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# An Optimised *in situ* Procedure for the Oxazaborolidine Catalysed Enantioselective Reduction of Prochiral Ketones

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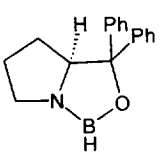
**Abstract:** A systematic study was conducted to formulate the optimal reaction parameters for the oxazaborolidine catalysed enantioselective reduction. The catalyst derived from diphenyl prolinol was found to be the best amongst several other analogues and a reduction temperature of 45 $^{0}$C is recommended for high enantioselectivity (92-99% *ee*) for the reduction of alkyl aryl ketones.

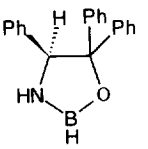

Stereoselective reduction of prochiral ketones has been one of the most actively studied areas in asymmetric synthesis.[1] In this context, oxazaborolidine catalysed reduction has emerged as the most prominent methodology of the decade.[2] A plethora of publications on this topic describes the use of structurally diverse chiral auxiliaries. Although the mechanism of the reduction is well understood,[3] there is a dearth of information regarding the optimum parameters which include the structural requirements of the catalyst, the stoichiometry of the reactants, the solvent and the temperature for the reduction etc. In fact a careful study of the literature reveals several conflicting statements, for example, "we were unable to prepare the corresponding borane complex of parent -BH oxazaborolidine"[4a] *vs* "excess borane-methylsulfide complex in THF at ambient temperature generated the oxazaborolidine",[4b] or "the level of enantioselection increased by decreasing the temperature"[4a] *vs* "reduction loses stereoselectivity at lower temperature".[4c] The present study was initiated during our investigations dealing with the stereoselective reduction of 1,2-diones.[5] We now provide here an efficient and convenient *in situ* procedure for the oxazaborolidine catalysed reduction of prochiral ketones.

**Selection of the catalyst**: To begin with, we studied the reduction of acetophenone with three representative oxazaborolidines (**1a - c**) derived from commonly available L- amino acids. Since geminal diphenyl substituents appear to be optimum for high enantioselectivity,[6] we excluded other structural modifications. As for the substitution at the boron atom, we opted for simple -BH derivatives for the following reasons: (a) It has been shown that increased steric bulk at boron atom leads to slightly decreased reaction rate whereas the enantioselectivity remains practically unchanged.[7] Also with mechanistic consideration, if the substitution at boron and $R_s$ of the carbonyl compound is indeed responsible for the selectivity as proposed,[3b] the smallest substituent (*viz.* H) should

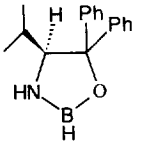
be preferred. (b) The other two commonly used oxazaborolidine derivatives *viz* -BMe and -BPh require a methyl or phenyl borane source that is later hydrolysed and discarded, whereas the -BH system only uses $BH_3$ which is the source of hydride for the reduction as well.




**1a**



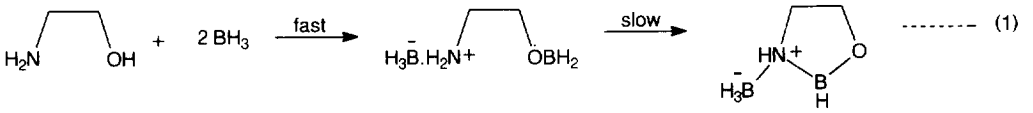

**1b**




**1c**

As for the substituent on nitrogen atom, we agree with the recommendation[6] that an alkyl substituent would create unfavorable interaction with the adjacent ($C_4$) substituent. That would lead to weaker coordination of borane ($BH_3$) to nitrogen atom and hence slower catalysis. It is for this reason, the pyrrolidine moiety appears to be the ideal substitution for an oxazaborolidine catalyst.

**Preparation of the catalyst**: Having selected the catalyst structures to be investigated, we turned our attention to the preparation of the catalyst. A survey of the literature reveals that a variety of conditions have been recommended for the preparation of oxazaborolidines with -BH substituent, for example, stirring the aminoalcohol at 35 °C with 2 equivalents of $BH_3$.THF followed by sublimation,[8a] refluxing the aminoalcohol with 2 equivalents of $BH_3$.THF under moderate pressure (1.7 bar),[8b] and more recently, stirring a mixture of aminoalcohol with excess of $BH_3.SMe_2$ at room temperature for 10 h.[4b] Clearly the last reported procedure is the most convenient one for the laboratory as well as industrial scale procedure. We found that the procedure works well for the preparation of **1b** and **1c**, but it was not satisfactory for **1a**. We believe that the formation of **1a** which involves a strained [3.3.0] fused ring system, was incomplete under the conditions described.




