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Enantioselective Reduction of Ketones Catalysed by 1,3,2-Oxazaborolidines Prepared from Phenylglycine

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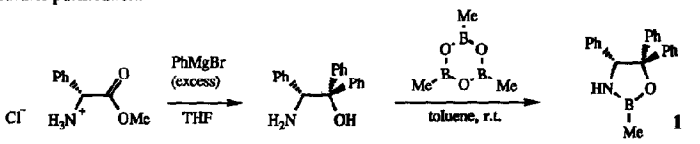
Abstract: (*R*)-*B*-methyl-4,5,5-triphenyl-1,3,2-oxazaborolidine (**1**) and (*R*)-*B*-allyl-4,5,5-triphenyl-1,3,2-oxazaborolidine (**2**), prepared from (*R*)-phenylglycine, catalyse the reduction of prochiral ketones with borane, to afford the corresponding secondary alcohols in good chemical yields and with moderate to high (61%–96%) enantiomeric excesses. These compounds gave the best results reported so far regarding the reduction of linear alkyl methyl ketones catalysed by oxazaborolidines.

The development of efficient stereoselective reactions is a challenging endeavour in organic chemistry. In this context, the enantioselective oxazaborolidine-catalysed reduction of prochiral ketones with borane, leading to the formation of chiral secondary alcohols, is a topic of current interest. After the pioneering work of Itsuno et al.,[1] Corey's group and others have developed several chiral 1,3,2-oxazaborolidines which can act as efficient catalysts in this reaction.[2]

In the present paper we describe the synthesis of two alternative oxazaborolidines, (*R*)-*B*-methyl-4,5,5-triphenyl-1,3,2-oxazaborolidine (**1**) and (*R*)-*B*-allyl-4,5,5-triphenyl-1,3,2-oxazaborolidine (**2**), in good yield, as well as the use of **1** and **2** in the reduction of some representative ketones.

Compound **1** can be readily synthesised in three steps from (*R*)-phenylglycine —its enantiomer is also available at a relatively low price— and trimethylboroxine[3] in 70% overall yield in multigram scale. During the addition of the Grignard reagent to the amino ester hydrochloride no racemisation was detected.[4] Compound **1** has been indentified as the only product in the reaction of the (*R*)-2-amino-1,1,2-triphenylethanol with the boroxine and has been fully characterised by ^{1}H, ^{13}C, and ^{11}B NMR. Oxazaborolidine **1** has been used without further purification.



Reductions were accomplished in up to 90% chemical yields in <5 min in THF at 0 °C when an equivalent amount of **1** and 1.2 equiv. of BH_3:Me_2S were employed.[5] The reductions are so fast that a slow addition of the ketone (1 mmol in 90 min) to a mixture of 0.1 equiv. of catalyst and 1.2 mmol of BH_3·Me_2S seems to mimic the stoichiometric conditions and the enantioselectivity is similar or only slightly lower than in the stoichiometric case,[6] as shown in Table I.

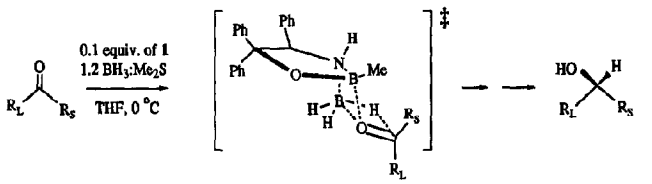
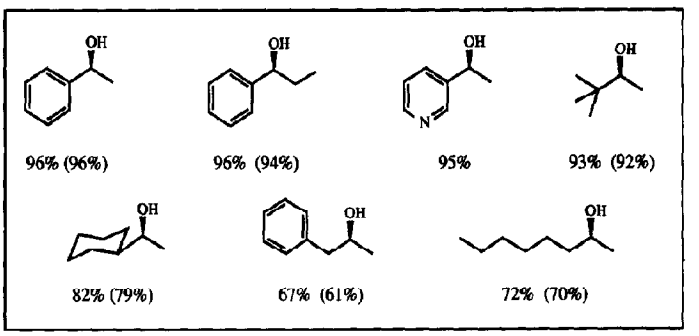


Table I.

E.e. of the alcohols arising from the reduction of the corresponding ketones by BH_3:Me_2S in the presence of **1**[a]

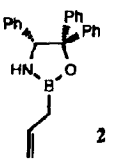


[a]Determined by GC of Mosher's esters (capilar column HP-5 crosslinked 5% PhMe silicone). E.e. values are given for reactions performed with 1 equiv. of catalyst. Within parentheses, e.e. values by using 0.1 equiv. of catalyst.

