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ENANTIOSELECTIVE CATALYTIC BORANE REDUCTIONS OF AROMATIC KETONES: SYNTHESES AND APPLICATION OF TWO CHIRAL β-AMINO ALCOHOLS FROM (*S*)-PORRETINE

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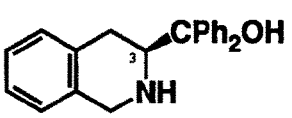
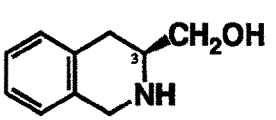
Summary : The *in situ* formed chiral oxazaborolidine catalysts from two optically active β-amino alcohols (*S*)-**1** and (*S*)-**2** from benzyl (*S*)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (*S*)-**3** have been used sucessfully in the enantioselective catalytic homogenous borane reductions of various aromatic ketones.

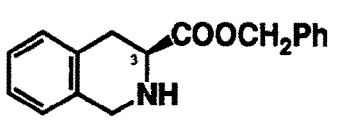
The development of efficient stereoselective reactions is a challenging and exciting endeavor in organic chemistry. A variety of asymmetric syntheses utilize amino acid-based chiral auxiliaries to prepare optically active products.[1] Particularly with structurally rigid proline derivatives great success was achieved.[2] The enantioselective synthesis of chiral alcohols which play an important role as intermediates in organic chemistry is a stimulating subject, and a plethora of methods for the asymmetric reduction of carbonyl compounds using microbial processes[3], heterogenous metal catalysts[4] or chirally modified hydride reagents[5] have been reported in recent years. Since the pioneering work of *Itsuno* and his coworkers[6] interest has been centered increasingly on homogenous catalytic ketone reductions with borane involving substoichiometric amounts of optically active β-amino alcohols as catalyst precursors.[7]



(*S*)-**1**



(*S*)-**2**



(*S*)-**3**

In continuation with our study on the preparation of new chiral auxiliaries prepared from proteinogenic and non proteinogenic amino acids[8] we wish to report herein on two new reduction catalyst precursors (*S*)-α,α-diphenyl-(1,2,3,4-tetrahydroisoquinolin-3-yl)methanol (*S*)-**1** and (*S*)-(1,2,3,4-tetrahydroisoquinolin-3-yl)methanol[9] (*S*)-**2** having a sterically rigid bicyclic structure.

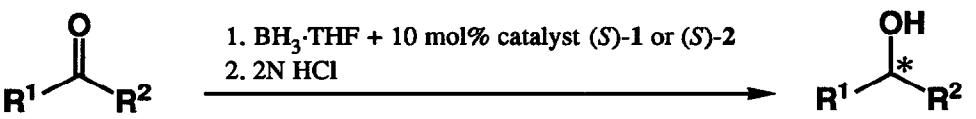
The synthesis of (*S*)-**1** and (*S*)-**2** was accomplished starting from (*S*)-porretine[10] which was easily made *via* a *Pictet-Spengler* reaction from (*S*)-phenylalanine and formaldehyde under acidic conditions as described in the literature.[10b] The esterification with benzyl alcohol and *p*-toluenesulfonic acid leads upon treatment with saturated aequous sodium hydrogen carbonate solution to the carboxybenzyl[11] (*S*)-**3**.

The *Grignard* reaction of the benzyl carboxylate (*S*)-**3** with a four fold excess of phenylmagnesium bromide (in dry ether, −10°C, than 3h reflux) leads upon treatment with ice cold 2N HCl to the crystalline tertiary amino alcohol hydrochloride (*S*)-**1**-HCl in 41% yield.[12] The free base[13] (*S*)-**1** was liberated by treatment with triethylamine as a colourless solid in >95% enantiomeric excess.[14]

The primary alcohol (*S*)-**2** was obtained by reduction of (*S*)-**3** with an excess lithium aluminium hydride in refluxing THF under inert gas and anhydrous conditions. Upon treatment with 10% KOH and extraction of the organic phase with 2N HCl the hydrochloride (*S*)-**2**-HCl was obtained in 53% chemical yield.[15] The free base (*S*)-**2**[16] was liberated by treatment with 2N NaOH and triethylamine as a colourless solid in 100% optical yield.[9]

The homogenous catalytic reductions of aromatic ketones with the *in situ* formed oxazaborolidine catalysts from (*S*)-**1** and (*S*)-**2** respectively has been investigated.The effect of reaction temperature was examined. The best enantioselectivities with (*S*)-**1** were realised when the reaction was carried out at 50°C. When (*S*)-**2** was used at 45°C the best results were obtained.

In a typical procedure to a solution of the catalyst (*S*)-**1** (0.2 mmol) and borane-THF complex (22 mmol) in dry THF was slowly added within 45 min. a mixture of the respective ketone (20 mmol) in dry THF at 50° C. After stirring for 16 hours at 50° C the reaction mixture was hydrolyzed with 2N HCl and extracted with diethyl ether. The precipitated white solid [amino alcohol hydrochloride (*S*)-**1**-HCl] was filtered off. The combined organic layers were sucessively washed with 2N NaOH and brine, dried and concentrated under reduced pressure. The obtained crude product was distilled through a *Vigreaux* column under *vacuo* to afford the respective optically active alcohol. The optical yields were determined by optical rotation analysis.



aromatic ketone chiral secondary alcohol

Catalytic reductions in the presence of (*S*)-**2** were carried out as desrcibed above at 45°C. The amino alcohol hydrochloride (*S*)-**2**-HCl is soluble in the aqueous layer but could be recycled from it and can be used in further enantioselective reductions as chiral catalyst precursor.

