Asymmetric Borane Reduction of Prochiral Ketone Using Chiral Bis(α,α-diphenyl-2-pyrrolidinemethanol) Carbonate

Takashi YANAGI,*[,a] Ken KIKUCHI,[a] Hideki TAKEUCHI,[a] Takehiro ISHIKAWA,[a] Toshihiro NISHIMURA,[a] Minoru KUBOTA,[a] and Iwao YAMAMOTO[b]

[a] *Central Research Laboratories, Kissei Pharmaceutical Co., Ltd.; Hotaka, Minamiazumi, Nagano 399–8304, Japan: and* [b] *Faculty of Textile Science and Technology, Shinshu University; Ueda, Nagano 386–8567, Japan.*

Received October 16, 2002; accepted November 29, 2002

Chiral bis(α,α-diphenyl-2-pyrrolidinemethanol) carbonate ($DPP_2 \cdot H_2CO_3$) is a useful asymmetric auxiliary for the asymmetric borane reduction of prochiral ketones. Chiral $DPP_2 \cdot H_2CO_3$ is recoverable from the reaction and directly reusable for the reaction. The intermediate of KUR-1246, which we are developing as a new uterine relaxant, was synthesized using the methodology.

Key words asymmetric borane reduction; α,α-diphenyl-2-pyrrolidinemethanol; carbonate; KUR-1246

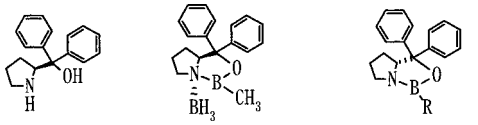
Several asymmetric borane reductions of prochiral ketones using a chiral oxazaborolidine catalyst prepared from a chiral β-amino alcohol have been reported.[1—6] Especially, the use of the oxazaborolidine, MeCBS or HCBS, prepared from chiral α,α-diphenyl-2-pyrrolidinemethanol (DPP) for the asymmetric borane reduction of various ketones showed high enantioselectivities (Fig. 1). HCBS could be synthesized from DPP and a reducing reagent such as the borane–dimethyl sulfide complex ($BH_3 \cdot Me_2S$) or the borane–tetrahydrofuran complex. However, the synthesis of HCBS requires a long reaction time in tetrahydrofuran (THF).[3] Masui and Shioiri reported the asymmetric reduction by $BH_3 \cdot Me_2S$ using a catalyst easily generated *in situ* from chiral DPP and trimethyl borate.[7] We have also reported the efficient catalyst prepared from aluminum triethoxide[8] and DPP for asymmetric borane reduction. However, the additive, trimethyl borate or aluminum triethoxide, is necessary to prepare the catalysts in these methods. Mathre *et al.* tried to prepare a borane complex of HCBS in toluene by the same procedure used to prepare a borane complex of MeCBS (Fig. 1), but they obtained only a dimer complex.[5] Salunkhe and Burkhardt reported that the complex generated from the chiral DPP and borane in toluene included the dimer complex.[6] Efforts to use the dimer complex as a catalyst resulted in a low enantioselectivity for the reduction of acetophenone.

In this paper, we report the asymmetric borane reduction of a prochiral ketone using a catalyst generated *in situ* from DPP and $BH_3 \cdot Me_2S$ in various solvents. We also report that the carbonate of DPP is useful for the reduction.

In our previous report,[8] we described that the asymmetric reduction of acetophenone using (*S*)-DPP and $BH_3 \cdot Me_2S$ in THF required a long reaction time (1.5 h) after the addition of the ketone and gave (1*R*)-1-phenylethanol with 94.7% ee. During the reaction, immediately after $BH_3 \cdot Me_2S$ was added to a solution of (*S*)-DPP in THF, the addition of the ketone to the solution was started. We thought that if the mixture of (*S*)-DPP and $BH_3 \cdot Me_2S$ was stirred to prepare a catalyst for a sufficient time before the addition of the ketone, the reaction time would be shorter and the optical purity of the alcohol would be higher.