As shown in Table I, enantioselectivity is excellent for aromatic ketones as well as for hindered methyl ketones (*t*-butyl methyl ketone) but the most significant fact is the good selectivity obtained for a linear methyl ketone (2-octanone). In fact, 72% e.e. is the higher value reported until now regarding the reduction of 2-octanone (or similar ketones) with this kind of catalysts.[7] It is worth noting that in many cases the results obtained are similar or only slighly lower than those reported for similar proline-derived catalyst.[8]

Cai et al. have very recently reported[9] that in some reductions using oxazaborolidines, two H atoms can arise from each BH_3, being the second transfer less stereoselective. Looking for a more constricted transition state system with an intramolecular donation of only one hydride ion, we synthesised *B*-allyloxazaborolidines **2** and **3** from triallylborane and the corresponding aminoalcohol according to the general procedure reported

by Reetz et al.[10] Addition of 1 equiv. of borane to a solution of **2** in THF at 0 °C gave, after 1 h, a clean solution which was used in the reduction of some ketones. The tentative involvement of **4**[11] as the reducing agent is supported by the following facts: **(i)** the addition of an excess of HCl/MeOH to the THF solution releases 2 mmol of hydrogen (corresponding to the two B-H bonds present in **4**); **(ii)** the solution reduces only 1 mmol of ketone per each mmol of **2** (probably the *pseudo*-axial B-H is involved); if more ketone is added the reaction is stopped when 1 mmol is consumed, while the addition of an excess of HCl/MeOH at this moment releases only 1 mmol of hidrogen; **(iii)** dipinacolyl ester derived from 1,3-propanediboronic acid can be isolated as the major product from the treatment of the THF solution with pinacol. This fact demonstrates that hydroboration is regioselective, the boron atom being bound at the terminal olefinic carbon.



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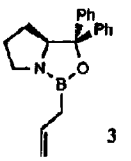

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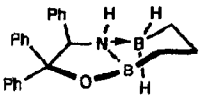

4

When the temperature was raised up to r.t. a release of 1 equiv. of hydrogen was observed (probably due to a B-N covalent bond formation from **4**) and the reducing ability was lost. If the *B*-allyl-1,3,2-oxazaborolidine **3** —in which the N-H group is not present— was used in place of **2**, the solution arising from the hydroboration can be manipulated at r.t. or boiling THF without evolvement of gas. Reductions of ketones with **2** or **3** and BH_3:Me_2S are also fast and show a slightly lower selectivity to than observed with **1**[9] (for instance, for the 2-octanone reduction the e.e. values were 64% and 59% e.e. for **2** and **3**, respectively, while for the acetophenone reduction the corresponding e.e. values were 79% and 77%).

In summary, the ready accessibility of **1** from cheap phenylglycine and its performance make this reagent an attractive choice for the reduction of prochiral ketones. Furthermore, *B*-allyloxazaborolidine-borane reagents derived from **2** and **3** are the first examples of reagents in which the reductor is covalently bound to an oxazaborolidine. The search for more efficient reducing agents based on phenylglycine is in course.

(*R*)-(+)-2-Amino-1,1,2-triphenylethanol. Methyl (*R*)-phenylglycinate hydrochloride (10.0 g, 0.050 mol) was added portionwise to phenylmagnesium bromide (150 mL, 3M in Et_2O) at 0 °C under Ar over 2 h. The cooling bath was removed and the reaction mixture was stirred at room temperature for 7 h. The solution was poured into crushed ice (300 g) and conc. hydrochloric acid (50 mL). The mixture was stirred vigorously for 1 h and the precipitate, amino alcohol hydrochloride, was collected by filtration and washed with diethyl ether. The filtrate was solved in 2M NaOH/MeOH solution and concentrated in vacuo. Afterwards, 200 mL of CH_2Cl_2 and 100 mL of water were added to the residue. The organic layer was washed with water (3 x 50 mL) and dried. The solvent was removed to afford the product as a white solid (10.2 g, 70%); mp 131-133 °C, $[\alpha]_D^{22}$ +235.0 (c = 1.0, $CHCl_3$).

(*R*)-*B*-Methyl-4,5,5-triphenyl-1,3,2-oxazaborolidine (1). Trimethylboroxine (0.87 g, 7 mmol) was added to a solution of (*R*)-(+)-2-amino-1,1,2-triphenylethanol (3.00 g, 10.4 mmol) in 20 mL of toluene, and the mixture was stirred under Ar at r.t. for 1 h. The solution was concentrated (1 atm) to ca. 5 mL. Toluene (20mL) was added and the solution was concentrated again at 1 atm. The process was repeated once more. This last concentrated solution was diluted with toluene up to 25 mL and stored under Ar.

Typical procedure: 1.2 mmol of BH_3:Me2S was added to 0.1 or 1 mmol of catalyst **1** (from the above-mentioned toluene solution after removing the solvent under vacuum) in 3 mL of THF, at 0 °C under Ar; 10 min later on, 1 mmol of ketone was introduced (over 30 min for 1 mmol of catalyst and over 90 min for 0.1 mmol). The reaction was monitored by TLC and quenched by addition of 2N HCl (3 mL). Addition of 5 mL of diethyl ether gave the hydrochloride of **1**, which was filtrated and washed with diethyl ether. After the usual work-up of the organic layer, the optically active alcohol was obtained as a colorless oil.

