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Enantioselective Reduction of Ketones with Borane Catalyzed by Cyclic β- Amino Alcohols Prepared from Proline[1]

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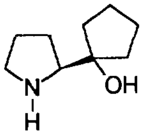
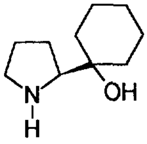
Abstract: New catalysts have been prepared from (*S*)- and (*R*)- proline and the asymmetric borane reduction of prochiral ketones using these catalysts has been studied. The secondary alcohols were obtained in 76-95% yield with 57- 96 % enantiomeric excesses. Copyright © 1996 Elsevier Science Ltd

The enantioselective oxazaborolidine-catalyzed reduction of prochiral ketones with borane led to the formation of chiral secondary alcohols[2]. After the pioneering work of Itsuno et al.[3], Corey's group and others have developed several chiral 1,3,2-oxazaborolidines which can act as efficient catalysts in this reaction[4].

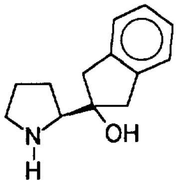
In our earlier work we examined the catalytical efficiency of the amino alcohols **1**, **2** and **3** for the enantioselective reduction of oxime ethers to amines (51-95% ee)[5]. In the present paper we describe the synthesis of both enantiomers of these three proline derivatives, as well as their use in the reduction of some representative ketones.



(S)-**1**



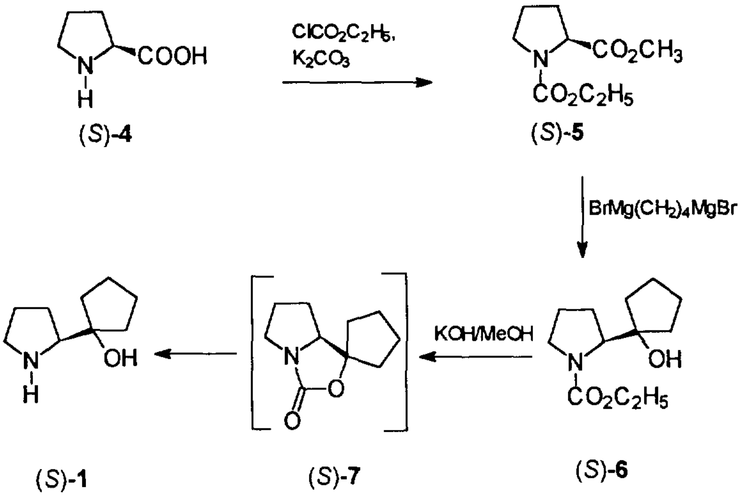
(S)-**2**



(S)-**3**

Compounds **1, 2** and **3** were readily synthesized in three steps from (*S*)- proline, and their enantiomers were also synthesized starting with (*R*)-proline using the same procedure. The formation of these amino alcohols is illustrated by the synthesis of (*S*)- **1** in Scheme 1. The reaction of (*S*)-proline with ethyl chloroformate in MeOH with K_2CO_3 gave N- and O-protected proline **5** in one pot operation[6]. The Grignard reaction of protected proline with 1,4-dibromobutane afforded prolinol derivative **6.** The deprotection of the N-carbamate was carried out through alkaline hydrolysis.

By the mechanism of alkaline hydrolysis of carbamate, the formation of intermediate 7 occurs first, which was isolated and fully characterized (by monitoring of the reaction with TLC). Additional reflux of 7 with KOH gave prolinol derivative **1** in good yield. The prolinol derivative **1** was also synthesized using phosgene via the formation of proline-N-carboxyanhydride followed by Grignard reaction[7]. The yield of this reaction was lower (15 %) than the reaction described in Scheme 1. The direct synthesis of the prolinol

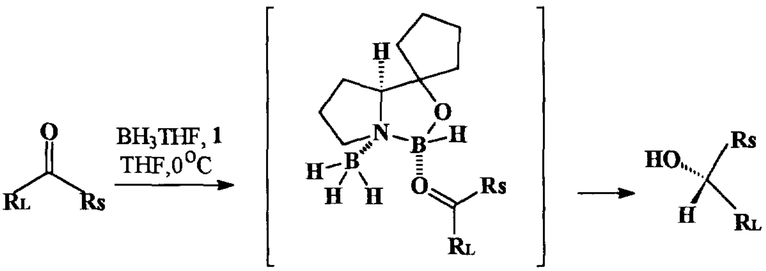


Scheme 1

derivative **1** from proline methylester hydrochloride and Grignard reagent was also possible, but the yield was again low (12%). Both enantiomers of **2** and **3** were also synthesized by the reaction of **5** with the corresponding Grignard reagents prepared from 1,5-dibromopentane and *o*-xylene dichloride and *o*-xylene dibromide[9].