(1)

The reaction of aminoalcohol in the presence of excess $BH_3$ is likely to proceed as described by eq. 1. Excess borane renders the nitrogen atom acidic and cyclisation takes place easily. Such a mode of cyclisation explains why the intermediate "ate" complex obtained by using 1 equivalent of borane requires prolong heating at 100 °C to cyclise,[9] whereas the cyclisation is facile in the presence of excess borane.[4b] We therefore stirred the aminoalcohol with large excess of $BH_3.SMe_2$ at 45 °C for 12-16 h (increasing the temperature beyond 50 °C leads to the loss of borane). The catalyst thus obtained reduced acetophenone within 15 min providing 88 % *ee* even at 1 mol % concentration of **1a** (Table 1, entry 3).

**The reaction temperature**: At the outset, we decided to use a 2 M solution of $BH_3.Me_2S$ in toluene. The choice was based on the consideration that the reagent deterioration on storage should be significantly slow in less volatile and non hygroscopic solvent such as toluene than in other solvents e.g. THF, $Et_2O$ or $CH_2Cl_2$. The reaction was conducted as 1 M solution in toluene-THF (~1:1). As we have stated earlier, the temperature at which the reduction should be conducted, remains controversial,[4a,4c] although there has been a definite study dealing with -BMe and -BPh derivatives of oxazaborolidine.[10]

We decided to examine the reaction at various temperatures, *viz.* 0 °C, 25 °C and 45 °C. It was surprising to find that the best results were obtained at 45 °C, at which one would normally expect the non- catalysd pathway to be competitive.[5] The reduction at 0 °C did not go to completion at all. We attribute the enhancement of enantioselectivity with temperature to the increase in catalytically active monomeric oxazaborolidine, as compared to the dimeric structure which one finds more at lower temperature. Indeed, the effect was more dramatic for the catalyst **1a** which has a more basic nitrogen atom as compared to the one in **1b** and **1c**. In this context it is noteworthy that **1c** with relatively large sterics around nitrogen atom, showed higher %ee at 25 °C (entry 8) than at 45 °C (entry 9). No significant change in the reaction outcome was observed by changing $BH_3.Me_2S$ from 0.6 equivalents to 1 equivalent.

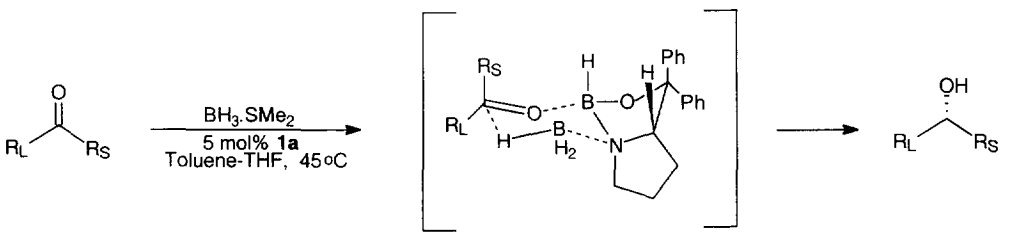



**Table 1**. Oxazaborolidine Catalysed Reduction of Acetophenone[a]

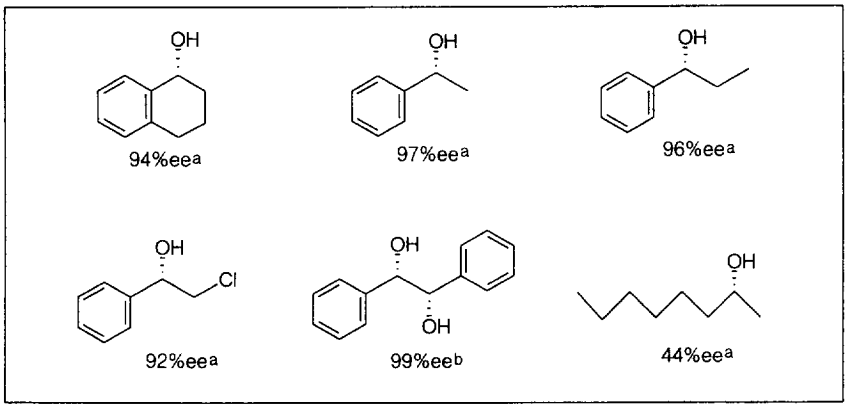
| Entry | Catalyst | Temp, °C | Time, min | *% ee* |
|---|---|---|---|---|
| 1 | **1a**, 1 mol % | 25[b] | *c* | |
| 2 | **1a**, 1 mol % | 25[d] | 60 | 40 |
| 3 | **1a**, 1 mol % | 45 | 15 | 88 |
| 4 | **1a**, 5 mol % | 45 | < 5 | **97** |
| 5 | **1a**, 5 mol % | 45[e] | < 5 | 96 |
| 6 | **1b**, 5 mol % | 25 | *c* | |
| 7 | **1b**, 5 mol % | 45 | < 5 | 47 |
| 8 | **1c**, 5 mol % | 25 | 15 | 89 |
| 9 | **1c**, 5 mol % | 45 | < 5 | 71 |

[a]All the reactions, except entry 5 were carried out using 0.6 equivalent of $BH_3.Me_2S$ in toluene-THF (~1:1). [b]Catalyst made at 25 °C, 10 h. [c]Incomplete reaction even after 2h. [d]Catalyst made at 45 °C, 16 h. [e]Using 1.0 equivalent of $BH_3.SMe_2$.

