMR data.
[c] All ee values reported here are based on maximum $[\alpha]_D^{21}$ –58.5 (*c* = 1.01, $CHCl_3$, >98% ee) for (1*S*,4*S*)-(–)-**2**[13] and the % of ee was calculated based on amount of *dl* (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-dione **1** was used.
[g] (*S*)-Proline (**5**) was added to BH_3·THF prepared in situ using $NaBH_4$/I_2.
[h] 20 mol% of **5** was used.
[i] BH_3·THF prepared in situ using $NaBH_4$/I_2 was added to (*S*)-proline (**5**).

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.

Reduction of 1,4-Diphenylbutane-1,4-dione (1) Using BH_3·THF Complex/(*S*)-(–)-α,α-Diphenyl-2-pyrrolidinemethanol (4)/$B(OMe)_3$ (10 mol%) Reagent Combination (Entry 3, Table 1)

$NaBH_4$ (0.76 g, 20 mmol) was suspended in anhyd THF (40 mL) under N_2. The reaction mixture was cooled to 0 °C and a solution of I_2 (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 $B(OMe)_3$ (1 mmol) in THF (10 ml) was added and the mixture was stirred for 10 min. To this mixture, was added slowly 1,2-dibenzoylethane (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 Et_2O. The combined organic extracts were washed with brine (10 mL) and dried ($MgSO_4$). 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; *dl*/*meso* ratio = 88:12; $[\alpha]_D^{21}$ +49.8 (*c* = 0.542, $CHCl_3$) {Lit.[13] $[\alpha]_D^{21}$ –58.5 (*c* = 1.01, $CHCl_3$, >98% ee) for (1*S*,2*S*)-(–)-**2**}.

^1H NMR (200 MHz, $CDCl_3$): δ = 1.2–1.9 (m, 4 H), 2.8 (s, 2 H), 4.6–4.7 (m, 2 H), 7.2–7.4 (m, 10 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 35.1 (*meso*), 36.0 (*dl*), 73.9 (*meso*), 74.4 (*dl*), 126.0, 127.4, 128.4, 144.8.

Reduction of 1,4-Diphenylbutane-1,4-dione (1) with $NaBH_4$/(*S*)-Proline (5) Complex (Entry 1, Table 2)

$NaBH_4$ (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) in THF (10 mL) 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 H_2O and the mixture was concentrated under reduced pressure and extracted with Et_2O. The organic extracts were washed with 10% HCl (10 mL), aq sat. $NaHCO_3$ solution (10 mL), brine (10 mL), and dried ($MgSO_4$). 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 (–)-**2** in 64% ee, yield: 0.36 g (60%); *dl*/*meso* ratio = 22:78; $[\alpha]_D^{21}$ –8.0 (*c* = 0.25, $CHCl_3$) {Lit.[13] $[\alpha]_D^{21}$ –58.5 (*c* = 1.01, $CHCl_3$), >98% ee for (1*S*,4*S*)-(–)-**2**}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.7–2.0 (m, 4 H), 2.4 (s, 2 H), 4.6–4.8 (m, 2 H), 7.2–7.4 (m, 10 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 35.0 (*meso*), 36.0 (*dl*), 74.1 (*meso*), 74.5 (*dl*), 125.9, 127.4, 128.4, 144.6.

Reduction of 1,4-Diphenylbutane-1,4-dione (1) using (*S*)-Proline (5) (20 mol%) and *N*,*N*-Diethylaniline·BH_3 Complex (Entry 4, Table 2)

To a stirred suspension of (*S*)-proline (**5**; 0.095 g, 0.83 mmol) in toluene (7 mL) was added a 1 M toluene solution of *N*,*N*-diethylaniline·BH_3 (0.83 mL, 0.83 mmol) at 25 °C. After stirring for a further 10 min, the reaction mixture was heated to reflux (110 °C). 1,2-Dibenzoylethane (0.476 g, 2 mmol) in THF (10 mL) was added, followed by dropwise addition of a 1 M toluene solution of *N*,*N*-diethylaniline·BH_3 (4 mL, 4 mmol) over 15 min. The mixture was further stirred for 0.5 h. After cooling to 25 °C, Et_2O (20 mL) was added. After work-up and purification, the (+)-1,4-diol (+)-**2** was obtained in 85% ee; yield: 0.36 g (75%); *dl*/*meso* ratio = 73:27, $[\alpha]_D^{21}$ +36.2 (*c* = 0.276, $CHCl_3$) {Lit.[13] $[\alpha]_D^{21}$ –58.5 (*c* = 1.01, $CHCl_3$), >98% ee for (1*S*,2*S*)-(–)-**2**}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.3–1.9 (m, 4 H), 2.6 (s, 2 H), 4.6–4.8 (m, 2 H), 7.2–7.4 (m, 10 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 35.0 (*meso*), 35.9 (*dl*), 74.0 (*meso*), 74.4 (*dl*), 126.0, 127.4, 128.4, 144.7.