The reductions of prochiral ketones were performed by slow addition of the substrate solution to a solution containing the oxazaborolidine-BH_3 complex in THF at 0^{0}C. The optically active alcohols were isolated in very good yield and with high ee's (Scheme 2).

Absolute configuration and enantiomeric excess were determined by gas chromatographic analysis of the corresponding (*S*)-O-Acetyllactyl esters of secondary alcohols[8] and comparison of the specific rotation with the literature value. As shown in Table, indanol derivative **3** shows to be most effective catalyst for the borane reductions of a variety of prochiral ketones to chiral secondary alcohols. The use of (*R*)- enantiomer of the catalysts gave the (*S*)- configured alcohol.



Scheme 2

Table. Reduction of prochiral ketones[a]

Ketone	Catalyst	Yield (%)	Abs. Config.	ee (%)
Acetophenone	(*S*)-1	95	*R*	67
Acetophenone	(*S*)-2	91	*R*	71
Acetophenone	(*S*)-3	86	*R*	96
Acetophenone	(*R*)-1	93	*S*	71
Acetophenone	(*R*)-3	79	*S*	88
1-Acetyl naphtalene	(*R*)-1	86	*S*	81
1-Acetyl naphtalene	(*S*)-1	83	*R*	76
1-Acetyl naphtalene	(*S*)-3	76	*R*	92
2- Octanone	(*S*)-1	90	*R*	57
2- Octanone	(*S*)-2	88	*R*	63
2- Octanone	(*S*)-3	78	*R*	91
Indanone	(*S*)-1	79	*R*	86
Indanone	(*S*)-3	83	*R*	96
2-Acetyl pyridine	(*S*)-1	78	*R*	79
2-Acetyl pyridine	(*S*)-3	81	*R*	87
1-Tetralone	(*S*)-1	88	*R*	62
1-Tetralone	(*S*)-3	76	*R*	91
1-(2-Furyl) propanone	(*S*)-1	81	*R*	83
1-(2-Furyl) propanone	(*S*)-3	76	*R*	94

(a) The absolute configuration and enantiomeric excess were determined by comparison of the specific optical rotation with that of the commercially available compound or with the literature value : Simone, B.D.; Savoia, D.;Tagliavini, E.; Umani-Ronchi, A. *Tetrahedron*: *Asymmetry* **1995**, *6*, 301. Burns, B.; King, N.P.; Studley, J.R.; Tye, H.;Wills, M. *Tetrahedron*: *Asymmetry* **1994**, *5*, 801. Berenguer, R.; Garcia, J; Vilarrasa, J. *Tetrahedron*: *Asymmetry* **1994**, *5*,165. Nakagawa, M. ; Kawate, T. ; Kakikawa, T. ; Yamada, H. ; Matsuhi, T. ; Hino, T. *Tetrahedron*, **1993**, *49*, 1739 and by GC of (*S*)-O-Acetyllactyl esters of the corresponding secondary alcohols [8] (capillary column HP-5 crosslinked 5%PhMe silicone).

EXPERIMENTAL

All reagents were of commercial quality, and reagent quality solvents were used without further purification. IR spectra were determined on a Philips model PU9700 spectrometer. ^{1}H NMR spectra were determined on a Bruker AC 80 MHz FT and Varian 200 MHz spectrometers. GC analyses were made on a HP 5890 gas chromatography. Mass spectra were obtained on VGTrio2 spectrometer at an ionization energy of 70 eV. Optical rotation values were measured with a Perkin Elmer P241 polarimeter. Elemental analyses were performed at the Middle East Technical University Analysis Center.

(*S*)-Proline-N-ethyl carbamate methyl ester (*S*)-5[6]: (*S*)-Proline (5.75 g, 50 mmol) was dissolved in dry methanol (80 ml). Anhydrous potassium carbonate (6.60 g, 50 mmol) was added, followed by the addition of ethylchloroformate (12.5 g ,110 mmol) in duration of 20 min at 25 °C. The reaction mixture was further stirred for 12 h at 25 °C. Methanol was evaporated and distilled water (40 ml) was added. The contents were extracted with chloroform. The organic extracts were washed with brine and dried over anhydrous magnesium sulfate. Evaporation of the solvent gave brown oil. The crude product was purified by column chromatography (flash silica gel, eluent: EtOAc/*n*-hexane 1:4, R_f-value: 0.22); yield: 9.7 g, (96.5%); IR (neat):

1710-1740 cm^{-1};^{1}H NMR ($CDCl_3$): δ 1.22 (t, 3H, CH_3), 1.37-2.04 (m, 4H, 2β-NCH_2), 2.68-3.25 (m, 3H,NCH_2, NCH), 3.71 (s, 3H, OCH_3), 4.18 (q, , 2H, CH_2).