Finally we reduced six representative ketones using the best conditions, that is, using 5 mol % of *in situ* generated **1a** as the catalyst, toluene-THF as the solvent and 45 °C as the temperature. In all the cases examined, the reduction was over in < 5 min after the addition of the last portion of ketone. The reactions were clean and the enantioselectivity (92-99 %) was comparable to the highest reported so far.

In conclusion, the present study has addressed several important issues regarding the experimental aspects of the oxazaborolidine catalysed reduction of ketones. An optimised protocol is presented that should be valuable for organic chemists interested to use the methodology.

**Table 2.** Enantioselective Reduction of Ketones Catalysed by **1a**




[a]Determined by comparing with the known maximum specific rotation. [b]% *de* 88:12, Reference 5.

## Experimental

**General.** Borane-dimethyl sulphide ($BH_3.Me_2S$) was purchased from Aldrich Chemical Company, diluted to a 2 M solution in toluene and estimated by gasimmetry. Toluene was distilled over $P_2O_5$, degassed and stored over molecular sieves. THF was freshly distilled over sodium benzophenone ketyl. (*S*)-Diphenyl valinol,[11a] (*R*)-diphenyl phenylglycinol[11b] and (*S*)-diphenyl prolinol[11c] were prepared according to the literature procedures. $^1H$ NMR spectra were recorded on Bruker 200 using $CDCl_3$ as the solvent and TMS as the internal standard. Optical rotations were recorded on a JASCO DIP-181 digital polarimeter.

**Preparation of Oxazaborolidine Catalyst and Reduction of Ketones.**

The following procedure for the preparation of **1a** and reduction of acetophenone is representative:

To a solution of $BH_3.Me_2S$ (3.25 ml of 2 M in toluene, 6.5 mM) a solution of (*S*)-diphenyl prolinol (0.126 g, 0.5 mM) in THF (3 ml) was added and the reaction mixture was stirred at 45 °C for 12-16 h under a static atmosphere of argon. To the resulting turbid solution of **1a**, a solution of acetophenone (1.2 g, 10 mM) dissolved in anhydrous THF (5 ml) was added dropwise (using a syringe pump) over a period of 30-35 min. After the

addition was over, the reaction mixture was continued to stir at the same temperature for 15 minutes. It was then cooled to room temperature and cautiously quenched with MeOH (2 ml). Solvent was evaporated and the residue was dissolved in ether. The ether phase was washed with 1N HCl followed by brine and dried over anhydrous $Na_2SO_4$. The residue obtained after the removal of ether was purified by "flash chromatography" followed by distillation using Kugelrohr to obtain pure (*R*)-(+)-1-phenyl ethanol; yield 1.02 g (84 %); $^1$H NMR δ= 1.5 (d, J=7.2 Hz, 3H), 2.25 (bs, 1H), 4.85 (q, J=7.2 Hz, 1H), 7.2-7.4 (m, 5H); $[\alpha]_D$ +44.12 (c=3, MeOH) [lit.[12] +45.9 (c=3.3, MeOH)]; $[\alpha]_D$ +41.85(neat) [lit.[4a] +43.6 (neat)].

Since recovery of the catalyst becomes important with larger scale reaction, the work-up procedure was modified as reported.[8b]

**(*R*)-(-)-1,2,3,4-Tetrahydro-1-naphthol.** $^1$H NMR δ= 1.7-2.1 (m, 5H), 2.65-2.95 (m, 2H), 4.25-4.35 (m, 1H), 7.1-7.5 (m, 4H); $[\alpha]_D$ -23.14 (c=1.3, MeOH) [lit.[4a] -24.6 (c=1.29, MeOH)].

**(*R*)-(+)-1-Phenyl-1-propanol.** $^1$H NMR δ= 1.0 (t, J=6.9 Hz, 3H), 1.85 (m, 2H), 2.9 (bs, 1H), 4.6 (t, J=6.9 Hz, 3H), 7.2-7.5 (m, 5H); $[\alpha]_D$ +43.03 (c=5.1, $CHCl_3$) [lit.[13] +45.45 (c=5.1, $CHCl_3$)].

**(*S*)-(+)-2-Chloro-1-phenyl ethanol** $^1$H NMR δ= 2.85 (bs, 1H), 3.62 (d, J=7.5 Hz, 2H), 4.82 (t, J=7.5 Hz, 1H), 7.3-7.4 (m, 5H); $[\alpha]_D$ +48.93 (c=2.8, cyclohexane) [lit.[14] +53.3 (c=2, cyclohexane)].

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