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Resolution of C_2-symmetric 2,3-diphenylbutane-1,4-diol and purification of diastereomeric 1,4-diphenylbutane-1,4-diol using (*S*)-proline and boric acid

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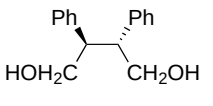
Abstract—Racemic 2,3-diphenylbutane-1,4-diol (±)-**1** is resolved to obtain the corresponding (*R*,*R*)-isomer in 98% e.e. through reaction with (*S*)-proline and boric acid. Partially resolved (*R*,*R*)-(−)-**1** and (*S*,*S*)-(+)-**1** have been enriched to obtain samples of 95 and 97% e.e. through reaction with (*S*)-proline and boric acid. Diastereomeric 1,4-diphenylbutane-1,4-diol **2** has been purified to obtain the (*R*,*R*)-isomer in 98% e.e. using (*S*)-proline and boric acid.

1. Introduction

Chiral auxiliaries derived from chiral diols, dicarboxylic acids, amines, diamines, amino acids and amino alcohols have proven synthetic applications in asymmetric synthesis.[1] These derivatives can be obtained either by resolution or by asymmetric synthesis.[2] Recently, we and others have reported the use of (*S*)-proline for the resolution of certain racemic diols through preparation of the corresponding diastereomeric borate complexes.[3] These results prompted us to examine the use of (*S*)-proline and boric acid for the resolution of C_2-symmetric 2,3-diphenylbutane-1,4-diol[5a] and 1,4-diphenylbutane-1,4-diol[6g] which have proven applications as starting materials for the synthesis of certain useful C_2-symmetric chiral ligands.[5a,6]



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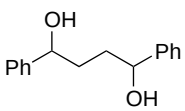

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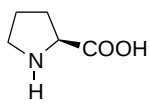

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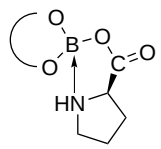

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followed by reduction using $NaBH_4/I_2$.[5,7,8] We have observed that the diol **1** can be resolved through the chiral borate of the type **4** derived from (*S*)-proline and boric acid following a convenient protocol (Scheme 1). It was found that the sample of (2*R*,3*R*)-**1** with 98% e.e. and the partially resolved (2*S*,3*S*)-**1** enantiomer can be readily isolated from the precipitate and filtrate fractions obtained by heating the racemic diol (±)-**1** with (*S*)-proline and boric acid in refluxing toluene or benzene (Scheme 1).

After filtration and decomposition of the precipitated complex with a mixture of THF/H_2O (1:1), (2*R*,3*R*)-**1** was isolated (37% yield, 98% e.e.). From the filtrate, the enantiomeric (2*S*,3*S*)-**1** was isolated (58% yield, 57% e.e., entry 1). It is of interest to note that the non-

2. Results and discussion

The racemic diol **1** was readily prepared through oxidative coupling of ethyl phenylacetate using $TiCl_4/Et_3N$ racemic samples of (2*S*,3*S*)-**1** (57% e.e.) and (2*R*,3*R*)-**1** (48% e.e.) were also further enriched to obtain samples of 97% e.e. (entry 2) and 95% e.e. (entry 3) following the same procedure. We have also examined the resolution of the racemic diol **1** using *n*-butyl borate in the place of boric acid. In this case, only partially resolved diols were obtained (entry 4, Table 1).

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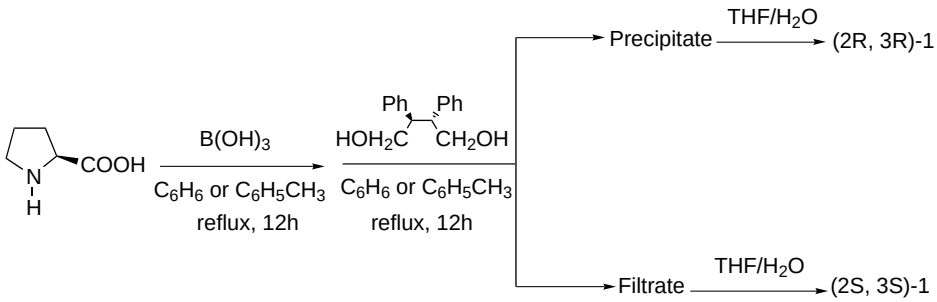


Scheme 1.