(1*R*,4*R*)-1,4-Bis(methanesulfonyloxy)-1,4-diphenylbutane (6)[13]

To methanesulfonyl chloride (0.4 mL, 5.3 mmol) in CH_2Cl_2 (20 mL) at –20 °C was added a solution of (1*R*,4*R*)-1,4-diphenylbutane-1,4-diol (**2**; 0.5 g, 2.06 mmol, 96% ee) and Et_3N (0.87 mL, 6.2 mmol) in CH_2Cl_2 (20 mL). The reaction mixture was stirred for 1.45 h at –20 °C and then quenched with aq sat. NH_4Cl (2 mL). It was brought to 25 °C and concentrated to approximately 17 mL. The solution was then diluted with EtOAc (80 mL) and washed successively with a mixture of H_2O–brine–aq sat. Na_2CO_3 (1:2:1, 2 × 20 mL), and aq sat. $NaHCO_3$ (2 × 20 mL). The organic layer was dried ($MgSO_4$), filtered through Celite and concentrated to approximately 8 mL. The solution was then cooled to 0 °C. The crude dimesylate was precipitated out by dropwise addition of hexane (80 mL). The resulting solid was filtered, dried and immediately used for the next reaction without further purification.

***N*-Substituted 2,5-Diphenylpyrrolidines; (2*S*,5*S*)-*N*-Benzyl-2,5-diphenylpyrrolidine (3a);Typical Procedure**

Benzylamine (21 mL, 196 mmol) was added at 0 °C to (1*R*, 4*R*)-1,4-bis(methanesulfonyloxy)-1,4-diphenylbutane (**6**; 0.32 g, 1 mmol) and the mixture was stirred at 0 °C for 14 h. After warming to 25 °C, the excess benzylamine was evaporated and the residue was dissolved in Et_2O (25 mL). The contents were successively washed with aq sat. $NaHCO_3$ (10 mL), brine (10 mL), dried ($MgSO_4$), and concentrated to afford the crude product as a gum. The crude product was purified on a silica gel column using hexane as eluent; yield: 0.234 g (75%); $[\alpha]_D^{21}$ –126 (*c* = 0.435, $CHCl_3$).

IR (neat): 3061, 1602 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.98–2.2 (m, 2 H), 2.4–2.8 (m, 2 H), 3.15 (d, *J* = 14 Hz, 1 H), 3.65 (d, *J* = 14 Hz, 1 H), 4.28 (m, 2 H), 7.1–7.3 (m, 15 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 33.4, 51.1, 65.5, 126.4, 127.0, 128.0, 128.2, 128.3, 128.4, 140.2, 144.1.

Anal. Calcd for $C_{23}H_{23}N$: C, 88.25; H, 7.40; N, 4.47. Found: C, 88.50; H, 7.65; N, 4.65.

(2*S*,5*S*)-*N*-Phenyl-2,5-diphenylpyrrolidine (3b)

Yield: 0.134 g (45%); mp 190–1 94 °C; $[\alpha]_D^{21}$ –31 (*c* = 0.236, $CHCl_3$).

IR (KBr): 3020, 2935, 1597, 1502, 1359, 748, 698 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.7–1.9 (m, 2 H), 2.5–2.7 (m, 2 H), 5.2–5.4 (m, 2 H), 6.4–6.7 (m, 3 H) 7.0–7.6 (m, 12 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 32.5, 63.3, 114.0, 115.7, 126.2, 126.7, 128.6, 128.8, 144.0, 145.1.

MS (EI): *m*/*z* = 299 (M^+).

(2*S*,5*S*)-*N*-(2-Methoxyphenyl)-2,5-diphenylpyrrolidine (3c)

Yield: 0.148 (45%); $[\alpha]_D^{21}$ –15 (*c* = 0.100, $CHCl_3$).

IR (KBr): 3052, 2965, 1596, 740, 700 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.9–2.1 (m, 2 H), 2.3–2.5 (m, 2 H), 3.4 (s, 3 H), 4.8–4.9 (t, 2 H, *J* = ? Hz), 6.6–6.9 (m, 4 H), 7.2–7.6 (m,10 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 34.5, 55.2, 67.8, 112.6, 120.8, 121.8, 122.0, 126.1, 126.5, 128.0, 139.0, 146.2, 153.1.

MS (EI): *m*/*z* = 329 (M^+).

(2*S*,5*S*)-*N*-(2-Hydroxyethyl)-2,5-diphenylpyrrolidine (3d)

Yield: 0.186 g (70%); $[\alpha]_D^{21}$ –123 (*c* = 0.155, $CHCl_3$).

IR (neat): 3375, 1602 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): 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).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 33.5, 49.1, 59.4, 66.5, 127.2, 127.7, 128.6, 144.1.

Anal. Calcd for $C_{18}H_{21}NO$: C, 80.97; H, 7.92; N, 5.24. Found: C, 81.35; H, 7.98; N, 5.50.

(2*S*,5*S*)-*N*-Butyl-2,5-diphenylpyrrolidine (3e)

Yield: 0.153 g (55%); $[\alpha]_D^{21}$ –90 (*c* = 0.140, $CHCl_3$).

IR (neat): 3063, 2959, 1602 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.5–0.71 (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* = ? Hz), 7.2–7.6 (m, 10 H)

^{13}C NMR (50 MHz, $CDCl_3$): 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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