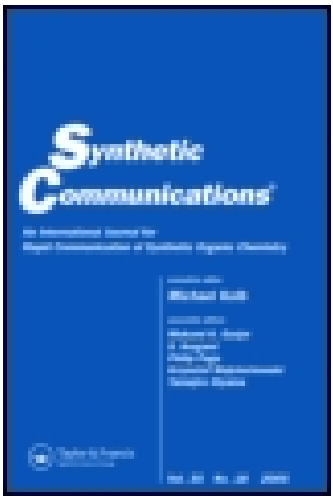

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Enantioselective Catalytic Borane Reductions of Achiral Ketones: Synthesis and Application Of New Catalysts Prepared from (S)-Tert-Leucine and (S)-Azetidinecarboxylic Acid

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ENANTIOSELECTIVE CATALYTIC BORANE REDUCTIONS OF ACHIRAL KETONES : SYNTHESIS AND APPLICATION OF NEW CATALYSTS PREPARED FROM (*S*)-*TERT*-LEUCINE AND (*S*)-AZETIDINECARBOXYLIC ACID

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Abstract: Enantiocontrolled reduction of prochiral ketones with borane in the presence of homochiral amino alcohols **1** – **3** as enantioselective catalysts afforded the corresponding secondary alcohols in moderate to high (69 to >99 %) optical yields.

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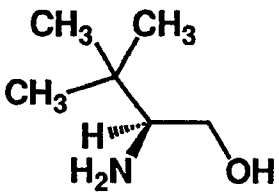
The asymmetric reduction of prochiral ketones with chiral hydride reagents has been intensively investigated[1]. Recently, much attention has been focused on the asymmetric borane reduction of ketones to optically active alcohols catalyzed by chiral oxazaborolidines. *Itsuno et al.* developed the oxazaborolidines as a new generation of reduction reagents[2]. Later other groups improved this new method[3]. As a reagent for asymmetric synthesis, *tert*-leucine enjoys the massive bulk of a *t*-butyl group adjacent to its stereogenic center. The steric demand imposed by this group are often superior in asymmetric transformations to other amino acids[4].



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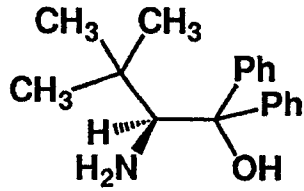
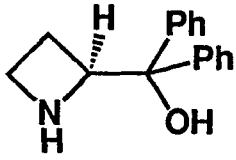


2

In the course of our study[5] on the synthesis and application of chiral auxiliaries prepared from chiral proteinogenic and nonproteinogenic amino acids, we prepared (*S*)-2-amino-3,3-dimethyl-1,1-diphenyl-1-butanol **2** and (*S*)-2-amino-3,3-dimethyl-1-butanol **1** from (*S*)-*tert*-leucine. The reagent (*S*)-2-amino-3,3-dimethyl-1-butanol **1** was prepared as previously described[6] and isolated by short-path

distillation. (*S*)-2-amino-3,3-dimethyl-1,1-diphenyl-1-butanol **2** was obtained *via* an efficient three-step procedure from (*S*)-*tert*-leucine. First, (*S*)-*tert*-leucine 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*)-*tert*-leucine ethyl ester hydrochloride was added to a ten-fold excess of phenylmagnesium bromide in ether to give (*S*)-2-amino-3,3-dimethyl-1,1-diphenyl-1-butanol hydrochloride **2**·HCl in 67% yield. The free base **2** was generated from the purified hydrochloride **2**·HCl by treatment with 2 N sodium hydroxide. (*S*)-α,α-Diphenyl-(azetidin-2-yl)methanol ## has been prepared from (S)-azetidinecarboxylic acid[7] **4a** *via* the methyl carboxylate **4b** by a similar approach.



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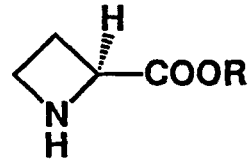


4a (R = H)
4b (R = CH_3)

The conversion of the homochiral amino alcohols **1** and **2** to the oxazaborolidines **5** and **6**, and their use as enantioselective catalysts in the borane reduction of prochiral ketones to form chiral secondary

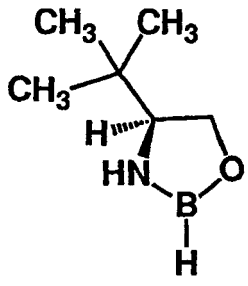
TABLE.