First we examined the asymmetric borane reduction of acetophenone using a catalyst generated *in situ* from DPP and $BH_3 \cdot Me_2S$ in various solvents. A catalyst solution was generated from (*S*)-DPP (0.5 mmol) and $BH_3 \cdot Me_2S$ (5 mmol) in each solvent (5 ml) by stirring at room temperature for 1 h. A solution of acetophenone (5 mmol) in each solvent (10 ml) was then added dropwise to the catalyst solution *via* a syringe pump at room temperature over 1 h. The reaction solution was stirred until the acetophenone disappeared based on TLC. The resulting solution was quenched with 1 mol/l HCl. The usual workup provided (1*R*)-1-phenylethanol. These results are shown in Table 1. The reaction in THF, ether, or hexane gave (1*R*)-1-phenylethanol with high optical purity (>98% ee). On the other hand, when toluene or CH_2Cl_2 was used as the solvent, the enantioselectivities were inadequate. It became evident that the solvent influenced this method of using HCBS generated *in situ*.

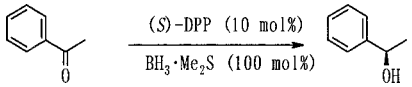
Next we intended to recover and reuse the catalyst. Corey *et al.* reported a method for the recovery of DPP as the hydrochloride salt **1**.[3] When we used (*R*)-MeCBS in the asymmetric borane reduction of a ketone, we found that (*R*)-DPP



(*S*)-DPP Borane complex of (*S*)-MeCBS R:H (*R*)-HCBS Me (*R*)-MeCBS

Fig. 1

Table 1. Asymmetric Reduction of Acetophenone Using (*S*)-DPP and $BH_3 \cdot Me_2S$ in Various Solvents[a)]

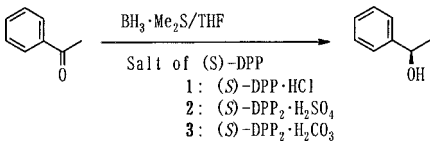


Entry	Solvent	Time[b)]	ee/%[c)]	Yield/%
1	THF	5 min	98.3	84
2	Ether	5 min	98.6	99
3	Hexane	5 min	98.6	85
4	CH_2Cl_2	1 h	71.5	97
5	Toluene	o.n.[d)]	73.8	96

a) The absolute configuration of the product was assigned by comparison of the retention time on an HPLC chiral column with the commercially available compound. *b*) Reaction time after the addition of the ketone. *c*) Determined by HPLC analysis using a chiral column (Chiralcel OJ). *d*) Overnight.

* To whom correspondence should be addressed. e-mail: takashi_yanagi@pharm.kissei.co.jp

Table 2. Asymmetric Borane Reduction of Acetophenone with a Catalyst Generated *in Situ* from the Salt of (*S*)-DPP and $BH_3 \cdot Me_2S$



Entry	Salt of (*S*)-DPP		Time[b]	ee/%[c]	Yeild/%
	Salt	mol%[a]			
1	**1**	10 (10)	1.5 h	78.9	88
2	**2**	5 (10)	1.5 h	90.7	93
3	**3**	5 (10)	5 min	97.9	97
4	**3**	2.5 (5)	5 min	96.2	91
5	**3**	1.0 (2)	o.n.[d]	36.4	83
6[e]	**3**	2.5 (5)	5 min	98.5	90
7[e]	**3**	1.0 (2)	5 min	95.1	93
8[e]	**3**	0.5 (1)	o.n.[d]	56.8	87

a) The value inside ( ) was mol% of (*S*)-DPP. *b*) Reaction time after the addition of the ketone. *c*) Determined by HPLC analysis using a chiral column (Chiralcel OJ). *d*) Overnight. *e*) The solvent was decreased to a fifth of the original quantity.

could easily be recovered as the carbonate [(*R*)-$DPP_2 \cdot H_2CO_3$, **4**] in 70—80%.[9] If these salts can be used as the catalyst for the asymmetric borane reduction, the recycling of the catalyst will be very simple and economical. We then investigated the possibility of the carbonate, the hydrochloride, and the sulfate of DPP as the catalyst for the asymmetric borane reduction of acetophenone using the above-mentioned method. These results are shown in Table 2.

