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Enantioselective Catalytic Borane Reduction of Prochiral Ketones: Synthesis and Application of New Rigid β-Amino Alcohols with a Cycloalkanol Subunit

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ENANTIOSELECTIVE CATALYTIC BORANE REDUCTION OF PROCHIRAL KETONES : SYNTHESIS AND APPLICATION OF NEW RIGID β-AMINO ALCOHOLS WITH A CYCLOALKANOL SUBUNIT

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Abstract: Enantiocontrolled reduction of prochiral ketones with borane in the presence of new enantiomerically pure bi- and tricyclic β-*sec*-amino alcohols **2-5** as stereodifferentiating catalysts afforded the optically active corresponding secondary alcohols in moderate to excellent (up to 98 % *op*) optical yields.

The stereoselective synthesis of optically active secondary alcohols is a well studied theme in organic chemistry. In particular 1,3,2-oxazaborolidines[1], borane modified with chiral β-amino alcohols, show a high ability to promote the enantioselective catalytic reduction of prochiral ketones affording the chiral reduction products with excellent enantiomeric excess up to 100 %. Many chiral auxiliaries, e.g. oxazaborolidine-catalysts are derived from homochiral natural compounds (amino acids, camphor, etc.).

Limitations in their structural and stereochemical modification can be a hindrance to achieve an efficient transformation in some cases. Using artificial chiral compounds, which can be suitably designed for each asymmetric process, could improve this situation[2].

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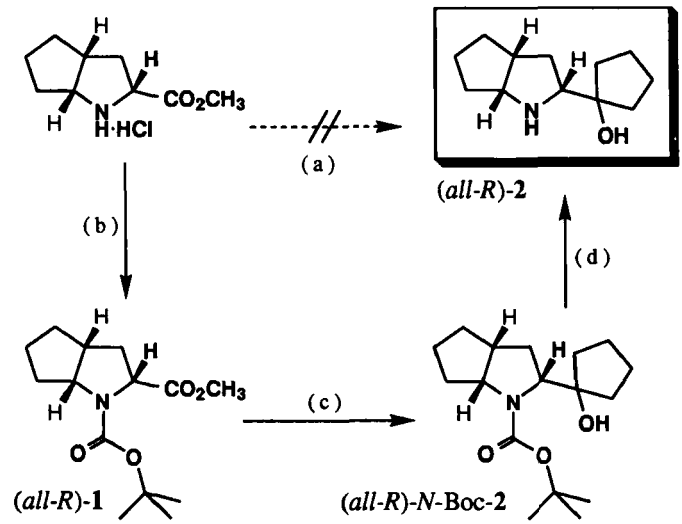
Besides this, optically active industrial waste materials – usually available in both enantiomeric forms – could be a cheap basis for the rational design of effective catalysts, e.g. catalyst precursors for stereocontrolled homogeneous catalytic reactions.

Results and Discussion

Here we report the synthesis of new bi- and tricyclic β-*sec*-amino alcohols with a characteristic cycloalkanol-subunit (starting from two *non*-proteinogenic amino acids) and their application in the oxazaborolidine catalyzed reduction of prochiral ketones.

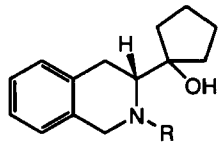


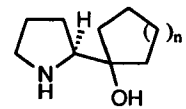
scheme 1: (a) : $Mg/Br(CH_2)_3Br$ in THF or Et_2O, (b) : $(Boc)_2O$, NEt_3; (c) : Mg, $Br(CH_2)_3Br$ in THF; (d) : 3N HCl, acetic acid

Previously, we have synthesized *mono*-cyclic β-amino alcohols with a cyclopentanol building-block by a reaction of amino acid ethyl ester hydrochlorides with 1,4-bis(brommagnesio)butane[3]. This method is not applicable to secondary amino acids such as proline and is limited to the formation of cyclopentanol derivatives. These products are usually not isolable because of strong contamination by impurities due to several side reactions (see scheme 1, step a).