Enantioselective catalytic reductions of aromatic ketones with amino alcohols **1-3** (10 mol %) and BH_3·THF

		Chiral alcohol obtained	
Ketone	Catalyst	Alcohol	Optical yield[a] [%]
Acetophenone	**1**	(*R*)-1-phenyl ethanol	80
Acetophenone	**2**	(*R*)-1-phenyl ethanol	89
Acetophenone	**3**	(*R*)-1-phenyl ethanol	98
ω-Bromo acetophenone	**2**	(*S*)-2-bromo-1-phenyl ethanol	>95
Propiophenone	**1**	(*R*)-1-phenyl propanol	85
Propiophenone	**2**	(*R*)-1-phenyl propanol	69
Propiophenone	**3**	(*R*)-1-phenyl propanol	>99
Methyl 2-naphthyl ketone	**1**	(*R*)-1-(2-naphthyl) ethanol	71
Methyl 2-naphthyl ketone	**2**	(*R*)-1-(2-naphthyl) ethanol	72

[a] Optical yield was calculated from optical rotation based on the following maximum rotations of each chiral alcohol : $[\alpha]_D^{20} = +43.1$ ($c = 7.19$, cyclopentane) for (*R*)-1-phenyl ethanol[9], $[\alpha]_D^{20} = -45.45$ ($c = 5.15$, chloroform) for (*S*)-1-phenyl propanol[10], $[\alpha]_D^{20} = +55.8$ ($c = 4.8$, chloroform) for (*R*)-1-[2-naphthyl] ethanol-(1)[11].

alcohols has been investigated (TABLE 1). The oxazaborolidines **5** and **6** have been prepared *in situ* and have not been isolated.



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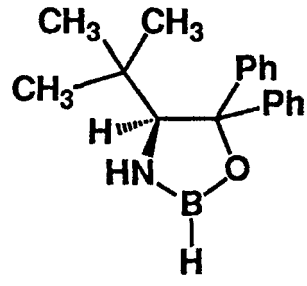
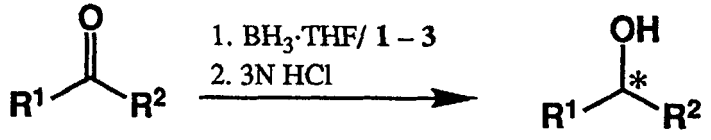


6

The catalytic enantioselective reduction of aromatic ketones using the cyclic catalyst precursor[8] **3** as source of chiral information has also been investigated (TABLE).



Prochiral Ketone Chiral Alcohol

Experimental Section

(*S*)-2-amino-3,3-dimethyl-1,1-diphenyl-1-butanol hydrochloride (2·HCl): A dry 1 L, three-necked, round-bottomed flask, was equipped with a pressur-equalizing 250 mL dropping funnel, a

thermometer, a large magnetic stirrer and a Liebig condenser. A Grignard reagent (400 mmol) was prepared from magnesium (9.7 g, 400 mmol) and bromo benzene (43.5 mL, 413 mmol) in diethyl ether (350 mL). (*S*)-*tert*-Leucine ethyl ester hydrochloride (10.0 g, 51 mmol) was added to the phenylmagnesium bromide solution over 1 h at 0 to –10 ^{0}C with ice-salt bath cooling. After the addition, the cooling bath was removed and the reaction mixture was allowed to warm to room temperature. The solution was heated at reflux for 2.5 h. The reaction mixture was poured with stirring into crushed ice (300 g) and conc. hydrochloric acid (50 mL). The first crop of the precipitated amine hydrochloride **2**·HCl was collected by filtration. The filtrate was concentrated under reduced pressure to remove diethyl ether and 200 mL water. The second crop of the precipitated amine hydrochloride **2**·HCl was collected by filtration. The combined precipitates were recrystallized from *tert*-butyl methyl ether to give colourless needles **2**·HCl (10.5 g, 67%), mp 236-238 °C, $[\alpha]_D^{20} = -48.0$ (c = 0.35, DMSO), IR (KBr): ν = 3600 - 3200 br (O-H···N), 3120 - 2900 m (Ar, CH), 1580, 1490 cm^{-1} m (Ar).^{1}H-NMR (300 MHz, d_6-DMSO) δ in ppm= 0.85 (s, 9H, methyl-H), 4.44 (m, 1H, 2-H), 6.39 (s, 1H, OH), 7.06 - 7.78 (m, 10 H, Ar-H), ^{13}C-NMR (DMSO) δ in ppm= 28.7 (3C, methyl-C), 35.3 (1C, C-3), 63.0 (1C, C-2), 79.9 (1C, C-1) 125.5 -128.5 (10C, Ar-C), 145.8, 146.5 (2C, Ar, 2 x ipso-C), Anal. calc. for $C_{18}H_{23}NO$·HCl (305.9): C, 70.68; H, 7.85; N, 4.58. Found: C, 70.23; H, 7.67; N, 4.65.