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References and notes.

1) S. Itsuno, Y. Sakurai, K. Ito, A. Hirao, S. Nakahama, *Bull.Chem.Soc.Jpn.* **1987**, *60*, 395, and references therein.

2) For recent reviews see: L. Deloux, M. Srebnik, *Chem.Rev.*, **1993**, *93*, 763; S. Wallbaum, J. Martens, *Tetrahedron:Asymmetry*, **1992**, *3*, 1475. For very recent works, see: R. Berenguer, J. García, M. González, J. Vilarrasa, *Tetrahedron:Asymmetry*, **1993**, *4*, 13; G.J. Quallich, T.M. Woodall, *Tetrahedron Lett.*, **1993**, *34*, 4145; C. Dauelsberg, J. Martens, *Synthetic Comm.*, **1993**, 209. This last paper describes the use of mixtures of several 2-aminoalcohols derived from phenylglycine with borane as reductor for aromatic ketones with acceptable selectivities (61-88% e.e.). It is worth noting that our experience with several chiral 2-aminoalcohols confirm the common observation that preformed oxazaborolidines are much more effective than a mixture formed *in situ*, where several active open-chain catalytic species may be present (see, for instance, D.J. Mathre, T.K. Jones, L.C. Xavier, T.J. Blacklock, R.A. Reamer, J.J. Mohan, E.T.T. Jones, K. Hoogsteen, M.W. Baum, E.J.J. Grabowski, *J.Org.Chem.*, **1991**, *56*, 751).

3) H.C. Brown, T.E. Cole, *Organometallics*, **1985**, *4*, 816. Trimethylboroxine is also commercially available.

4) The optical purity of the aminoalcohol was shown to be up to 99.5% e.e. by HPLC of the amide derivative of Mosher's acid (Spherisorb S 3W, SiO_2 3μ; hexane/THF, 9:1).

5) Freshly opened commercial solution of borane in THF can also be used. Other conditions attempted, by changing temperature (-20 °C, rt, or boiling THF) or solvent (methylene chloride, pentane, toluene) gave worse results. When two or more equiv. of **1**, for each mol of ketone were utilised, the results did not improve.

6) In fact, a slow addition of ketone has showed to be crucial in order to obtain a good enantioselectivity even in the stoichiometric case. For instance, in the reduction of cyclohexyl methyl ketone, a fast addition of the ketone reduces the selectivity from 82% e.e. to 64% e.e. In the reduction of 3-acetylpyridine, 2 equiv. of borane was needed and only 71% e.e. was obtained when 0.1 equiv. of catalyst **1** was employed.

7) 2-Octanone: 58% e.e., S. Itsuno, K. Ito, A. Hirao, S. Nakahama, *J.Org.Chem.*,**1984**, *49*, 555; 46% e.e., I.K. Youn, S.W. Lee, C.S. Pak, *Tetrahedron Lett.*, **1988**, *29*, 4453. *L*-Proline derived *B*-methyl-5,5-diphenyloxazaborolidine gives, in our hands, 66% e.e. 2-Pentanone: 59% e.e., Y.H. Kim, D.H. Park, I.S. Byun, *J.Org.Chem.*, **1993**, *58*, 4511. Reductions with 1 equiv. of the related *B*-butyl derivative, instead of **1**, gave generally lower selectivities.

8) For instance: acetophenone, propiophenone, and *t*-butyl methyl ketone 97% e.e.; cyclohexyl methyl ketone 84% e.e. (E.J. Corey, R.K. Bakshi, S. Shibata, Ch.-P. Chen, V.K. Singh, *J.Am.Chem.Soc.*, **1987**, *109*, 7925).

9) D. Cai, D. Tschaen, Y.-J. Shi, T.R. Verhoeven, R.A. Reamer, A.W. Douglas, *Tetrahedron Lett.*, **1993**, *34*, 3243.

10) M.T. Reetz, T. Zierke, *Chem.&Ind.*, 1988, 663. Also see: H.C. Brown, U.S. Racherla, P.J. Pellechia, *J.Org.Chem.*, **1990**, *55*, 1868.

11) In fact, ^{11}B NMR analysis of the hydroboration mixture at -20°C showed that more than one species was present. In view of the successful crystallisation of some oxazaborolidine-borane complexes (D.J. Mathre, A.S. Thompson, A.W. Douglas, K. Hoogsteen, J.D. Carroll, E.G. Corley, E.J.J. Grabowski, *J.Org.Chem.*, **1993**, *58*, 2880) we tried to isolate **4**. When hydroboration of **2** was carried out in pentane at 0 °C a viscous oil was separated from the former homogeneous solution in a few minutes. When the pentane layer was cannulated at 0 °C and the residue was dissolved in THF at the same temperature, the solution showed the same behaviour (chemical yield and enantioselectivity) that the solution derived directly from the hydroboration of **2** in THF. Attempts to obtain a crystalline solid from that residue failed.

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