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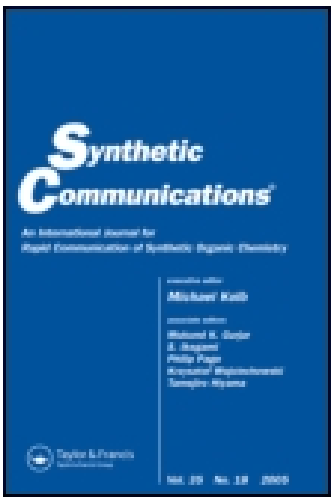

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Enantioselective Catalytic Borane Reductions of Achiral Ketones: Synthesis and Application of New Rigid Catalysts Prepared from (R)-Phenylglycine and (S)-Phenylalanine

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SYNTHETIC COMMUNICATIONS, 23(15), 2091-2099 (1993)

ENANTIOSELECTIVE CATALYTIC BORANE REDUCTIONS OF ACHIRAL KETONES : SYNTHESIS AND APPLICATION OF NEW RIGID CATALYSTS PREPARED FROM (*R*)-PHENYLGLYCINE AND (*S*)-PHENYLALANINE

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Abstract: Enantiocontrolled reduction of prochiral ketones with borane in the presence of homochiral amino alcohols **1 – 4** as enantioselective catalysts afforded the chiral corresponding secondary alcohols in moderate to high (55 to 88 %) optical yields.

The asymmetric reduction of prochiral ketones with chiral hydride reagents has been intensively investigated[1]. *Itsuno et al.* developed the oxazaborolidines as a new generation of reduction reagents[2]. Later other groups improved this new method[3]. Five years after the discovery of the mechanism of action of chiral

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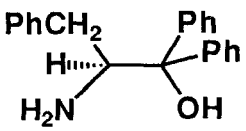
oxazaborolidines in the catalytic enantioselective reduction of ketones the number of applications of oxazaborolidine[4] derivatives and other related systems still appears to be growing. Most oxazaborolidines are derivatives of β-amino alcohols, obtained from α-amino acids or natural camphor. In this communication the *in situ* synthesis of new rigid oxazaborolidines from aromatic α-amino acids (phenylalanine, phenylglycine) is described. As a reagent for asymmetric synthesis, phenylalanine and phenylglycine contains a benzyl or phenyl group adjacent to theirs stereogenic center[5]. In the course of our study[6] on the synthesis and application of chiral auxiliaries prepared from optically active proteinogenic and nonproteinogenic amino acids, we prepared (*S*)-2-amino-1,1,3-triphenylpropanol **1** and (*S*)-1-(1′-amino-2′-phenylethyl)cyclopentanol **2** from natural (*S*)-phenylalanine.



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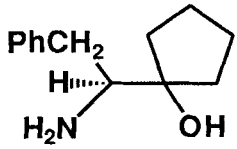

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The reagent (*S*)-2-amino-1,1,3-triphenylpropanol **1** was prepared as described[7]. (*S*)-1-(1′-amino-2′-phenylethyl)cyclopentanol **2** was obtained *via* an efficient three-step procedure from (*S*)-phenylalanine. First, (*S*)-phenylalanine was converted to the corresponding ethyl ester hydrochloride by treatment with ethanol/ $SOCl_2$. The salt was employed as such in the *Grignard* reaction, rather than as free base, in order to minimize the possibility of diketopiperazine formation. Thus, (*S*)-phenylalanine ethyl ester hydrochloride was added to a four-fold excess of 1,4-bis(bromomagnesio)butane[8] in ether to give (*S*)-1-(1′-amino-2′-phenylethyl)cyclopentanol hydrochloride **2**·HCl in 51% yield after work-up with hydro-

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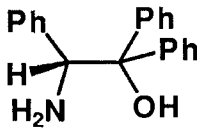
chloric acid. The free base **2** was generated from the hydrochloride **2**·HCl by treatment with 2 N sodium hydroxide.

The new cyclic amino alcohol (*R*)-1-(1′-amino-1′-phenylmethyl)cyclopentanol **4** has been prepared from (*R*)-phenylglycine by a similar approach.

The synthesis of the less rigid (*R*)-2-amino-1,1,2-triphenyl-ethanol **3** from (*R*)-phenylglycine is described in the literature[9].



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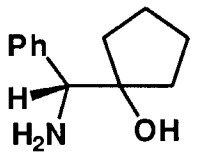

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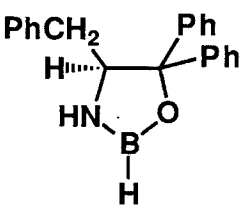
The conversion of the described homochiral amino alcohols **1**-**4** to the 1,3,2-oxazaborolidines **5**-**8** and their use as enantioselective catalysts in the borane reduction of prochiral ketones to form chiral secondary alcohols has been investigated (Table 1). The oxazaborolidines **5**-**8** have been prepared *in situ* and have not been isolated.