Table 1. Enantioselective reductions of aromatic ketones with (*S*)-**1** (10 mol%) and (*S*)-**2** (10 mol%) respectively and BH_3·THF.[a]

Educt	Product	Catalyst	Opt. yield[b] [%]
acetophenone	(*R*)-1-phenylethanol	(*S*)-**1**	51
acetophenone	(*R*)-1-phenylethanol	(*S*)-**2**	71
propiophenone	(*R*)-1-phenyl-1-propanol	(*S*)-**1**	35
propiophenone	(*R*)-1-phenyl-1-propanol	(*S*)-**2**	42
α-tetralone	(*R*)-1,2,3,4-tetrahydro-1-naphthol	(*S*)-**1**	32
α-tetralone	(*R*)-1,2,3,4-tetrahydro-1-naphthol	(*S*)-**2**	44

[a] The chemical yields of the chiral alcohols were > 99% in each case (controlled by TLC).– [b] Optical yields of chiral secondary alcohols obtained were calculated from optical rotations based on the following maximum rotations of each alcohol: $[\alpha]_D^{20} = +43.1$ ($c = 7.19$, cyclopentane) for (*R*)-1-phenylethanol[17], $[\alpha]_D^{r.t.} = -45.45$ ($c = 5.15$, $CHCl_3$) for (*S*)-1-phenyl-1-propanol[18], $[\alpha]_D^{17} = +32.65$ ($c = 2.5$, $CHCl_3$) for (*S*)-1,2,3,4-tetrahydro-1-naphthol[19].

As can be seen from Table 1 the above procedure was effectively applied to reductions of acetophenone, propiophenone and α-tetralone. In each case the (*R*)-enantiomer of the secondary alcohol was formed preferentially. Surprisingly we obtained the best optical yields when the primary β-amino alcohol (*S*)-**2** was applied to enantioselective reductions instead of the *tert*-alcohol (*S*)-**1**. This result does not follow the expected pattern as observed with other catalysts.[7]
Further studies in order to improve the optical yields are still under progress.

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12 (*S*)-α,α-Diphenyl-(1,2,3,4-tetrahydroisoquinolin-3-yl)methanol hydrochloride (*S*)-**1**-HCl: mp.: 269°C; $[\alpha]_D^{20}$ = –37.9 (*c* = 0.70, MeOH); ^{1}H-NMR (MeOD): δ in ppm = 2.88 and 3.27 (2 dd, $J_{3,4}$ = 4.2 und $J_{3,4}$ = 11.8 Hz, $J_{geminal}$ = 17.2 Hz, 2H, H4), 4.28 und 4.51 (2d, J = 15.6 Hz, 2H, H1), 4.84 (dd, J=4.3 und J=9.8 Hz, 1H, H3), 7.12-7.46 (m, 10H, 2xC_6H_5), 7.56-7.73 (m, 4H, Ar-H); MS (CI; i-Butan): 316 (MH^+–HCl, 100%), 632 (M_2H^+–HCl, 3.6%).

13 (*S*)-α,α-Diphenyl-(1,2,3,4-tetrahydroisoquinolin-3-yl)methanol (*S*)-**1**: mp.: 98°C; $[\alpha]_D^{20}$ = –93.7 (*c* = 0.83, $CHCl_3$); ^{1}H-NMR($CDCl_3$): δ in ppm = 2.39 and 2.93 (2 dd, $J_{3,4}$ = 3.7 and $J_{3,4}$ = 11.0 Hz, $J_{geminal}$ = 16.5 Hz, 2H, H4), 3.96 (dd, J = 3.9 und J = 11.0 Hz, 1H, H3), 3.96 und 4.13 (2 d, J=15.6 Hz, 2H, H1), 6.92-7.34 (m, 10H, 2x C_6H_5), 7.48-7.62 (m, 4H, Ar-H); MS (CI, *i*-Butan): 316 (MH^+, 100%), 632 (M_2H^+, 14%).

14 The *ee* values were calculated from ^{1}H-NMR spectra of the derived (1*S*)-camphanic acid esters.

15 (1,2,3,4-Tetrahydroisoquinolin-3-yl)methanol hydrochloride (*S*)-**2**-HCl: mp.: 225-227°C; $[\alpha]_D^{20}$ = –54.5 (*c* = 0.76, MeOH); ^{1}H-NMR (d_6-DMSO): δ in ppm = 2.93 (dd, J=2.5 und J=9.1 Hz, 2H, –CH_2OH), 3.47 (m,1H, H3), 3.66 und 3.78 (2 dd, $J_{3,4}$ = 6.1 und $J_{3,4}$ = 4.4 Hz, $J_{geminal}$ = 11.5Hz, 2H, H4), 4.23 (2 d, J = 14.4 Hz, 2H, H1), 7.17-7.30 (m, 4H, Ar-H), 7.50 and 7.74 (2s, 2H, OH, NH); MS (CI, *i*-Butan): 164 (MH^+–HCl, 100%), 327 (M_2H^+–HCl, 2%).

16 (1,2,3,4-Tetrahydroisoquinolin-3-yl)methanol (*S*)-**2**: mp.: 117 °C; $[\alpha]_D^{20}$ = –101.3 (*c* = 1.92, EtOH) [ref. 10 : mp.: 118-119°C; $[\alpha]_D^{20}$ = –101.4 (*c* = 2, EtOH)].

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