We found that the conversion of the corresponding *N*-Boc-protected amino acid

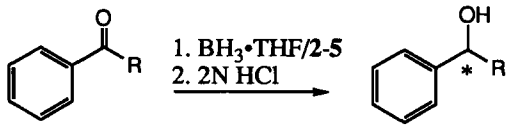
esters was much more effective for the synthesis of (primary *and* secondary) amino alcohols with a cyclopentanol- (or cyclohexanol) subunit. In addition to high yields (up to 82.5 %, using (*S*)-*N*-Boc-proline ethyl ester hydrochloride) the utilization of the Boc-protecting group eases the work-up either by crystallization or (flash-)chromatography. In the course of our studies on the utilization of industrial waste materials[4] and *non*-proteinogenic amino acids (*all-R*)-1'-[2-azabicyclo[3.3.0]octane-3-yl]cyclopentanol (*all-R*)-**2** and (*R*)-1'-[1,2,3,4-tetrahydroisochinolin-3-yl]cyclopentanol (*R*)-**3** were prepared *via* this efficient three-step procedure (scheme 1, steps b to d). For comparison the bicyclic amino alcohols (*S*)-**4** and (*S*)-**5** has also been synthesized from (*S*)-proline by the same approach[5].





(*R*)-*N*-Boc-**3** (R = Boc) (*S*)-**4** (n = 1)
(*R*)-**3** (R = H) (*S*)-**5** (n = 2)

For these β-amino alcohols based on a five-membered, respectively six-membered cyclic backbone the introduction of a second (or third) ring – further enhancing the rigidity – was exspected to influence positively their inductive ability in the enantioselective catalysis.



6a (R = CH_3) **7a** (R = CH_3)
6b (R = CH_2Cl) **7b** (R = CH_2Cl)

The conversion of the described homochiral amino alcohols **2-5** to the corresponding 1,3,2- oxaborolidines was accomplished by treating with BH_3·THF. Their use as enantioselective catalysts in the borane reduction of prochiral ketones to form optically active secondary alcohols **7a,b** has been investigated (the results are shown in the table below).

table: Enantioselective catalytic reduction of aromatic ketones **6a,b** with amino alcohols **2-5** and BH_3•THF to yield secondary alcohols **7a,b**

cat.* (conc.)	temp. [°C]	ketone	yield [%]	$[\alpha]_D^{20}$ (*c*)[a]	*op* [%][b]	config.
(*all-R*)-**2** (10 mol %)	66	**6a**	84	– 21.3 (7.19)	50	*S*
(*all-R*)-**2** (5 mol %)	66	**6b**	77	– 27.9 (1.88)	58	*R*
(*R*)-**3** (5 mol %)	66	**6a**	82	– 32.6 (7.09)	76	*S*
(*R*)-**3** (5 mol %)	66	**6b**	80	– 35.7 (1.91)	74	*R*
(*S*)-**4** (10 mol %)	0	**6a**	93	+ 9.5 (7.13)	22	*R*
(*S*)-**4** (10 mol %)	20	**6a**	86	+ 25.7 (7.20)	60	*R*
(*S*)-**4** (10 mol %)	40	**6a**	76	+ 28.8 (7.16)	67	*R*
(*S*)-**4** (10 mol %)	66	**6a**	69	+ 36.9 (7.02)	86	*R*
(*S*)-**4** (5 mol %)	66	**6a**	80	+ 36.2 (6.98)	84	*R*
(*S*)-**4** (5 mol %)	66	**6b**	78	+ 47.0 (1.84)	98	*S*
(*S*)-**4** (2 mol %)	66	**6b**	82	+ 45.3 (1.73)	94	*S*
(*S*)-**5** (5 mol %)	66	**6a**	78	+ 25.4 (7.08)	59	*R*
(*S*)-**5** (5 mol %)	66	**6b**	79	+ 32.7 (1.78)	68	*S*

a) **6a**: measured in cyclopentane, **6b**: measured in cyclohexane, (b) *op* : optical purity was calculated from optical rotation based on the following maximum rotations of the respective alcohol: **6a** : $[\alpha]_D^{20} = + 43.1$ ($c = 7.19$, cyclopentane) for (*R*)-1-phenyl-ethanol [6], **6b** : $[\alpha]_D^{20} = - 48.1$ ($c = 1.8$, cyclohexane) for (*R*)-2-chloro-1-phenyl-ethanol [7].

The oxazaborolidines have been prepared *in situ* and have not been isolated. Beside acetophenone **6a**, α-chloro-acetophenone **6b** was chosen as model substrate due to the fact that the resulting chlorohydrin is a versatile synthon in organic synthesis[8].

The new homochiral bi- and tricyclic β-*sec*-amino alcohols **2-5** with cycloalkanol framework show convincing stereodifferentiating efficiency affording the optically active secondary alcohols **7a,b** in moderate to excellent optical yields (up to 98 % *op*).

