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ENANTIOSELECTIVE REDUCTIONS OF KETONES WITH OXAZABOROLIDINES DERIVED FROM (R) AND (S)-α,α-DIPHENYL-2-PIPERIDINE METHANOL

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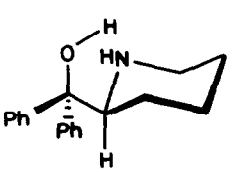
Summary: Oxazaborolidines obtained from (R) and (S)-α,α-diphenyl-2-piperidine methanol have been used as catalysts in the enantioselective reductions of ketones with borane.

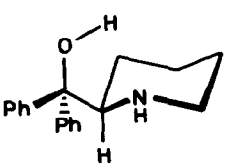
Enantioselective reductions of prochiral ketones (**1**) with oxazaborolidines leading to the formation of chiral secondary alcohols (**2**) is a topic of current interest[1,2]. Studies by Corey's

1 **2**

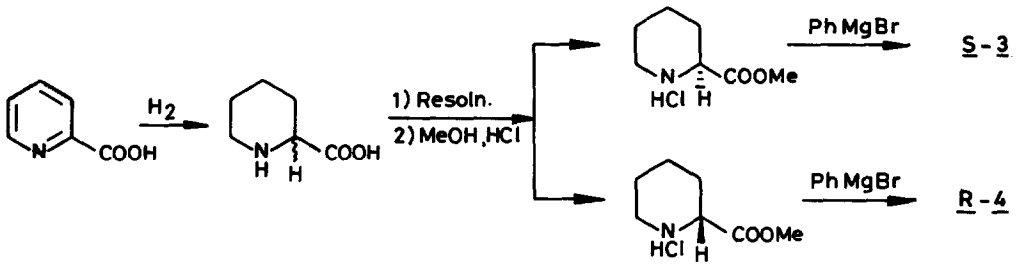
group[2] demonstrating the use of oxazaborolidine in catalytic amount were a landmark achievement in this endeavour. Most of the oxazaborolidines prepared in vivo or in vitro are derived from L-amino acids, thus restricting the application only to one enantiomer of the secondary alcohol (**2**). However, to realise[1b] the antipode of **2**, involves the generation of oxazaborolidines from the expensive and not readily accessible D-amino acids. Therefore, we felt that the development of new oxazaborolidines that are comparable in activity with the existing ones but more importantly easily accessible in both the enantiomeric forms, is a worthwhile proposition[3]. Our attention was drawn towards (S)- and (R)-α,α-diphenyl-2-piperidine methanol (**3** and **4**) as chiral substrates for generating S and R-oxazaborolidines (**5** and **6**). This communication describes enantioselective reductions of ketones with borane in the presence of catalysts (**5** and **6**).



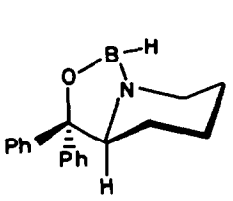
S - 3



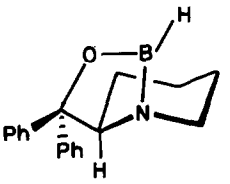
R - 4



Both the amino alcohols, S-3 [m.p. 99°C, $[\alpha]_D$ -59.5° (MeOH)] and R-4 [m.p. 99°C, $[\alpha]_D$ +60° (MeOH)] were synthesized[4] from α-picolinic acids by successive: i) hydrogenation, ii) resolution (tartaric acid), iii) esterification and iv) the Grignard reaction (PhMgBr). The preparation of oxazaborolidines, for instance of S-5, was carried out by heating a mixture of S-3 with 3 equivalents of 0.9M borane-THF solution under inert and anhydrous condition for 4 h followed by evaporation of the reaction mixture to dryness under vacuo. The solid product (5)[5] revealed a molecular ion peak in CI-MS at m/z 277 and was found to be stable under inert and anhydrous conditions for a few days.



S-5



R-6

The reductions of ketones (1) with boranes in the presence of S-5 and R-6 as catalysts were conducted to afford chiral secondary alcohols (2) with good enantiomeric excess (e.e.) (Table 1). The chemical yields of the secondary alcohols were between 85-95%. It is pertinent to mention that the stereochemical outcome (R and S) of the isolated secondary alcohol with catalysts (5 and 6) follows the expected pattern as observed for the reported catalysts[1,2].