Table 1. Resolution of racemic diol **1** and purification of the diastereomeric diol **2** using (*S*)-proline and boric acid

S. No.	Substrate, % e.e.	Solvent	Diols **1** and **2** obtained from[c]			
			Precipitate		Filtrate	
			% e.e.[a] (conf.)	Yield (%)[b]	% e.e.[a] (conf.)	Yield (%)[b]
1	**1**, 00	Benzene	98 (2*R*,3*R*)	37	57 (2*S*,3*S*)	53
2	(2*S*,3*S*)-**1**, 57	Benzene	97 (2*S*,3*S*)	63	10 (2*S*,3*S*)	23
3	(2*R*,3*R*)-**1**, 48	Benzene	95 (2*R*,3*R*)	53	30 (2*S*,3*S*)	34
4[d]	**1**, 00	Benzene	53 (2*R*,3*R*)	24	15 (2*S*,3*S*)	60
5	**1**, 00	Toluene	92 (2*R*,3*R*)	25	50 (2*S*,3*S*)	60
6	(1*R*,4*R*)-**2**, 84[e]	Benzene	98 (1*R*,4*R*)	84	0	8
7	(1*R*,4*R*)-**2**, 45[e]	Benzene	98 (1*R*,4*R*)	40	17 (1*R*,4*R*)[e]	45
8	(1*R*,4*R*)-**2**, 84[e]	Toluene	98 (1*R*,4*R*)	75	10 (1*R*,4*R*)[e]	10

[a] All e.e. values reported here are based on the reported maximum $[\alpha]_D^{21} = -48.2$ (*c* 0.249, $CHCl_3$) for (1*R*,2*R*)-(−)-**1**,[10] $[\alpha]_D^{21} = +48.2$ (*c* 0.249, $CHCl_3$) for (2*S*,3*S*)-(+)-**1**,[10] and $[\alpha]_D^{21} = -58.5$ (*c* 1.01, $CHCl_3$, >98% e.e.) for (1*S*,2*S*)-(−)-**2**.[6g] (For entries 6–8 the ^{13}C NMR spectrum of the (1*R*,4*R*)-**2** diol obtained from the precipitate fraction indicated the absence of the corresponding *meso* isomer.)

[b] The yields are of the recovered products, based on the total amount of the starting isomeric mixture used (e.g. entry 1, total yield 95%).

[c] For entries 1–3 and 5–8, the experiments were carried out using the following procedure: (*S*)-proline (1.1 equiv.) and boric acid (1.1 equiv.) were dissolved in dry solvent (8 mL) and heated under reflux for 12 h. The corresponding diol (1 equiv.), dissolved in dry solvent (8 mL), was added and heated under reflux for a further 12 h (Dean–Stark set-up).

[d] (*S*)-Proline (5.5 mmol), *n*-butyl borate (5.5 mmol) and the (±)-**1** diol (5 mmol) were taken in dry benzene (80 mL) and heated under reflux for 24 h.

[e] Diastereomeric mixture with the (1*R*,4*R*)-isomer present in excess over the sum of racemic and *meso* compounds.

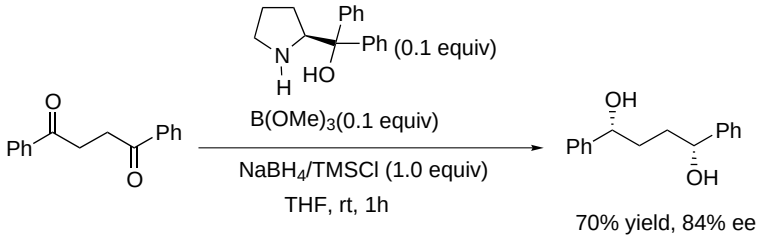
Efforts were also undertaken to characterize the complex formed through analyses of the precipitate obtained (Scheme 1 and entry 5, Table 1) using IR, ^1H, ^{13}C NMR, elemental analysis. The data are in accordance with the formation of the complex of the type **4**. Previously similar cyclic borate ester complexes were reported by Shan et al.[4]

To examine whether the resolution can be carried out in a more acceptable solvent, we examined the use of toluene (entry 5, Table 1). In this run, the diol (2*R*,3*R*)-**1** was isolated (25% yield, 92% e.e.) from the precipitate fraction and the (2*S*,3*S*)-**1** isomer was isolated with (60% yield, 50% e.e.) from the filtrate fraction (entry 5, Table 1). The present method has an advantage over previously reported procedures that require resolution of racemic dicarboxylic acids followed by reduction.[3f,9,10] In the present procedure, the resolution is carried out after the reduction and hence there is no wastage of chiral product after the resolution. Accordingly, the present method would serve as a simple alternative procedure for the preparation of the chiral diol **1**.