Experimental Section

All reactions were carried out in oven dried glassware, under argon atmosphere using anhydrous solvents. Melting points were taken on a melting point apparatus according to Dr. Linström and are uncorrected. Optical rotations were measured on a Perkin-Elmer automatic polarimeter. IR spectra were recorded on a Philips PU 9706 spectrophotometer. The ^{1}H-NMR and ^{13}C-NMR spectra were registrated on a Bruker AM 300 spectrometer using TMS as internal standard. Mass spectra were recorded on a Finnigan-MAT 212 (data system 300; CI, *i*-butane). Elemental analyses (C, H, N) were performed on a Carlo Erba Stumentalione (MOD 1104) analyzer.

(*all-R*)-*N*-Boc-2-azabicyclo[3.3.0]octane-3-carboxylic acid methyl ester (*all-R*)-**1**
(*all-R*)-2-Azabicyclo[3.3.0]octane-3-carboxylic acid methyl ester hydrochloride[9] 10.7 g (52 mmol) was suspended in 200 ml THF and Et_3N (11.6 g, 114 mmol) is added dropwise with stirring of the reaction mixture. The resulting white suspension was cooled to 0 °C and a solution of $(Boc)_2O$ (11.28 g, 51.7 mmol) in 80 ml THF was added within 45 min. The mixture was allowed to warm to room temperature and stirred for 18 h. The solvent is removed *in vacuo*, and the residue partitioned between Et_2O (150 ml) and H_2O (100 ml). The aqueous phase was extracted with Et_2O (2x 80 ml) and the combined organic phases washed with 2N HCl (2x 60 ml), 4% $NaHCO_3$ (2x 80 ml) and brine (80 ml). Drying ($MgSO_4$) and evaporation of the solvent under reduced pressure afforded (*all-R*)-**1** as a colourless oil; yield: 13.1 g (94 %), $[\alpha]_D^{20} = -12.7$ (c = 2.05, CH_2Cl_2), IR (NaCl): ν = 1750-1660 cm^{-1} (-C=O), ^{1}H-NMR ($CDCl_3$): δ = 1.29–1.86, 1.86–2.04, (3m, 16H, $C(C\underline{H}_3)_3$, H5, 2xH6, 2xH7, 2xH8), 2.29-2.46 (m, 1H, 1xH4), 2.57-2.74 (m, 1H, 1xH4), 3.71 (s, 3H, $OC\underline{H}_3$), 4.09-4.42 (m, 2H, H1, H3), ^{13}C-NMR ($CDCl_3$): δ = major rotamer: 28.26 ($OC(\underline{C}H_3)_3$), 25.01, 31.81, 33.12, 35.51 (C4, C6, C7, C8), 41.98 (C5), 51.81, 60.89, 64.23 (C1, C3, $O\underline{C}H_3$), 79.67 ($O\underline{C}(CH_3)_3$), 149.76 ($R_2N\underline{C}O_2R$), 162.47 ($R\underline{C}O_2CH_3$); minor rotamer: 28.26 ($C(\underline{C}H_3)_3$), 24.56, 31.99,

34.02, 34.32 (C4, C6, C7, C8), 43.01 (C5), 51.81, 60.36, 64.23 (C1, C3, O$\underline{C}H_3$), 79.67 ($\underline{C}(CH_3)_3$), 148.45 ($R_2N\underline{C}R$), 161.34 ($R\underline{C}O_2CH_3$); MS (CI, *i*-butane): *m/z* (%) = 270 (100) [MH^+]; Anal. calc. for $C_{14}H_{23}NO_4$ (269.1): C, 62.42; H, 8.61; N, 5.20; found: C, 62.31; H, 8.72; N 5.02.

N-Boc-amino alcohols: (*all-R*)-*N*-Boc-2, (*R*)-*N*-Boc-3, General procedure:
A *Grignard*-reagent was prepared under argon atmosphere from magnesium (134 mmol) and 1,4-dibrombutane (65 mmol) in dry THF (200 ml). The ethyl ester of *N*-Boc-protected amino acids (20 mmol) was added to the bis(brom-magnesio)alkane 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 was allowed to warm to room temperature. After 16 hours the reaction mixture was hydrolyzed with saturateted NH_4Cl solution. The organic layer was separated and the aqueous layer was extracted with diethyl ether. The combined organic extracts were evaporated under reduced pressure to remove the solvents. The residue was dissolved in 150 ml diethyl ether, washed with brine, dried over anhydrous magnesium sulfate and concentrated again under reduced pressure. The obtained crude products were purified by flash chromatography. The individual work-up is described below.