(*R*)-Proline-N-ethyl carbamate methyl ester (*R*)-5[6] : Obtained according to the same procedure as (*S*)-5 by using (*R*)- proline. Colorless oil.Yield 8.8 g (87.5%).

(*S*)-1-(2-N-Ethoxycarbonylpyrrolidinyl)cyclopentanol (*S*)-6[5]: Magnesium turnings (1.94 g, 80 mmol) were placed in a dried two-necked round-bottom flask with a reflux condenser attached. 1,4-Dibromobutane (6.04 g , 28 mmol) in dry THF (5 ml) was added dropwise in period of 20 min. under nitrogen.The contents were further stirred 1h. The (*S*)-proline-N-ethyl carbamate methyl ester (2.25 g, 11.2 mmol) was dissolved in dry THF (200 ml) and added through a cannula under nitrogen atmosphere at 0 °C . The contents were further stirred at RT for 4 h. The reaction mixture was quenched with saturated ammonium chloride solution (20 ml) and extracted with chloroform (2X50 ml). The combined organic extracts were washed with saturated sodium chloride solution and dried over anhydrous magnesium sulfate. Evaporation of the solvent gave the crude product which was purified by column chromatography (flash silica gel, eluent:EtOAc/*n*-hexane 1:3, R_f-value: 0.26); yield:1.57 g, (62%); $[\alpha]_D^{20}$= -60.8 (c=0.4, toluene); IR (neat): 3400, 2950, 1680 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.21 (t, , 3H, CH_3), 1.36-2.10 (m, 12H, 6 CH_2), 2.81-3.38 (m, 3H, NCH_2, NCH), 4.08-4.25 (m, 2H, OCH_2); ^{13}C NMR ($CDCl_3$) : δ 14.40, 23.22, 24.15, 28.47, 35.21, 38.25, 47.98, 61.43, 85.39, 157.83; MS (EI) m/z (% b.p.) 227(15, M+), 209 (85), 201(50), 182(60),180(58), 164(22), 154(40), 153(56), 152(28), 144(18), 143(85), 142(88), 136(44), 114(100), 98(42), 91(23), 71(12), 70(56); Anal.calc.for $C_{12}H_{21}NO_3$(227.30) : C, 63.41; H, 9.31; N, 6.16. Found: C, 63.67; H,9.21; N, 6.48.

(*R*)-1-(2-N-Ethoxycarbonylpyrrolidinyl)cyclopentanol (*R*)-6:yield:1.75 g (69%), $[\alpha]_D^{20}$= 61.7 (c=0.4, toluene).

(*S*)-1-(2-Pyrrolidinyl)cyclopentanol (*S*)-1[5]: into a flask containing dry methanol (20 ml), (*S*)-1-(2-N-Ethoxycarbonylpyrrolidinyl)cyclopentanol (4) (1.5 g, 6.6 mmol) and potassium hydroxide (3.7 g) were added. The final mixture was refluxed for 4 h, then methanol was distilled off. Distilled water (15 ml) was added and the content was extracted with chloroform (2X50 ml). Organic layer was washed with saturated sodium chloride solution and dried over anhydrous magnesium sulfate. After evaporation of the solvent, the desired product was obtained as a brown oil. Purification by flash column chromatography afforded colorless oil (Lit.[5] m.p. 34 °C). Yield: 0.73 g, (73%). $[\alpha]_D^{20}$= -35.4(c=0.3, CH_2Cl_2); IR (neat): 3650, 3390 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.32-2.12 (m, 12H, 6 CH_2), 2.78-3.22 (m, 4H, NH, NCH_2, NCH). ^{13}C NMR ($CDCl_3$): δ 24.15, 24.51, 26.15, 36.86, 40.13, 47.16 , 66.20 , 82.03 ; MS (EI) m/z (%b.p.) 155 (M+, 70), 154 (13), 153(40), 152(15), 139(6), 138(15), 136(12), 125(15), 124(20), 122(10), 109(65), 96(70), 95(65), 84(12), 80(43), 70(100), 69(80), 68(55), 55(54). Anal. calc. for $C_9H_{17}NO$(155.13): C, 69.62; H 11.04; N, 9.03. Found: C, 69.38; H,11.32; N, 8.81.