Using 5 mol% of the carbonate [(*S*)-$DPP_2 \cdot H_2CO_3$, **3**] of (*S*)-DPP gave (1*R*)-1-phenylethanol with the excellent optical purity of 97.9% ee (entry 3). When the hydrochloride **1** or the sulfate **2** of (*S*)-DPP was used as the catalyst for the reduction, the reaction times were 1.5 h and the optical purities of the alcohol were lower (78.9% ee and 90.7% ee, respectively) (entry 1, 2). Furthermore, we examined the possibility of decreasing the quantity of **3**. Using 2.5 mol% of **3** under these conditions led to a good result (96.2% ee, entry 4). When the solvent was decreased to a fifth of its original quantity, the reduction of acetophenone using 1 mol% of **3** gave (1*R*)-1-phenylethanol with 95.1% ee (entry 7). However, a further reduction of the amount of **3** to 0.5 mol% at the high concentration gave the alcohol with the unsatisfactory optical purity of 56.8% ee (entry 8). From these results, chiral $DPP_2 \cdot H_2CO_3$ is quite useful for the asymmetric borane reduction, and the obtained optical purity of the chiral alcohol is affected by the concentration of both the catalyst and the ketone in the reaction solution.

Furthermore, we examined the recovery of the carbonate of DPP from a reaction mixture and the reduction using the recovered carbonate. The first asymmetric reduction of acetophenone (12.02 g) using 2.5 mol% of **4** (1.42 g) gave (1*S*)-1-phenylethanol with 98.1% ee after distillation and **4** was recovered in 69% yield. We reused the recovered **4** for the same reduction. The optical purity of the alcohol was 98.0% ee.

Finally, we used the method for the synthesis of the bromohydrine **6** as shown in Chart 1. Compound **6** is an intermediate of KUR-1246 that we are developing as a uterine relaxant.[10,11] The asymmetric borane reduction of the phenacyl bromide **5** using 2.5 mol% of **4** and 120 mol% of $BH_3 \cdot Me_2S$

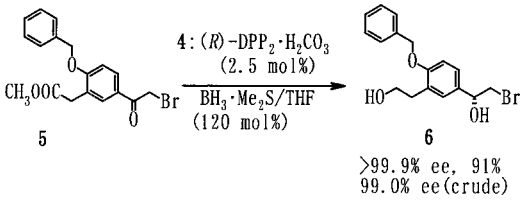


Chart 1

reduced both the ketone and the ester groups to give the crude **6** with the excellent optical purity of 99.0% ee. After crystallization, **6** was then obtained in 91% yield with >99.9% ee.

In conclusion, the asymmetric borane reduction of a prochiral ketone using the catalyst generated from a chiral DPP and $BH_3 \cdot Me_2S$ *in situ* in THF, ether, or hexane at room temperature for 1 h gave the corresponding chiral alcohol with an excellent optical purity. However, the optical purity of the chiral alcohol, which was obtained from the reduction in CH_2Cl_2 or toluene, was inadequate. (*R*)- and (*S*)-$DPP_2 \cdot H_2CO_3$ could be used for the catalyst as same as DPP. Furthermore, they were easily recovered from the reaction. (*R*)- and (*S*)-$DPP_2 \cdot H_2CO_3$ are useful, recoverable, and reusable catalysts for the asymmetric borane reduction of prochiral ketones.

Experimental

All melting points were determined on a Yanagimoto melting point apparatus and are uncorrected. IR spectra were recorded on a Nicolet 510 FT-IR spectrometer. ^{1}H- and ^{13}C-NMR spectra were recorded on a Bruker DRX-500 using tetramethylsilane as the internal standard. Mass spectra were measured using a JEOL JMS-SX102A mass spectrometer. Optical rotations were measured with a JASCO DIP-370 polarimeter.