In a typical procedure (entry 1) a solution of 3-methoxyacetophenone (10 mmol) in dry THF was slowly added to a solution of S-5 (1 mmol) and borane-THF complex (6 mmol) at 0°C. After 5 min, the reaction was quenched with methanol followed by addition of saturated solution of hydrogen chloride in ether. The precipitated S-3 hydrochloride[6] was filtered. The mother liquor was concentrated and partitioned between water and ethyl acetate. The organic layer was dried and concentrated to afford the residue which was distilled under vacuo to afford (R)-1-hydroxyethyl-3-methoxybenzene in 90% yield. The e.e. of 92% was determined by HPLC analysis (silica column, 1% isopropanol in n-heptane) of the derived Mosher ester[7].

Table

ENTRY	R^1	R^2	Cat. S-5	2(ee)[b,e]	Cat. R 6	2(ee)[b,e]
1	3-OMe-C_6H_4[a]	Me	0.1eq[d]	R (92)	0.1eq	S (96)
2	C_6H_5	Me	0.1eq	R (87)	0.1eq	S (87)
3	4-$Me_2CHCH_2C_6H_4$	Me	0.1eq	R (89)	0.1eq	S (89)
4	4-OMe-C_6H_4	Me	0.1eq	R (90)	0.1eq	S (88)
5	C_6H_5	CH_2Cl	0.1eq	S (85)[c]	0.1eq	R (85)[c]

a Ketones (1) are commercially available; b ee were determined by HPLC of the derived mosher esters; c ee was determined by optical rotation; d all the reactions were performed at 0°C except the entry 5 at 23°C; e yields of the secondry alcohols were between 85-95%.

In essence, the oxazaborolidines (S-5 and R-6) are indeed suitable for use as catalysts for the reductions of ketones with borane, thus providing on easy access to both the enantiomers of the secondary alcohols. Further studies such as developing methylboronates and their applications will be forthcoming.

References and Footnotes

1. a) S. Itsuno, K. Ito, A. Hirao and S. Nakahama, J.C.S. Chem. Commun, 469 (1983).
   b) S. Itsuno, M. Nakano, K. Miyazaki, H. Masuda, K. Ito, A. Hirao and S. Nakahama, J. Chem. Soc. Perkin Trans 1, 2039 (1985).
   c) S. Itsuno, M. Nakano, K. Ito, A. Hirao, M. Owa, N. Kanda and S. Nakahama, J. Chem. Soc. Perkin Trans 1, 2615 (1985).
2. a) E.J. Corey, R.K. Bakshi and S. Shibata, J. Am. Chem. Soc., **109**, 5551 (1987).
   b) E.J. Corey, R.K. Bakshi, S. Shibata, C.P. Chen and V.K. Singh, J. Am. Chem. Soc., **109**, 7925 (1987).
   c) E.J. Corey, S. Shibata and R.K. Bakshi, J. Org. Chem., **53**, 2861 (1988).

3. Recently, the Harvard group [E.J. Corey, C.P. Chen and G.A. Reichard, Tetrahedron Lett., 5547 (1989)] has demonstrated (1S, 5R, 8S)-8-phenyl-2-azabicyclo[3.3.0]octane-8-ol N,O-methylboronate and its enantiomers as useful catalysts for enantioselective syntheses of R and S enantiomers of secondary alcohols in high e.e

4. a) V.W. Rodwell, Methods in Enzymology, Vol. 17, Part B, p. 174; Academic Press, London, 1971.

   b) P.S. Portoghese, T.L. Pazdernik, W.L. Kuhn, G. Hite and A. Shafi'ee, J. Med. Chem., **11**, 12 (1968).

5. m.p.150-154°C, the isomeric R-**6** was prepared by the same approach.

6. The aqueous solution of the hydrochloride was basified with potassium carbonate followed by extraction with ethyl acetate. The organic layer was washed with water (2x), dried and concentrated to afford S-**3** ($[\alpha]_D$ -58.9° (88%) which could be used for the preparation of oxazaborolidine derivative S-**5**.

7. J.A. Dale and H.S. Mosher, J. Am. Chem. Soc., **95**, 512 (1973).

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