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ENANTIOSELECTIVE CATALYTIC BORANE REDUCTIONS OF ACHIRAL KETONES : SYNTHESES AND APPLICATION OF TWO CHIRAL β-AMINO ALCOHOLS FROM (*S*)-2-INDOLINE CARBOXYLIC ACID

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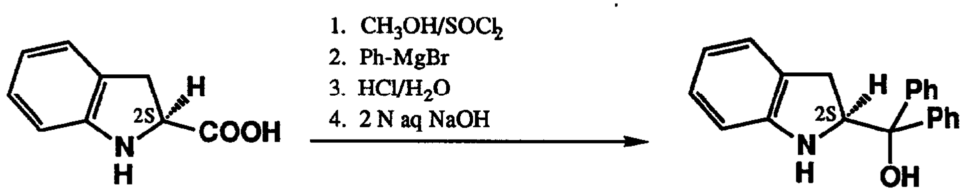
Summary : The synthesis of (*S*)-α,α-diphenyl-(indolin-2-yl)methanol **1** makes available the chiral oxazaborolidine **2** which is an excellent catalyst for borane reduction of prochiral ketones to chiral secondary alcohols, e.g. acetophenone, in high optical purity The new chiral auxiliary **1** is sythesized from (*S*)-2-indoline carboxylic acid in a two step procedure. (*S*)-(Indolin-2-yl)methanol **3** is converted to the oxazaborolidine **4** which served also as an enantioselective catalyst in the reduction of aromatic ketones with BH_3·THF.

This paper reports the synthesis of the chiral amino alcohol **1**, (*S*)-2-(diphenylhydroxymethyl)indoline, its conversion to the oxazaborolidide **2**, and the use of **2** as an enantioselective catalyst in the borane reduction of achiral ketones to form chiral secondary alcohols. Although, methods for asymmetric reduction of carbonyl



(*S*)-2-Indoline carboxylic acid

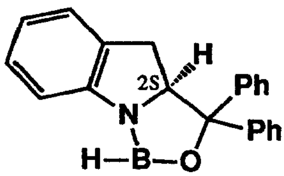
1

compounds with stochiometric quantities of chiral reagents[1] or heterogeneous metal catalysts[2] have been extensively reported in recent years, useful *enantioselective homogeneous catalytic reductions* have been relatively neglected.[3]

The synthesis of the chiral amino alcohol **1** was accomplished starting from (*S*)-2-indoline carboxylic acid.[4] First methyl (*S*)-2-indoline carboxylate was prepared in 75% yield from (*S*)-2-indoline carboxylic acid with methanol/thionyl chloride. This methyl carboxylate was added dropwise to the Grignard reagent prepared from phenylbromide to give after hydrolysis with ammonium chloride the crystalline alcohol **1**·HCl.[5] in 8 %

yield. The free base of (*S*)-α,α-diphenyl-(indolin-2-yl)methanol[6] **1** is liberated from the hydrochloride **1**·HCl by treatment with 2 N aq. sodium hydroxide.

Conversion of **1** to oxazaborolidine **2** was accomplished by treatment with an excess of BH_3·THF. However, **2** was not isolated and used as prepared *in situ*. Oxazaborolidine **2** was shown to be a highly effective catalyst for the borane reduction of a varity of achiral ketones to chiral secondary alcohols. Results are summarized in Table1. Reductions were performed with either 2 or 10 mol% of catalyst by addition of ketone over 30-60 min to a mixture of catalyst and BH_3 in THF at 30 °C. The catalyst was easily recovered as the colorless hydrochloride salt **1**·HCl or **2**·HCl by addition of 4.5 equiv methanolic HCl and ether followed by filtration. The resulting optically active alcohols obtained by asymmetric reduction of prochiral ketones could be isolated in >90% yield by concentration of the filtrate followed by ether extraction, drying ($MgSO_4$), and removal of ether. For further analysis, the residue was distilled under reduced pressure (Kugelrohr).



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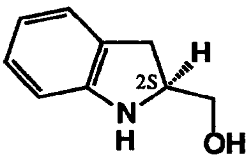
We have also synthesized (*S*)-(indolin-2-yl)methanol **3** from (*S*)-2-indoline carboxylic acid as previously described by Pak *et al.*[7] Conversion of the β-amino alcohol **3** to oxazaborolidine **4** was accomplished by treating **3** with BH_3·THF. Again, the oxazaborolidine **4** was used *in situ* in enantioselective reductions of various prochiral ketones (Table 1).