General Procedure. Asymmetric Borane Reduction of Acetophenone $BH_3 \cdot Me_2S$ (10 mol/l, 0.5 ml, 5 mmol) was added to a suspension of (*S*)-DPP (127 mg, 0.50 mmol) in THF (5 ml) under a N_2 atmosphere, and the mixture was stirred at room temperature for 1 h. A solution of acetophenone (601 mg, 5 mmol) in THF (10 ml) was added dropwise over 1 h *via* a syringe pump. The reaction mixture was stirred until the acetophenone disappeared on TLC. The mixture was quenched with 1 mol/l HCl (10 ml), and extracted with ether (3×15 ml). The organic layers were combined, washed with water (10 ml) and brine (10 ml), dried over $MgSO_4$, and concentrated under reduced pressure. The resulting residue was purified using silica gel chromatography (Fuji Silysia Co. Ltd., BW-350; eluent, AcOEt : hexane=1 : 10) to give (1*R*)-1-phenylethanol (611 mg, 100%) as a colorless oil. The ee of the alcohol was determined to be 97.5% by HPLC using a chiral column [column, Chiralcel OJ 4.6 mm i.d.×250 mm, Daicel Chemical Industries Co., Ltd.; mobile phase, hexane–iso-PrOH, 95 : 5; flow rate, 1.0 ml/min; detection, UV at 220 nm].

(*S*)-α,α-Diphenyl-2-pyrrolidinemethanol Hydrochloride [(*S*)-DPP·HCl, 1] Ether (10 ml) was added to a solution of (*S*)-DPP (507 mg, 2 mmol) in 2.4 mol/l HCl/MeOH (2 ml), and the precipitate was collected by filtration, washed with ether, and dried to give **1** (182 mg, 63%) as a white solid. mp 246 °C. IR (KBr): 3251, 2885, 1448, 1393, 750, 695 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.73—1.96 (4H, m), 3.13 (2H, t, J=6.1 Hz), 4.88 (1H, t, J=7.3 Hz), 6.55 (1H, br s), 7.19—7.23 (2H, m), 7.30—7.36 (4H, m), 7.25 (2H, d, J=7.6 Hz), 7.63 (2H, d, J=8.1 Hz), 8.31 (1H, br), 9.33 (1H, br). ^{13}C-NMR (DMSO-d_6) δ: 26.53, 28.47, 49.20, 67.56, 79.58, 127.93, 128.31, 129.46, 129.67, 130.70, 130.88, 147.13, 147.55. $[\alpha]_D^{29}$ +57.1° (c=0.84, MeOH). *Anal.* Calcd for $C_{17}H_{20}ClNO$: C, 70.46; H, 6.96; N, 4.83. Found: C, 70.43; H, 6.92; N, 4.85.

Bis[(*S*)-α,α-diphenyl-2-pyrrolidinemethanol] Sulfate [(*S*)-$DPP_2 \cdot H_2SO_4$, 2] 1 mol/l H_2SO_4 (2 ml) was added to a solution of (*S*)-DPP (507 mg, 2 mmol) in THF (8 ml), and the precipitate was collected by filtration, washed with water, and dried to give **2** (369 mg, 61%) as a white solid. mp 260—262 °C. IR (KBr): 3171, 2980, 1449, 1069, 699 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.06—1.77 (4H, m), 2.93—3.04 (2H, m), 4.56 (1H, t, J=7.4 Hz), 7.15—

7.33 (6H, m), 7.62 (2H, d, J=8.5 Hz), 7.58 (2H, d, J=8.5 Hz). ^{13}C-NMR (DMSO-d_6) δ: 25.24, 26.65, 47.23, 64.94, 77.58, 125.84, 126.32, 126.86, 128.34, 128.43, 146.25, 146.72. $[\alpha]_D^{29}$ −22.7° (c=0.3, DMSO). *Anal.* Calcd for $C_{34}H_{40}N_2O_6S$: C, 67.53; H, 6.67; N, 4.63. Found: C, 67.42; H, 6.66; N, 4.56.