(*R*)-1-(2-Pyrrolidinyl)cyclopentanol (*R*-1): yield: 0.81 g, (81%). $[\alpha]_D^{20}$= +37.3, (c=0.3, CH_2Cl_2).

Preparation of compound 7 : into a flask containing dry methanol (20 ml), (*S*)-1-(2-N-Ethoxycarbonylpyrrolidinyl)cyclopentanol (6) (1.5 g, 6.6 mmol) and potassium hydroxide (3.7 g) were added. The final mixture was refluxed for 1 h (monitored by TLC, EtOAc/*n*-hexane 1:3), then methanol was distilled off. Distilled water (15 ml) was added and the content was extracted with chloroform (2X50 ml). Organic layer was washed with saturated sodium chloride solution and dried over anhydrous magnesium sulfate. After evaporation of the solvent, the crude product was obtained as a brown oil. The product were separated by flash column chromatography (flash silica gel, eluent:EtOAC/*n*-hexane 1:3). The isolation and characterization of the products showed that more polar product was the cyclic intermediate 7 (0.56 g, 40%).. $[\alpha]_D^{20}$= -55.2 , (c= 0.5, $CHCl_3$); IR(neat): 2830- 2920, 1660 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.21-2.34 (m, 12H, 6 CH_2), 3.13-3.68 (m, 3H, NCH, NCH_2); ^{13}C NMR ($CDCl_3$) δ 22.82, 23.02, 25.02, 27.34 , 33.62, 40.03, 45.60, 67.35, 90.45, 161.35. Anal. calc. for $C_{10}H_{15}NO_2$ (181.23): C, 66.27; H, 8.34; N, 7.73. Found: C, 66.57; H, 8.12; N, 7.42. The less polar product was *S*-1.

(*S*)-1-(2-N-Ethoxycarbonylpyrrodiniyl)cyclohexanol (*S*)-8: yield: 2.35 g, (86%). $[\alpha]^{20}_D$= -48.3 (c=0.5, toluene); IR(neat) : 3430, 2940, 1680, 1600 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.14- 1.88 (m, 18H, cycl. CH_2, 2β CH_2, CH_3, NH), 2.68- 3.18 (m, 3H, NCH_2, NCH), 3.88- 4.18 (m, 2H, OCH_2). Anal. calc. for $C_{13}H_{23}NO_3$ (241.33) : C, 64.70; H, 9.61; N, 5.80. Found: C, 64.92; H, 9.52; N, 5.48.

(*R*)-1-(2-N-Ethoxycarbonylpyrrodiniyl)cyclohexanol (*R*)-8: yield: 2.11 g, (77%); $[\alpha]^{20}_D$= + 47.1 (c=0.5, toluene).

(*S*)-1-(2-Pyrrolodinyl)cyclohexanol (*S*)-2[5]: yield: 0.98 g (88%); m.p. 47-48°C; $[\alpha]^{20}_D$= - 47.2 (c=0.5, CH_2Cl_2); IR(KBr): 3400, 2950, 1680, 1600 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.10- 1.80 (m, 15H cycl. CH_2, 2β CH_2,NH), 2.78-3.12 (m, 3H, NCH_2, NCH); ^{13}C NMR ($CDCl_3$): δ 22.11, 22.16, 25.21, 25.83, 25.97, 34.12, 36.81, 47.06, 66.15, 71.60. Anal. calc. for $C_{10}H_{19}NO$(169.15): C, 70.94; H, 11.32; N, 8.28. Found: C, 7123; H, 11.65; N, 7.93.

(*R*)-1-(2-Pyrrolodinyl)cyclohexanol (*R*)-2: yield: 0.90 g (81%); $[\alpha]^{20}_D$= + 47.7 (c=0.5, CH_2Cl_2).