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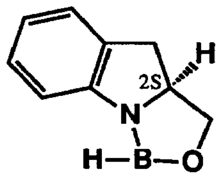

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The results obtained with oxazaborolidines **2** (from ligand **1**) and **4** (from ligand **3**) as catalysts for the reduction of acetophenone and a range of other ketones by borane in THF are summarized in Table 1. Under optimum conditions excellent yields and enantioselectivities are obtained for a varity of ketones. More than 90% of the ligand **1** and **3**, respectively, is easily recovered upon workup, making the method especially attractive for large-scale synthesis of optically active secondary alcohols. It should be noted that the enantioselectivity of these reductions often increases somewhat with increasing temperature (e.g., 0-30 °C).[8]

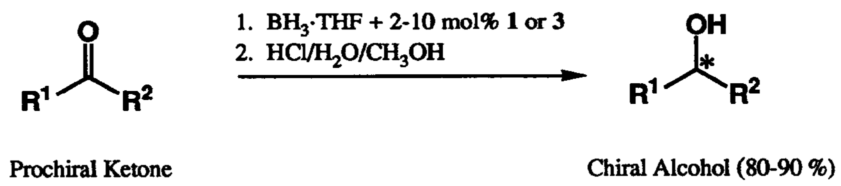

Table 1. Asymmetric reduction of aromatic ketones with chiral catalyst and excess borane in THF

Ketone	Ligand (equiv)[b]	Chiral alcohol obtained: Optical yield[a] [%]	Absolute configuration
Acetophenone	1 (0.1)	91	*R*
Acetophenone	1 (0.02)	93	*R*
Propiophenone	1 (0.1)	88	*R*
Propiophenone	1 (0.02)	81	*R*
Methyl-2-naphthylketone	1 (0.02)	85	*R*
α-Tetralone	1 (0.02)	79	*R*
Acetophenone	3 (0.1)	8	*R*
Acetophenone	3 (0.02)	3	*R*
Propiophenone	3 (0.1)	14	*R*
Propiophenone	3 (0.02)	6	*R*

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-1-ethanol[9], $[\alpha]_D^{20}$ = –45.45 (*c* = 5.15, chloroform) for (*S*)-1-phenyl-1-propanol[10], $[\alpha]_D^{20}$ = +55.8 (*c* = 4.8, chloroform) for (*R*)-1-(naphth-2-yl)-ethan-1-ol[11], $[\alpha]_D^{20}$ = +30.0 (*c* = 4.5, chloroform) for (*S*)- 1,2,3,4-tetra–hydro-naphth-1-ol[12].

Further investigation of optically active oxazaborolidines with (*S*)-(indolin-2-yl)methanol skeleton and other chiral 2-amino-1-alkanol derivatives of proteinogenic and nonproteinogenic amino acids is in progress.

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5 (*S*)-α,α-Diphenyl-(indolin-2-yl)methanol hydrochloride **1**·HCl : m.p. 187 - 190 °C. $[\alpha]_D^{20} = -30.3$ (c= 0.55, DMSO); IR (KBr) ν 3310 s (NH), 3060 - 3020 m-s (Ar), 2800 s-m (CH), 1490 - 1440 (Ar, CH), 1360 cm^{-1} (C-N); ^1H-NMR (DMSO) δ = 3.00 - 3.20 (m, 2 H, 3-H), 5.52 -5.59 (m, 1H, 2-H), 7.10-7.75 (m, 14 H, Ar-H); ^{13}C-NMR (DMSO) δ = 31.4 (1C,C-3),65.8 (1C, C-a.), 77.3 (1C, C-2), 125.2-128.3 (17Ar-C) 145.0 (1C, C-8).

6 (*S*)-α,α-Diphenyl-(indolin-2-yl)methanol **1** : m.p. 151 - 153 °C, $[\alpha]_D^{20} = -105.5$ (c= 0.38, ethanol), IR (KBr) ν = 3500 s (O-H), 3400 m (N-H), 3060, 2920 w (Ar, CH), 1600, 1480 cm^{-1} m-s (Ar); ^1H-NMR (DMSO) δ = 2.65 (dd, ^2J = 16.0 Hz 1H, 3-H), 2.86(dd ^2J = 16.0 , 1H, 3-H), 5.35 (s, 1H, OH), 5.15 (m, 1H, 2-H), 6.45 - 6.62 (m, 14H, Ar-H); ^{13}C-NMR (DMSO) δ = 31.2 (1C, C-3), 64.952 (1C, C-a), 77.6 (1C, C-2), 109.3 - 151.9 (14C, Ar-C).

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