Bis[(*S*)-α,α-diphenyl-2-pyrrolidinemethanol] Carbonate [(*S*)-DPP$_2$·H$_2$CO$_3$, 3] Sat. $NaHCO_3$ (5 ml) was added to a solution of (*S*)-DPP (253 mg, 1 mmol) in a mixture of THF (1 ml), 1 mol/l HCl (5 ml), and H_2O (10 ml). The precipitate was collected by filtration, washed with water, and dried to give **3** (254 mg, 89%) as a white solid. mp 106—108 °C. IR (KBr) 2984, 1618, 1541, 1448, 1377, 701 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.35—1.65 (4H, m), 2.79—2.97 (2H, m), 4.27 (1H, t, J=7.4 Hz), 5.15 (1H, br), 7.09—7.32 (6H, m), 7.46 (2H, d, J=8.0 Hz), 7.57 (2H, d, J=7.6 Hz). ^{13}C-NMR (DMSO-d_6) δ: 26.09, 27.08, 47.34, 64.23, 77.83, 125.74, 126.27, 126.38, 126.67, 128.08, 147.12, 148.48. $[\alpha]_D^{27}$ −19.2° (c=1.0, MeOH). *Anal.* Calcd for $C_{35}H_{40}N_2O_5$: C, 73.92; H, 7.09; N, 4.93. Found: C, 74.33; H, 7.02; N, 4.90.

Bis[(*R*)-α,α-diphenyl-2-pyrrolidinemethanol] Carbonate [(*R*)-DPP$_2$·H$_2$CO$_3$, 4] Sat. $NaHCO_3$ (10 ml) was added to a solution of (*R*)-DPP (253 mg, 1 mmol) in a mixture of THF (1 ml) and 1 mol/l HCl (5 ml). The precipitate was collected by filtration, washed with water, and dried to give **4** (261 mg, 92%) as a white solid. mp 108—109 °C. IR (KBr) 2984, 1618, 1541, 1448, 1377, 701 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.35—1.65 (4H, m), 2.79—2.97 (2H, m), 4.28 (1H, t, J=7.7 Hz), 5.15 (1H, br), 7.09—7.32 (6H, m), 7.46 (2H, d, J=8.4 Hz), 7.57 (2H, d, J=8.1 Hz). ^{13}C-NMR (DMSO-d_6) δ: 26.09, 27.08, 47.35, 64.23, 77.83, 125.73, 126.28, 126.38, 126.66, 128.09, 147.11, 148.47. $[\alpha]_D^{27}$ +17.4° (c=1.0, MeOH). *Anal.* Calcd for $C_{35}H_{40}N_2O_5$: C, 73.92; H, 7.09; N, 4.93. Found: C, 73.58; H, 7.11; N, 4.80.

Recover and Reuse of (*R*)-DPP$_2$·H$_2$CO$_3$ (4) BH_3·Me_2S (10 mol/l, 8 ml, 80 mmol) was added to a suspension of **4** (1.42 g, 2.50 mmol) in THF (20 ml) under a N_2 atmosphere, and the mixture was stirred at room temperature for 1 h. A solution of acetophenone (12.02 g, 100 mmol) in THF (40 ml) was added dropwise over 1 h. The reaction mixture was stirred until the acetophenone disappeared on TLC (10 min). The mixture was quenched with 1 mol/l HCl (25 ml) and extracted with AcOEt (2×100 ml). The organic layers were combined, washed with water (10 ml) and brine (10 ml), dried over $MgSO_4$, and concentrated under reduced pressure. The obtained oil was distilled under reduced pressure to give (1*S*)-1-phenylethanol (8.39 g, 69%) as a colorless oil. The ee of the alcohol was determined to be 98.1% by HPLC using the chiral column.

The aqueous layers of the above procedure were combined and adjusted to pH 8 by sat. $NaHCO_3$. After the mixture was stirred overnight, the precipitate was collected by filtration, washed with water, and dried to give **4** (0.98 g, 69%) as a white solid.

The recovered **4** (0.71 g, 1.25 mmol) was used for the asymmetric borane reduction of acetophenone (6.01 g, 50 mmol) as the above procedure. (1*S*)-1-Phenylethanol (4.92 g, 81%) was obtained, and the ee of the alcohol was determined to be 98.0% by HPLC using the chiral column.

