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Enantioselective catalytic reductions of ketones with new four membered oxazaborolidines : Application to (S)-Tetramisole

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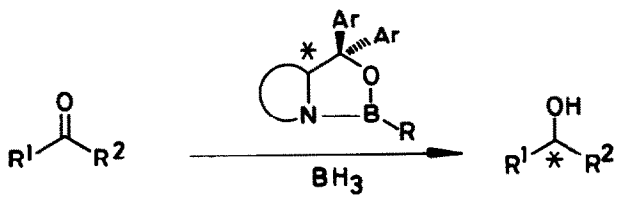
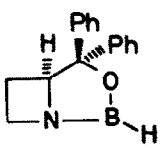
Abstract: Enantioselective catalytic reduction of ketones with both the enantiomers of new four membered oxazaborolidines is described.

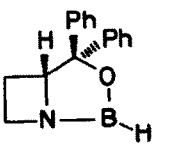
In our earlier communication[1] we have demonstrated the utility of the six membered oxazaborolidines, obtainable from α,α-diphenyl-2-piperidine methanol, in the enantioselective catalytic reductions of prochiral ketones[2,3]. Although the distinctive advantage of having simultaneously both the enantiomers of six membered oxazaborolidines was obvious over other oxazaborolidines[3], the enantiomeric excess of the derived chiral alcohols were consistent-



ly low by a factor of 5-10%. This we assumed was due to steric influence being less in the case of six membered catalyst compared to the five membered oxazaborolidines[3]. If our assumption was correct we expected that the two four membered oxazaborolidines (R)-**1** and (S)-**1** would be structurally more rigid and thus improve the enantioselectivity. Herein we report two new four membered oxazaborolidines (R)-**1** and (S)-**1**, prepared from the corresponding α,α-diphenyl-2-azetidine methanols (R)-**9** and (S)-**9** respectively.