We have also examined the purification of the synthetically useful C_2-symmetric 1,4-diphenylbutane-1,4-diol **2** through synthesis of the corresponding borate complex with (*S*)-proline. Previously, the diol **2** has been prepared in enantiomerically pure form by the asymmetric reduction of 1,4-diphenylbutanedione using Ipc_2BCl[6h] or *B*-methoxy oxazaborolidine/$BH_3{\cdot}SMe_2$.[6g] We have found that the reduction of 1,4-diphenylbutanedione by *B*-methoxy oxazaborolidine (10 mol%)/$NaBH_4$–TMSCl system gives diol **2** in 84% e.e. and 70% yield (Scheme 2). Also, the diol **2** (84% e.e.) obtained in this way can be readily purified to obtain a sample of 98% e.e. (entry 6 and 8, Table 1).

3. Conclusion

In conclusion, the new methods of resolution of the racemic diol **1** and enrichment of optical purity of the diastereomeric diol **2** described here would stimulate further studies on the application of these procedures involving inexpensive reagents for the resolution of



Scheme 2.

racemic diols. Also, since the chiral diols **1** and **2** have proven synthetic applications, the methods described here should be useful for further synthetic exploitation of these useful C_2-symmetric chiral compounds.

4. Experimental

4.1. Resolution of racemic diol 1 using (*S*)-proline and boric acid (entry 5, Table 1)

(*S*)-Proline (0.64 g, 5.5 mmol) and boric acid (0.34 g, 5.5 mmol) were stirred under reflux in dry toluene (40 mL) for 12 h. The water produced was removed using Dean–Stark apparatus. Diol-(±)-**1** (1.21 g, 5 mmol) dissolved in toluene (40 mL) was added to the reaction mixture under nitrogen pressure through a cannula. The slurry becomes homogeneous and precipitation starts after 3 h. The contents were stirred under reflux for a further 9 h. The precipitate was filtered in hot condition and the solution was concentrated. The residue obtained was decomposed using a 1:1 mixture of THF and water (30 mL). Aqueous HCl (3N, 15 mL) was added and stirred at rt for 2 h. It was extracted with ethyl acetate (2×25 mL). The combined organic extract was washed successively with water, brine and dried over anhydrous $MgSO_4$, filtered and concentrated. Purification by column chromatography on silica gel using hexane:ethyl acetate (3:1) as eluent, afforded (2*S*,3*S*)-(+)-2,3-diphenylbutane-1,4-diol **1** (0.726 g, 60% yield, 50% e.e.); $[\alpha]_D^{25}=+24.1$ (*c* 0.41, $CHCl_3$), lit.[10] $[\alpha]_D^{21}=+48.2$ (*c* 0.249, $CHCl_3$). The complex obtained from the precipitate fraction (Scheme 1) was characterized by CHN, IR, ^1H and ^{13}C NMR analysis. Mp 273°C; IR (KBr): 3200, 3088, 3030, 1747, 1602, 1494, 1450, 1385, 1315, 1296, 1269, 1163, 1136, 1101, 1057, 912, 831, 756, 700 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ (ppm) 1.5–2.5 (m, 6H), 3.0–4.4 (m, 9H), 6.9–7.3 (m, 10H); ^{13}C NMR (50 MHz, CD_3CN+ $CDCl_3$): δ (ppm) 24.2 28.0, 46.6, 53.1, 53.3, 62.2, 66.8, 67.1, 125.3, 127.0, 127.2, 127.3, 141.1, 141.5, 172.3. Anal. calcd for $C_{21}H_{24}BNO_4$: C, 69.03; H, 6.623; N, 3.83; Found: C, 68.77; H, 6.21; N, 3.65). The precipitate obtained was decomposed using THF/water/dil. HCl. After work-up, the (2*R*,3*R*)-(−)-2,3-diphenylbutane-1,4-diol **1** was isolated, (0.3 g, 25% yield, 92% e.e.); $[\alpha]_D^{25}=-44.3$ (*c* 0.324, $CHCl_3$), lit.[10] $[\alpha]_D^{21}=-48.2$ (*c* 0.249, $CHCl_3$). After recrystallization from hexane, the (2*R*,3*R*)-**1** diol was obtained in 98% e.e.