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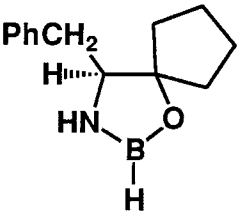

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Table 1 Enantioselectivecatalytic reduction of aromatic ketones with amino alcohols **1-4** and BH_3-THF

Ketone	Catalyst	Chiral alcohol obtained[h] Alcohol	Optical yield[g][%]
Acetophenone	**5** [a,e]	(*S*)-1-phenyl ethanol	67
Acetophenone	**5** [a,f]	(*S*)-1-phenyl ethanol	82
Acetophenone	**6** [a,e]	(*S*)-1-phenyl ethanol	55
Acetophenone	**6** [a,f]	(*S*)-1-phenyl ethanol	63
Acetophenone	**7** [a,e]	(*S*)-1-phenyl ethanol	75
Acetophenone	**7** [a,f]	(*S*)-1-phenyl ethanol	79
Acetophenone	**8** [a,d]	(*S*)-1-phenyl ethanol	79
Acetophenone	**8** [a,e]	(*S*)-1-phenyl ethanol	88
Acetophenone	**8** [a,f]	(*S*)-1-phenyl ethanol	88
Acetophenone	**8** [b,e]	(*S*)-1-phenyl ethanol	82
Acetophenone	**8** [c,e]	(*S*)-1-phenyl ethanol	82
Propiophenone	**8** [a,e]	(*S*)-1-phenyl propanol	81
Propiophenone	**8** [a,f]	(*S*)-1-phenyl propanol	85
Isopropylphenylketone	**8** [a,e]	(*S*)-2-methyl-1-phenyl propanol	70
Methyl-1-naphthylketone	**8** [a,e]	(*S*)-1-(1-naphthyl) ethanol	61
Methyl-2-naphthylketone	**8** [a,e]	(*S*)-1-(2-naphthyl) ethanol	88
1-Indanone	**8** [a,e]	(*S*)-1-indanol	82
ω-Bromo acetophenone	**8** [a,e]	(*R*)-2-bromo-1-phenyl ethanol	82

[a]Temperature 30°C.– [b]Temperature 40°C.– [c]Temperature 50°C.–
[d]Catalyst concentration: 1 mol %.– [e]Catalyst concentration: 2 mol %.–
[f]Catalyst concentration: 10 mol %.– [g]Optical yield was calculated from optical rotation based on the following maximum rotations of each chiral alcohol: $[\alpha]_D^{22} = +43.1$ ($c = 7.19$, cyclopentane) for (*R*)-1-phenyl ethanol[11], $[\alpha]_D^{22} = -45.45$ ($c = 5.15$, chloroform) for (*S*)-1-phenyl propanol[12], $[\alpha]_D^{22} = +47.7$ ($c = 6.8$, diethyl-ether) for (*R*)-2-methyl-1-phenyl propanol)[11], $[\alpha]_D^{22} = -74.7$ ($c = 5.0$, ethanol) for (*S*)-1-(1-naphthyl) ethanol[13], $[\alpha]_D^{22} = +55.8$ ($c = 4.8$, chloroform) for (*R*)-1-(2-naphthyl) ethanol[14], $[\alpha]_D^{22} = -30.1$ ($c = 1.13$, chloroform) for (*R*)-1-Indanol[15], $[\alpha]_D^{22} = -34.0$ ($c = 8.0$, chloroform) for (*R*)-2-bromo-1-phenyl ethanol[16].-
[h]Chemical yield; 94 to >99%.-

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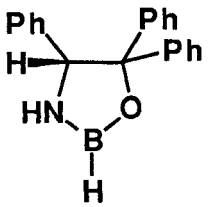

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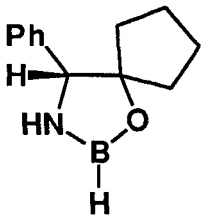

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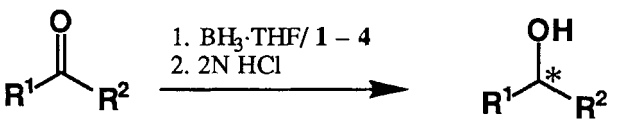
The catalytic enantioselective reduction of aromatic ketones using the chiral cyclic catalyst precursors[10] **1-4** as source of chiral information has also been investigated.