(*S*)-α,α-Diphenyl-(azetidin-2-yl)methanol hydrochloride (3·HCl) was similary prepared from methyl (*S*)-azetidinecarboxylate **4b** in 58% yield: m.p. 238-240°C; ^{1}H-NMR (DMSO): δ = 2.20 - 2.32 (m, 1H, 3-H), 2.55 - 2.68 (m, 1H, 3-H), 3.60 - 3.66 (m, 1H, 4-H), 3.80 - 3.86 (m, 1H, 4-H), 5.58 (t, ^{3}J = 9.4 Hz, 1H, 2-H), 6.74 (s, wide, 1H, OH), 7.22 - 7.52 (m, 10H, Ar-H), 8.94 (s, wide, 2H, NH_2^+);^{13}C-NMR (DMSO): δ = 19.6 (C-3), 41.2 (C-4), 64.6 (C-2), 76.5 (C-α), 125.9 - 128.3 (Ar-C), 142.5, 142.9 (Ar, 2 x ipso-C).

(*S*)-2-amino-3,3-dimethyl-1,1-diphenyl-1-butanol (2) : The hydrochloride **2**·HCl (3.0 g, 9.8 mmol) was suspended in dichloro methane (200 mL) and treated with 2 N aqueous sodium hydroxide solution with vigorous stirring until the aqueous phase turns alkaline. The resulting mixture was treated with triethyl amine (30 mL), strirred for 5 h and extracted with dichloromethane. The combined extracts were dried over anhydrous magnesium sulfate, and evaporated under reduced pressure to give a solid, which was recrystallized from methanol and *tert*-butyl methyl ether to give the amino alcohol **2** (2.1 g, 71%) as colorless crystalls, mp 138°C $[\alpha]_D^{20}$ = – 147.4 (c = 0.4, ethanol), IR (KBr) ν = 3400 - 3250 br (O-H···N), 3080, ^{1}H-NMR (DMSO) δ in ppm = 0.79 (s, 9H, methyl-H), 3,78 (s, 1H, 2-H), 5.29 (s, 1H, OH), 7.02 - 7 .60 (m, 10H, Ar-H), ^{13}C-NMR (DMSO) δ in ppm = 29.4 (3C, methyl-C), 35.8 (1C, C-3), 62.8 (1C, C-2), 81.1 (1C,

C-1), 125.6 - 128.0 (10C, Ar-C), 147.4, 150.0 (2C, Ar, 2 x ipso-C. Anal. calc. for $C_{21}H_{19}NO$ (269.4) : C, 80.25; H, 8.61; N, 5.20. Found: C, 79.83; H, 9.07; N, 5.27.

(*S*)-α,α-Diphenyl-(azetidin-2-yl)methanol (3) was similary prepared from **3·HCl** : m.p. 103-105 °C;$[\alpha]_D^{20} = -32.9°$ (*c* = 0.99 in $CHCl_3$); ^{1}H-NMR ($CDCl_3$): δ = 1.91 - 2.01 (m, 1H, 3-H), 2.34 - 2.46 (m, 1H, 3-H), 3.16 - 3.23 (m, 1H, 4-H), 3.53 - 3.61 (m, 1H, 4-H), 4.85 (t, ^{3}J = 7.9 Hz, 1H, 2-H), 7.13 - 7.30, 7.37 - 7.42 (2m, 10H, Ar-H). ^{13}C-NMR ($CDCl_3$): δ = 21.9 (C-3), 42.3 (C-4), 64.7 (C-2), 76.6 (C-α), 125.9, 126.1, 126.56, 126.6, 127.9, 128.0 (Ar-C), 143.5, 146.5 (Ar, 2 x ipso-C).

Asymmetric reduction of prochiral ketones (typical procedure) : A solution of ω-bromo acetophenone (2.0 g, 10 mmol) in dry THF (15 ml) was added in 50 min to a mixture of catalyst **2** (0.269 g, 1 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 **2**·HCl by addition of methanol (5 ml) and 3 N hydrochloric acid (15 ml) followed by filtration. The resulting optically active (*S*)-2-bromo-1-phenylethanol (1.84 g, 92%) could be isolated by

ether extraction of the filtrate, drying over anhydrous magnesium sulfate, and removal of ether under reduced pressure. $[\alpha]_D^{20} = +36.8$ (c=8.52, $CHCl_3$) {Lit[12]. $[\alpha]_D^{25} = -34$ (c=8.0, $CHCl_3$) for (*R*)-2-bromo-1-phenyl ethanol}.

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