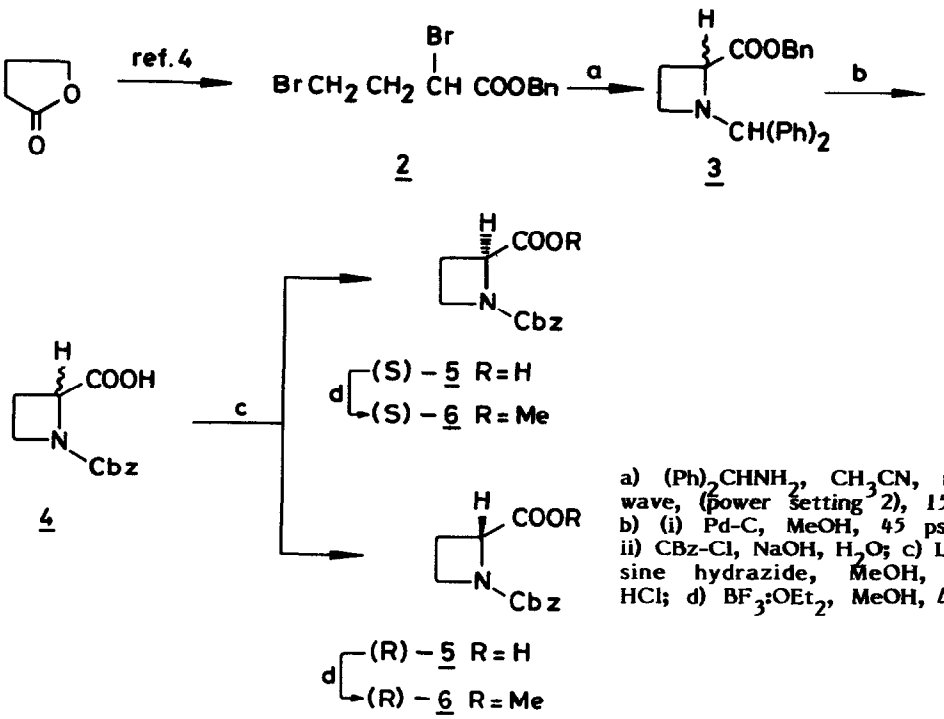


(S)-**1**



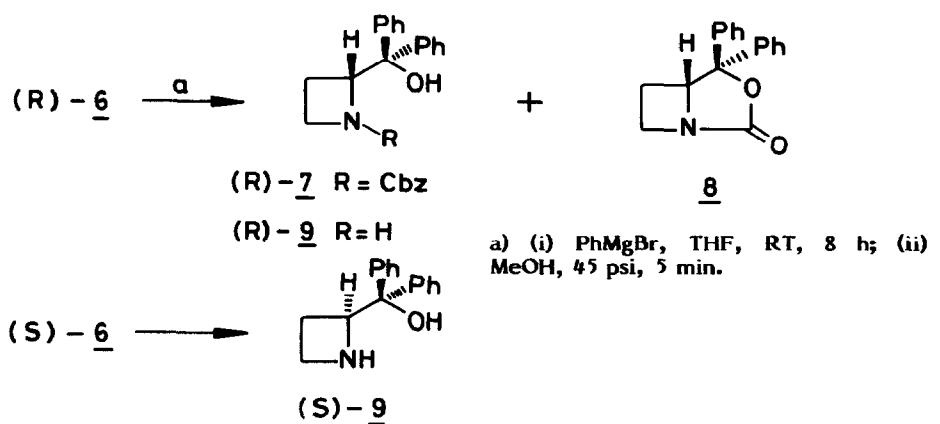
(R)-**1**

Synthesis of (R)-**9** and (S)-**9** were carried out as follows. Condensation of the dibromide (**2**) with benzhydrylamine according to the literature[4] procedure needed at least 24 h under reflux to afford the azeditine derivative (**3**) in 82%. We observed that the same condensation when carried out in acetonitrile under microwave irradiation (power setting 2, range 1-7), was completed in just 15 min. giving **3** in 96% yield. Subsequent hydrogenolysis (Pd-C, H_2, 45 psi) of **3** followed by protection (Cbz-Cl, NaOH, H_2O) of the NH group then afforded (±)-**4**. Resolution[5] of (±) **4** was conveniently carried out by using L-tyrosine hydrazide as



a) $(Ph)_2CHNH_2$, CH_3CN, microwave, (power setting 2), 15 min; b) (i) Pd-C, MeOH, 45 psi, 6h; ii) CBz-Cl, NaOH, H_2O; c) L-tyrosine hydrazide, MeOH, conc. HCl; d) BF_3:OEt_2, MeOH, Δ, 2h.

a resolving agent. Thus the enantiomerically pure acid (R)-5 {$[\alpha]_D$ + 100.5 ($CHCl_3$)} and (S)-5 {$[\alpha]_D$ - 101 ($CHCl_3$)} were synthesised. (R)-5 was converted (BF_3:OEt_2, MeOH, Δ) into the methyl ester derivative (R-6) which was then subjected to the Grignard reaction (PhMgBr, THF, RT, 8h) to give a mixture of two products. Separation by chromatography and identification by spectral studies revealed the structure (8) (17%) for the faster moving component and (R)-7 (68%) for the slower moving component. Compound 7 was hydrogenated (Pd-C, H_2, 45 psi, 5 min) to cleave the Cbz group and give rise to the required product (R)-9 (75%)

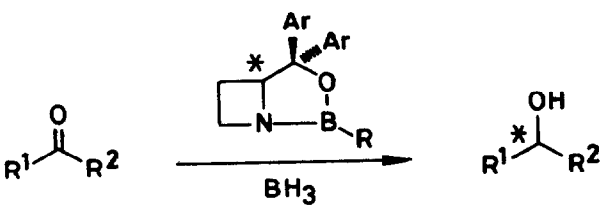


a) (i) PhMgBr, THF, RT, 8 h; (ii) Pd-C, MeOH, 45 psi, 5 min.

[m.p. 116°C $[\alpha]_D$ +75 (MeOH)]. The enantiomer (S)-**9** [m.p. 114.5° $[\alpha]_D$ -74.5 (MeOH)] was prepared by the same sequence of reactions from the corresponding acid (S)-**5**.

The oxazaborolidine (R)-**1** was easily generated[1] from (R)-**9** by the treatment with 3 eq of 1M borane-THF solution. The reaction was completed at 60° within 3 h to give the crystalline product (R)-**1** confirmed by its mass spectrum: m/z 249 (M^+). Similarly the other enantiomer (S)-**1** was obtained from (S)-**9**.

Reduction of ketones with 1M borane:THF solution (0.6 eq) in the presence of both the new catalysts (0.1 eq) were studied and are summarised in the Table. The results clearly indicated a marked improvement in the enantioselective reductions of ketones to afford chiral alcohols with 95-97% ee. The chemical yields of the isolated alcohols were more than 90%. The ee of the alcohol was determined by the ^{1}H-NMR spectral studies of the Mosher ester and/or comparison of optical rotations. Except the reduction for entries 2 and 4 carried out at 23°C, all other reductions were performed at 0°C.