(*S*)-2-(2-N-Ethoxycarbonylpyrrolidinyl)-2-indanol (*S*)-9: to a suspension of magnesium turnings (1.94 g, 80 mmol) in dry THF (40 ml) was added dropwise a solution of *o*-xylene dichloride(4.90 g, 28 mmol) in THF (500 ml) over a period of 4 h. After adding few drops of *o*-xylene dichloride, sometimes to initiate the reaction, gentle heating was necessary. The mixture was stirred for 3 h at RT and then was reduced in volume by half *in vacuo*[9]. The (*S*)- proline-N-ethyl carbamate methyl ester (2.25 g, 11.2 mmol) was dissolved in dry THF (200 ml) and was added to the mixture at RT. The mixture was stirred at RT for 12 h. The reaction was quenched with saturated ammoniumchloride solution (40 ml) and extracted with chloroform (2X100 ml). The combined organic extracts were washed with saturated sodiumchloride solution and dried over anhydrous magnesium sulfate. Evaporation of the solvent gave the crude product which was purified by column chromatography (flash silica gel, eluent: EtOAc/*n*-hexane 1:3); yield: 2.34 g (76%); m.p. 79-81°C; $[\alpha]^{20}_D$= -71.1 (c= 0.4, toluene); IR(KBr): 3600, 3450, 1670, 1600 cm^{-1}; ^1H NMR($CDCl_3$): 1.23(t, 3H, CH_3), 1.29- 1.82 (4H, 2β CH_2), 2.74- 3.21(7H, NCH_2, NCH, 2 benzyl. CH_2), 3.98- 4.21 (m, 2H, OCH_2). Anal. calc. for $C_{16}H_{21}NO_3$ (275.15): C, 69.78; H, 7.69; N, 5.09. Found: C, 69.96; H, 7.52; N, 4.82.

(*R*)-2-(2-N-Ethoxycarbonylpyrrolidinyl)-2-indanol (*R*)-9: yield: 2.12 g (69%); $[\alpha]^{20}_D$= +72.8 (c= 0.4, toluene).

(*S*)-2-(2-Pyrrolidinyl)-2-indanol (*S*)-3: into a flask containing dry methanol (30 ml), (*S*)-2-(2-N-Ethoxycarbonylpyrrolidinyl)-2-indanol (S-9) (2.8 g, 8.0 mmol) and potassium hydroxide (4.0 g) were added. The final mixture was refluxed for 4 h (monitored by TLC), then methanol was distilled off. Distilled water (20 ml) added and the content was extracted with chloroform (2X50 ml). Organic layer was washed with saturated sodium chloride solution and dried over anhydrous magnesium sulfate. After evaporation of the solvent, the desired product was obtained as a brown semisolide which was purified by flash column chromatography flash silica gel, eluent: EtOAc/*n*-hexane 1:3); yield:1.32 g, (81%); m.p. 71-72°C; $[\alpha]^{20}_D$= - 63.4(c=0.3, $CHCl_3$). IR(KBr); 3600, 2950 cm^{-1}; ^1H NMR($CDCl_3$): δ 1.31- 1.89 (m, 4H, 2β CH2), 2.77- 3.18 (m, 8H, NCH_2, NCH, NH, 2 benzyl. CH_2), 7.31- 7.82 (m, 4H, Ar- H); ^{13}C NMR($CDCl_3$): δ 24.92, 25.21, 25.32, 34.33, 47.41, 64.16, 124.22, 125.61, 143.12, 143.38. Anal. calc. for $C_{13}H_{17}NO$(203.13): C, 76.80; H, 8.43; N, 6.89. Found: C, 76.56; H, 8.18; N, 6.65.

(*R*)-2-(2-Pyrrolidinyl)-2-indanol (*R*)-3: yield: 0.92 g (69%); $[\alpha]^{20}_{D}$= +62.1 (c= 0.3,$CHCl_3$).

Enantioselective Reduction of Prochiral Ketones Catalyzed by 1, 2 and 3 (typical procedure):

BH_3THF (5 mmol) and 1-(2-pyrrolidinyl) cyclohexanol (155 mg ,1 mmol) containing dry THF (10 ml) were placed in a 200 ml round-bottom two-necked flask provided with condenser and calcium chloride tube. The mixture was refluxed for 2 h, then BH_3THF (5mmol) were added. The mixture was cooled to 0 °C with an ice-bath and acetophenone (0.84 g ,7 mmol) containing dry THF (2 ml) was introduced over 90 min. The reaction was monitored by TLC and quenched by the addition of 2N HCl solution (7 ml). Ether (25 ml) was added to the mixture and organic layer was separated, washed with sodiumbicarbonate and saturated sodium chloride solution, and dried over anhydrous magnesium sulfate. Removing of the ether gave the desired product which was purified by flash column chromatography (silica gel, eluent:EtOAc/*n*-hexane 1:3) and identified by comparison of the spectroscopic properties with those reported in the literature.

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