(*all-R*)-*N*-Boc-**2** : substrate: 5.4 g (20.0 mmol) (*all-R*)-*N*-Boc-2-azabicyclo–[3.3.0]octane-3-carboxylic acid methyl ester (*all-R*)-**1**, yield: 3.46 g (58.5 %), work-up: purification by flash-chromatography (silica gel 60, eluent: *n*-hexane/EtOAc 8 : 2, R_f-value: 0.40), product: colurless oil, $[\alpha]_D^{20} = +6.2$ (*c* = 0.63, CH_2Cl_2), IR (NaCl): ν = 3690-3220 cm^{-1} (OH), 1690-1650 (-C=O), ^{1}H-NMR ($CDCl_3$): δ = 1.14–2.00 (m, 15H, 4x cyclopentyl-CH_2, H5, 2xH6, 2xH7, 2xH8), 1.43 (s, 9H, OC($C\underline{H}_3$)$_3$), 2.03-2.20 (m, 1H, 1xH4), 2.40-2.59 (m, 1H, 1xH4), 3.91-4.06 (m, 1H, H1), 4.06-4.23 (m, 1H, H3), 6.49 (s, breit, 1H, COH), ^{13}C-NMR ($CDCl_3$): δ = 28.36 (OC($\underline{C}H_3$)$_3$), 23.28, 23.56, 25.07, 30.58, 33.40, 34.69, 35.59, 38.21, 39.79 (4x cyclopentyl-CH_2, C4, C5, C6, C7, C8), 65.85 (C1), 69.22 (C3), 80.02 (COH), 83.23 (O$\underline{C}$(CH$_3$)$_3$), 157.42 ($R_2N\underline{C}O_2R$); MS (CI, *i*-butane): *m/z* (%) = 296 (100) [MH^+]; Anal. calc. for $C_{17}H_{29}NO_3$ (295.2): C, 68.87; H, 10.21; N, 4.73; found: C, 68.64; H, 10.06; N, 4.58.

(*R*)-*N*-Boc-**3** : substrate: 5.82 g (20.0 mmol) (*R*)-*N*-(Boc)-1,2,3,4-tetrahydro–isochinolin-3-carboxylic acid methyl ester, yield: 3.1 g (49 %), $[\alpha]_D^{20}$ = + 8.7 (*c* = 1.26, CH_2Cl_2), IR (NaCl): ν = 3620-3160 cm^{-1} (OH), 1690-1640 (-C=O) cm^{-1}, ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.14–1.91 (2m, 8H, 4x cyclopentyl-CH_2), 1.91 (s, 9H, $OC(C\underline{H}_3)_3$), 2.94 (dd, *J* = 16.5 Hz, 4.4 Hz, 1H, 1xH4), 3.08 (dd, *J* = 16.5 Hz, 7.2 Hz, 1H, 1xH4), 4.20-4.43 (m, 2H, 2xH1), 4.69-4.90 (m, 1H, H3), 6.94-7.26 (2m, 4H, aromat.-H), ^{13}C-NMR ($CDCl_3$): δ = 22.56, 23.12, 23.49, 29.42 (4 x cyclopentyl-CH_2), 28.37 ($OC(\underline{C}H_3)_3$), 37.70 (C4), 45.64 (C3), 55.98 (C1), 80.07 ($O\underline{C}(CH_3)_3$), 86.33 (COH), 125.58, 125.96, 126.54, 126.78 (aromat.-C), 128.14, 134.44 (q. aromat.-C), 157.13 ($R_2N\underline{C}O_2R$); MS (CI, *i*-butane): *m/z* (%) = 318 (100) [MH^+]; Anal. calc. for $C_{19}H_{27}NO_3$ (317.2): C, 71.88; H, 8.58; N, 4.41; found: C, 72.01; H, 8.62; N, 4.34.

Amino alcohols (*all-R*)-2, (*R*)-3, General procedure:
The protected amino alcohol (5 mmol) was treated at room temperature with 50 ml 3N HCl in 50 mL acetic acid (alternative procedure: a mixture of 1 equiv. anisole and 10 equiv. *p*-toluenesulfonic acid in 50 ml dioxane with 10 ml 2N HCl can be used). After 3 h the mixture was concentrated under reduced pressure and the residue washed twice with diethyl ether. The aqueous layer was basified with 20 % aqueous NaOH followed by an extraction with CH_2Cl_2 (4 x 40 ml). The combined organic layers were dried over $MgSO_4$. Evaporation under vacuo afforded the pure amino alcohol.