4.2. Reduction of 1,4-diphenylbutane-1,4-dione

Freshly distilled chlorotrimethylsilane (3.12 g, 28.8 mmol) was added to a suspension of $NaBH_4$ (1.08 g, 28.8 mmol) in dry THF (120 mL). The mixture was heated at 70°C for 1 h and then cooled to rt. A solution of *B*-methoxy oxazaborolidine[6g] [prepared using α,α-diphenyl-2-pyrrolidine methanol (2.4 mmol) and trimethyl borate (3 mmol) in THF (15 mL)] was added. A solution of 1,4-diphenylbutane-1,4-dione (2.8 g, 12 mmol) in THF (25 mL) was added slowly with a pressure equalizer over a 2 h period at 10°C. After stirring at rt for a further 1 h, the reaction mixture was hydrolyzed with aqueous HCl (5N, 60 mL) and extracted with ether (3×25 mL). The combined organic extract was washed successively with H_2O, brine and dried over $MgSO_4$, filtered and concentrated. Purification on a silica gel column using hexane:ethyl acetate (3:1) as eluent gave diol **2** as a gummy liquid which solidified on standing at rt (1.99 g, 70% yield, 84% e.e.); $[\alpha]_D^{25}=+50.1$ (*c* 0.454, $CHCl_3$), lit.[6g] $[\alpha]_D^{21}=-58.5$ (*c* 1.01, $CHCl_3$, >98% e.e.) for (1*S*,2*S*)-(−)-**2**; mp 62–64°C; IR (KBr): 3339, 3025, 1207, 990 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ (ppm) 1.8–2.0 (m, 4H), 2.6–2.8 (br s, 2H), 4.7 (m, 2H), 7.3–7.2 (m, 10H); ^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) 35.0, 36.0, 73.9, 74.3, 126.0, 127.3, 128.4, 144.8.

4.3. Purification of the non-racemic diol 2 using (*S*)-proline and boric acid

(*S*)-Proline (0.26 g, 2.2 mmol) and boric acid (0.13 g, 2.2 mmol) were dissolved in dry toluene (16 mL) and refluxed for 12 h. Water produced was removed using a Dean–Stark apparatus. The non-racemic **2** (0.48 g, 2 mmol, 84% e.e.), dissolved in dry toluene (16 mL), was added to the reaction mixture under, nitrogen atmosphere through a cannula. The slurry became homogeneous and precipitation started after 3 h. The contents were refluxed for a further 9 h. The precipitate was filtered hot and the solution was concentrated. The precipitate obtained was decomposed using a 1:1 mixture of THF and water (20 mL) and HCl (3N, 10 mL) was added and stirred at rt for 5 h. The precipate was then extracted with ethyl acetate (2×25 mL). The combined organic extracts were washed successively with water, brine and dried over anhydrous $MgSO_4$. After evaporation of the solvent and purification by column chromatography on silica gel using hexane:ethyl acetate (3:1) as eluent; the (1*R*,4*R*)-diphenylbutane-1,4-diol was obtained as a gummy liquid which solidified on stand-

ing at rt (0.36 g, 75% yield, 98% e.e.); $[\alpha]_D^{25}=+58$ (*c* 0.42, $CHCl_3$), lit.[6g] $[\alpha]_D^{21}=-58.5$ (*c* 1.01, $CHCl_3$, >98% e.e.) for (1*S*,2*S*)-(−)-**2**; mp 68–70°C; IR (KBr): 3339, 3025, 1207, 990 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ (ppm) 1.8–2.0 (m, 4H), 2.6–2.8 (br s, 2H), 4.7 (m, 2H), 7.3–7.2 (m, 10H); ^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) 35.9, 74.4, 125.9, 127.3, 128.4, 144.7. The filtrate was evaporated and decomposed using THF/water mixture. After work-up, the diol **2** was isolated, (0.03 g, 10% yield, 10% e.e.); $[\alpha]_D^{25}=+5.9$ (*c* 0.25, $CHCl_3$), lit.[6g] $[\alpha]_D^{21}=-58.5$ (*c* 1.01, $CHCl_3$, >98% e.e.) for (1*S*,2*S*)-(−)-**2**.

Acknowledgements

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