(1*R*)-1-[4-Benzyloxy-3-(2-hydroxyethyl)phenyl]-2-bromoethan-1-ol (6) BH_3·Me_2S (10 mol/l, 0.6 ml, 6 mmol) was added to a suspension of **4** (377 mg, 0.66 mmol) in THF (10 ml) under a N_2 atmosphere, and the mixture was stirred at room temperature for 1 h. A solution of methyl (2-benzyloxy-5-bromoacetylphenyl)acetate (**5**)[11] (10.00 g, 26.5 mmol) in THF (25 ml) was added dropwise over 1 h. After 10 min, the mixture was stirred for 2 h at 50 °C, quenched with MeOH (10 ml), and concentrated under reduced pressure. AcOEt (30 ml) and 1 mol/l HCl (10 ml) were added to the resulting residue, and then the separated aqueous layer was extracted with AcOEt (20 ml). The organic layers were combined, washed with water (10 ml), sat. $NaHCO_3$ (10 ml), and brine (10 ml), dried over $MgSO_4$, and concentrated under reduced pressure. The resulting residue was recrystallized from AcOEt–hexane to give **6** (8.52 g, 91%) as a white solid. The ee of **6** was determined to be >99.9% by HPLC using a chiral column [column, Chiralpak AD 4.6 mm i.d.×250 mm, Daicel Chemical Industries Co., Ltd.; mobile phase, hexane–iso-PrOH, 9 : 1; flow rate, 1.0 ml/min; detection, UV at 230 nm]. mp 86—87 °C. IR (KBr): 3249, 1568, 1448, 1253 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.85 (1H, s), 2.89—2.95 (3H, m), 3.51 (1H, dd, J=8.9, 10.4 Hz), 3.57 (1H, dd, J=3.6, 10.4 Hz), 3.80—3.87 (2H, m), 4.79—4.84 (1H, m), 5.07 (2H, s), 6.90 (1H, d, J=8.1 Hz), 7.15—7.20 (2H, m), 7.29—7.42 (5H, m). ^{13}C-NMR ($CDCl_3$) δ: 34.55, 40.53, 62.94, 70.55, 73.83, 112.19, 125.91, 127.65, 128.19, 128.44, 129.07, 129.16, 133.11, 137.22, 157.21. $[\alpha]_D^{29}$ −17.6° (c=1.0, MeOH). HR-MS (FAB) m/z: Calcd for $C_{17}H_{19}BrO_3$ M^+: 350.0518. Found: 350.0509. *Anal.* Calcd for $C_{17}H_{19}BrO_3$: C, 58.13; H, 5.45. Found: C, 57.97; H, 5.52.

References and Notes

1) Itsuno S., Ito K., Hirao A., Nakahara S., *J. Chem. Soc., Chem. Commun.*, **1983**, 469—470 (1983).
2) Corey E. J., Bakshi R. K., Shibata S., *J. Am. Chem. Soc.*, **109**, 5551—5553 (1987).
3) Corey E. J., Bakshi R. K., Shibata S., *J. Org. Chem.*, **53**, 2861—2863 (1988).
4) Corey E. J., Helal C. J., *Angew. Chem., Int. Ed.*, **37**, 1986—2012 (1998).
5) Mathre D. J., Thompson, A. S., Douglas A. W., Hoogsteen K., Carroll J. D., Corley E. G., Grabowski E. J. J., *J. Org. Chem.*, **58**, 2880—2888 (1993).
6) Salunkhe A. M., Burkhardt E. R., *Tetrahedron Lett.*, **38**, 1523—1526 (1997).
7) Masui M., Shioiri T., *Synlett*, **1997**, 273—274 (1997).
8) Yanagi T., Kikuchi K., Takeuchi H., Ishikawa T., Nishimura T., Kamijo T., *Chem. Lett.*, **1999**, 1203—1204 (1999).
9) After the reaction mixture was quenched, the solution was washed with 1 mol/l HCl. The 1 mol/l HCl washing was adjusted to pH 8 with $NaHCO_3$ solution, and then the precipitate was collected and dried to give the carbonate **4**.
10) Kobayashi M., Takeda K., Murata S., Kojima M., Akahane M., Inoue Y., Kitamura K., Kawarabayashi T., *J. Pharmacol. Exp. Ther.*, **297**, 666—671 (2001).
11) Yanagi T., Kikuchi K., Takeuchi H., Ishikawa T., Nishimura T., Yamamoto I., *Chem. Pharm. Bull.*, **49**, 1018—1023 (2001).