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ENANTIOSELECTIVE CATALYTIC REDUCTION OF ACETOPHENONE WITH BORANE IN THE PRESENCE OF CYCLIC α-AMINO ACIDS AND THEIR CORRESPONDING β-AMINO ALCOHOLS

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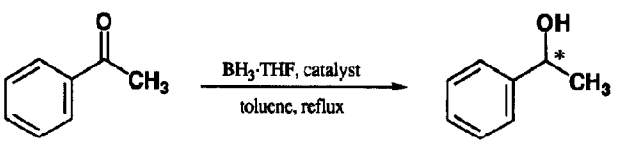
Summary : The direct application of α-amino acids as chiral auxiliaries in the enantioselective catalytic reduction of acetophenone with borane in refluxing toluene has been investigated. A comparison with the corresponding β-amino alcohols as optically active catalysts is involved.

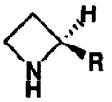
The stereoselective synthesis of optically active secondary alcohols is a well studied theme in organic chemistry. In particular the 1,3,2-oxazaborolidines[1], borane modified with chiral β-amino alcohols, show a high ability to promote the asymmetric reduction of prochiral ketones and the desired end products were obtained in excellent *ee*'s up to 100 %.



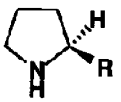
acetophenone 1-phenethanol

In earlier reports we described the synthesis of chiral ligands derived from α-amino acids and their succesful application in asymmetric transformation reactions such as the enantioselective addition of diethylzinc to aldehydes and the stereoselective reduction of achiral ketones with BH_3·THF.[2]

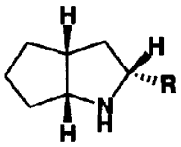
The publication of *Buono et al.*[3] prompts us to report our results using cyclic and rigid α-amino acids and their corresponding β-amino alcohols as chiral auxiliaries with borane as the reducing reagent.



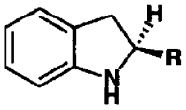
(*S*)-**1a** (R=COOH)
(*S*)-**1b** (R=CH_2OH)



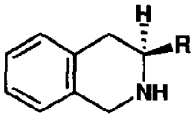
(*S*)-**2a** (R=COOH)
(*S*)-**2b** (R=CH_2OH)



(*all-R*)-**3a** (R=COOH)
(*all-R*)-**3b** (R=CH_2OH)



(*S*)-**4a** (R=COOH)
(*S*)-**4b** (R=CH_2OH)



(*S*)-**5a** (R=COOH)
(*S*)-**5b** (R=CH_2OH)

In a typical procedure under argon atmosphere the α-amino acid **1a**-**5a** (1 mmol) was suspended in dry toluene and 0.1 ml (1 mmol) of a 1 M solution of borane-THF complex was added via syringe. The mixture was stirred for 10 min at room temperature and then heated to reflux (110 °C). First acetophenone (10 mmol) in dry toluene was added dropwise to the clear solution, followed by 10 ml (10 mmol) of BH_3·THF via syringe over a period of 15 min. Within this time the reaction temperature decreases from 110 °C to 88-85 °C. The mixture was refluxed for further 15 min and then cooled to room temperature. The reduction was quenched with 2 N HCl and the aqueous layer was extracted was diethyl ether. The combined organic layers were successively washed with 2N NaOH and water, dried ($MgSO_4$) and concentrated under reduced pressure. The crude product obtained was distilled under *vacuo* (Kugelrohr) to afford 1-phenethanol. The optical yield was determined by optical rotation analysis.

As can be seen from table 1, the enantioselective reduction of acetophenone with borane catalyzed by α-amino acids (*S*)-**1a**[4], (*S*)-**2a**[4], (*all-R*)-**3a**[5], (*S*)-**4a**[6] and (*S*)-**5a**[7] provides only low to moderate enantiomeric excess (17-33 % *ee*) in the synthesis of 1-phenethanol of predictable absolute stereochemistry.

Table 1. Enantioselective reduction of acetophenone in the presense of chiral catalysts (*S*)-**1a/b**, (*S*)-**2a/b**, (*all-R*)-**3a/b**, (*S*)-**4a/b** respectively (*S*)-**5a/b** and borane in refluxing toluene.

		1-phenethanol[a]	
entry	catalyst (mol %)	*ee*[b] [%]	configuration
1	(*S*)-**1a** (1)	17	*S*
2	(*S*)-**1a** (10)	0	–
3	(*S*)-**1b** (10)	0	–
4	(*S*)-**2a** (10)	28	*R*
5	(*S*)-**2b** (10)	48	*R*
6	(*all-R*)-**3a** (1)	3	*S*
7	(*all-R*)-**3a** (10)	22	*S*
8	(*all-R*)-**3b** (10)	33	*S*
9	(*S*)-**4a** (1)	13	*R*
10	(*S*)-**4a** (10)	20	*R*
11	(*S*)-**4b** (10)	51	*R*
12	(*S*)-**5a** (1)	25	*R*
13	(*S*)-**5a** (10)	30	*R*
14	(*S*)-**5b** (10)	45	*R*

[a] The isolated yield of the chiral alcohol was 80–95%. – [b] The *ee*-value of the chiral secondary alcohol obtained was calculated from optical rotation based on the following maximum rotation $[\alpha]_D^{20} = +43.1$ ($c = 7.19$, cyclopentane) for (*R*)-1-phenethanol[8].

In comparison the amino alcohols (*S*)-**1b**[9], (*S*)-**2b**[10], (*all-R*)-**3b**[11], (*S*)-**4b**[12] and (*S*)-**5b**[7] show slighty better results (entries 3, 5, 8, 11 and 14). Further studies to optimize the reaction conditions are in progress.

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