(*all-R*)-**2** : substrate: 1.02 g (3.45 mmol) (*all-R*)-*N*-Boc-**2**, yield: 0.6 g (89 %), colourless solid, m.p.: 153-161 °C, $[\alpha]_D^{20}$ = – 7.2 (*c* = 0.46, CH_2Cl_2), IR (NaCl): ν = 3620-3120 cm^{-1} (OH, NH), ^{1}H-NMR ($CDCl_3$): δ = 1.14–2.20 (4m, 16H, 4x cyclopentyl-CH_2, H5, 2xH6, 2xH7, 2xH8, NH), 2.20-2.38 (m, 1H, 1xH4), 2.69-2.92 (m, 1H, 1xH4), 3.31-3.48 (m, 1H, H1), 4.08-4.26 (m, 1H, H3), 6.63 (s, 1H, COH), ^{13}C-NMR ($CDCl_3$): δ = 23.54, 23.73, 23.86, 30.75, 31.85, 32.32, 37.93, 39.63, 41.73 (4x cyclopentyl-CH_2, C4, C5, C6, C7, C8), 64.39 (C1), 70.11 (C3), 79.15 (COH); MS (CI, *i*-butane): *m/z* (%) = 196 (100) [MH^+]; Anal. calc. for $C_{12}H_{21}NO$ (195.2): C, 73.78; H, 10.84; N, 7.18; found: C, 73.71; H, 10.82; N, 7.10.

(*R*)-**3** : substrate: 1.0 g (3.15 mmol) (*R*)-*N*-Boc-**3**, yield: 0.57 g (83 %), $[\alpha]_D^{20}$ = + 77.9 (*c* = 0.29, CH_2Cl_2), IR (NaCl): ν = 3600-3120cm^{-1} (OH, NH), ^{1}H-NMR (300

MHz, $CDCl_3$): δ = 1.54–2.00 (m, 8H, 4x cyclopentyl-CH_2), 2.69-2.93 (m, 4H, 2xH4, 2xH1), 3.97-4.11 (m, 1H, H3), 6.91-7.00 (m, 1H, aromat.-H), 7.07-7.23 (m, 3H, aromat.-H), ^{13}C-NMR ($CDCl_3$): δ = 23.93, 23.97, 29.60, 35.61 (4x cyclopentyl-CH_2), 37.91 (C4), 48.57 (C3), 61.30 (C1), 83.22 (COH), 125.68, 125.86, 126.19, 129.34 (aromat.-C), 134.66, 135.21 (q. aromat.-C); MS (CI, *i*-butane): *m/z* (%) = 218 (100) [MH^+]; Anal. calc. for $C_{14}H_{19}NO$ (217.2): C, 77.37; H, 8.82; N, 6.45; found: C, 77.42; H, 8.86; N, 6.40.

Asymmetric reduction of prochiral ketones : In a typical procedure a mixture of acetophenone (10 mmol) or ω-chloro-acetophenone (10 mmol) in 10 ml dry THF was slowly added within 30 min to a solution of the catalysts (*all-R*)-**2**, (*R*)-**3**, (*S*)-**4** or (*S*)-**5** (2, 5 or 10 mol%) and borane-THF complex (11 mmol, 1.0 M solution in THF) in 30 ml dry THF at the respective reaction temperature (see table given above). After stirring for 6 hours at constant temperature the reaction mixture was hydrolyzed with 40 ml 2 N HCl and extracted three times with 30 ml diethyl ether. The combined organic layers were washed sucessivley with 30 ml 2N NaOH and 10 ml NaCl solution, dried ($MgSO_4$) and concentrated under reduced pressure. The optical purity (*op*) was calculated after fractional distillation from the optical rotation based on the following maximum rotations of the respective alcohols: **7a** : $[\alpha]_D^{20}$ = + 43.1 (*c* = 7.19, cyclopentane) for (*R*)-1-phenyl-ethanol[6] and **7b** : $[\alpha]_D^{20}$ = – 48.1 (*c* = 1.8, cyclohexane) for (*R*)-2-chloro-1-phenyl-ethanol[7].

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