Prochiral Ketone Chiral Alcoho

Experimental Section

(*S*)-1-(1'-amino-2'-phenylethyl)cyclopentanol (2): A dry 500 mL, three-necked, round-bottomed flask, was equipped with a pressure-equalizing 250 mL dropping funnel, a thermometer, a large magnetic stirrer and a Liebig condenser. A Grignard reagent (103 mmol) was prepared from magnesium (5 g, 206 mmol) and 1,4-dibrombutane (12.2 mL, 103 mmol) in diethyl ether (350 mL). (*S*)-Phenylalanine ethyl ester hydrochloride (6.0 g, 26 mmol) was added to the 1,4-bis(brommagnesio)butane solution over 30 min at 0 to 5 °C with ice-salt bath cooling. After the addition, the cooling bath was removed and the reaction mixture

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was allowed to warm to room temperature. The solution was heated at reflux for 3 h. The reaction mixture was poured with stirring into crushed ice (300 g) and conc. hydrochloric acid (20 mL). The filtrate was concentrated under reduced pressure to remove diethyl ether. The residue was extracted with light petroleum and the water layer was concentrated under reduced pressure to remove 250 mL water. The residue was intensively extracted with dichloro methane and the combined organic layers were washed with brine, dried over anhydrous magnesium sulfat and concentrated under reduced pressure. The obtained crude product 3.23 g (51%) was suspended in dichloro methane (150 ml) and treated with 2 N aqueous sodium hydroxide with vigorous stirring for 10 h. After extraction with dichloro methane, the combined extracts were dried over anhydrous magnesium sulfat, and evaporated under reduced pressure to give a yellow oil, which slowly crystallisated at – 12°C. Recrystallization from *n*-hexane give the amino alcohol **2** as a colourless solid (1.5 g, 74 %), mp 30-34 °C, $[\alpha]_D^{20} = -35.1$ (c = 1.39, chloroform), IR (KBr): ν = 3520 - 3220 br (O-H···N), 2960 - 2860 s (CH), 1580, 1490 cm^{-1} m (CH); ^{1}H-NMR (300 MHz, d_6-DMSO) δ in ppm= 1.52-1.77 (m, 8H, cyclop.-H), 2.30, 2.70 (2dd, J_{gem} = 13.3 Hz, J_{vic} = 10.7 and 2.3 Hz, 2H, 2´-H), 2.90 (dd, 1H, 1´-H), 7.13 - 7.31 (m, 5 H, Ar-H); ^{13}C-NMR (DMSO) δ in ppm= 23.8, 24.0 (2C, cyclop. C-3,-4), 36.6, 36.7 (2C, cyclop. C-2,-5), 39.5 (1C, C-2´), 60.5 (1C, C-1´), 83.7 (1C, cyclop. C-1), 125.5 -129.1 (5C, Ar-C), 141.1 (1C, Ar, 1 x ipso-C); Anal. calc. for $C_{13}H_{19}NO$ (205.3): C, 76.06; H, 9.33; N, 6.82. Found: C, 75.93; H, 9.62; N, 6.94.

(*R*)-1-(1'-amino-1'-phenylmethyl)cyclopentanol (4) was similary prepared from (*R*)-phenylglycine ethyl ester hydrochloride: m.p. 82-84 °C; $[\alpha]_D^{20}$ = –23.8 (*c* = 0.998, choroform); IR (KBr): ν = 3400-3200 br (O-H...N), 2930 s (CH), 1470 cm^{-1} m (CH). ^{1}H-NMR (300 MHz, $CDCl_3$) δ in ppm= 1.08-1.72 (m,

8H, cyclop.-H), 3.78 (s, 1H, 1´-H), 7.12 - 7.23 (m, 5 H, Ar-H); ^{13}C-NMR ($CDCl_3$) δ in ppm= 24.0, 23.5 (2C, cyclop. C-3,-4), 36.5, 38.1 (2C, cyclop. C-2,-5), 63.01 (1C, C-1´), 83.8 (1C, cyclop. C-1), 127.0 -127.8 (5C, Ar-C), 142.6 (1C, Ar, 1 x ipso-C); Anal. calc. for $C_{12}H_{17}NO$ (191.3): C, 75.35; H, 8.96; N, 7.32. Found: C, 75.40, H, 9.04; N, 7.32.

Asymmetric reduction of prochiral ketones (typical procedure) : A solution of acetophenone (1.22 g, 10 mmol) in dry THF (15 ml) was added in 45 min to a mixture of catalyst **4** (0.038 g, 2 mmol) and BH_3-THF-complex (11 mmol) in THF (15 ml) at 30 °C; reactions were complete in 2 h after addition of the last reagent. The amino alcohol was easily recovered as the colourless hydrochloride salt **4**·HCl by addition of 2 N hydrochloric acid (40 ml) followed by filtration. The resulting optically active (*S*)-1-phenyl ethanol (1.20 g, 98%) could be isolated by ether extraction of the filtrate, drying over anhydrous magnesium sulfate, and removal of ether under reduced pressure. $[\alpha]_D^{20} = -37.8$ (c = 7.05, cyclopentane) {Lit[11] $[\alpha]_D^{22} = +43.1$ (c = 7.19, cyclopentane) for (*R*)-1-phenyl ethanol}.

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