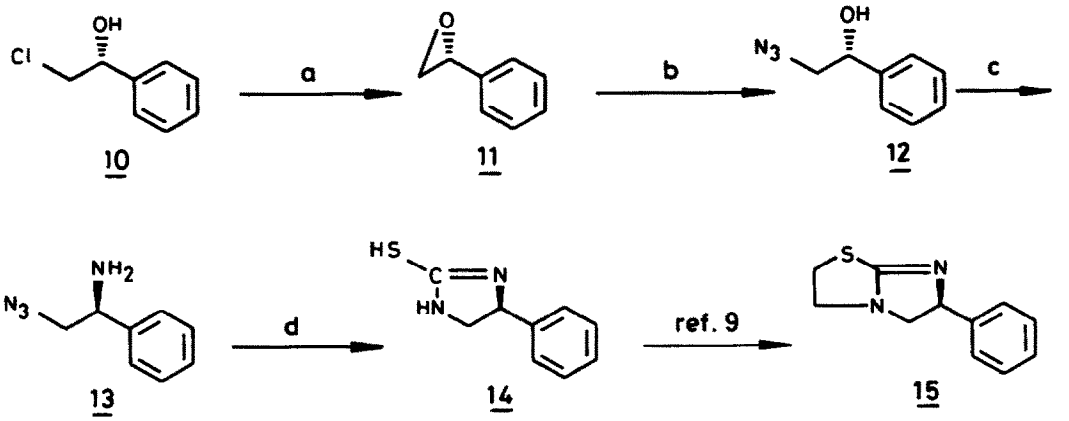
TABLE

Entry	R^1	R^2	Catalyst (0.1 eq)	ee	Stereo chemistry
1	3-OMe-C_6H_4	Me	(S)-**1**	95%	R
2	C_6H_5	CH_2Cl	(S)-**1**	97%	S
3	4-$Me_2CHCH_2C_6H_4$	Me	(S)-**1**	95%	R
4	C_6H_5	CH_2Cl	(R)-**1**	95%	R
5	C_6H_5	CH_3	(R)-**1**	95%	S

Due to the ready availability of chiral alcohols by the above technique, there is a current renaissance[6] to develop practical applications of these chiral alcohols to synthesise biologically active and enantiomerically pure molecules. For example, the availability of **10** (entry 4) has prompted us to undertake the first chiral synthesis of tetramisole (**15**) (anthelmentic) whose 'S' isomer is two times more active than the racemic mixture and several times more than the 'R' isomer[7]. Upon exposure to an alkali (NaOH, H_2O, MeOH), compound **10** was converted into styrene epoxide (**11**) in almost quantitative yield. The ring opening of epoxide with azide anion (NaN_3, DMF, 80°) gave a regiomeric mixture (14:86) of azido-alcohol from which the major regiomer (**12**) was isolated by chromatography (80%). Treatment of **12** with phthalimide under Mitsunobu conditions[8] (TPP, DIAD, THF) followed by hydrolysis (NH_2NH_2, EtOH, Δ) furnished **13**. Its reduction (Pd-C, H_2) and cyclisation with CS_2 afforded

the intermediate **14** $[\alpha]_D$ +32 (MeOH), lit.[7] $[\alpha]_D$ +34±2 (MeOH) in 95% yield. **14** has been transformed into (S)-tetramisole (**15**) in a one step reaction[7,9].

Scheme



a) 2M NaOH, MeOH, RT, 3 h; b) NaN_3, DMF, 80°, 8 h; c) (i) DIAD, TPP, Phthalimide, THF, RT, 8 h; (ii) NH_2NH_2, EtOH, Δ, 1 h; d) (i) Pd-C, MeOH, 1 atm, 2 h; (ii) 2M KOH, CS_2, 0°-RT, 15 min.

References

1. A V Rama Rao, M K Gurjar, P A Sharma and V Kaiwar, Tetrahedron Lett, **31**, 2341 (1990).
2. E J Corey, R K Bakshi and S Shibata, J Am Chem Soc. **109**, 5551 (1987).
3. E J Corey, Pure Appl. Chem. **62**, 1209 (1990) and references cited therein.
4. B A Phillips and N H Cromwell, J Het Chem. **10**, 795 (1973).
5. R M Rodebangh and N H Cromwell, J Het Chem. **6**, 993 (1969).
6. E J Corey and J O Link, Tetrahedron Lett. **30**, 601 (1990); T K Jones, J J Mohan, L C Xavier, T J Blacklock, D J Mathre, P Sohar, E T T Jones, R A Reamer, F E Roberts and E J J Grabowski, J Org Chem. **56**, 763 (1991).
7. A H Raeymaekers, L F C Roevens and P A J Janssen, Tetrahedron Lett. **16**, 1467 (1967).
8. O Mitsunobu, Synthesis, 1 (1981).
9. A H Raeymaekers, F T N Allewijn, J Vandenberk, P J A Demoen, T T T Van Offenwert and P A J Janssen, J Med Chem, **9**, 545 (1966).

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