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Effects of Triethylamine in Asymmetric Reduction using Oxazaborolidine Reagents

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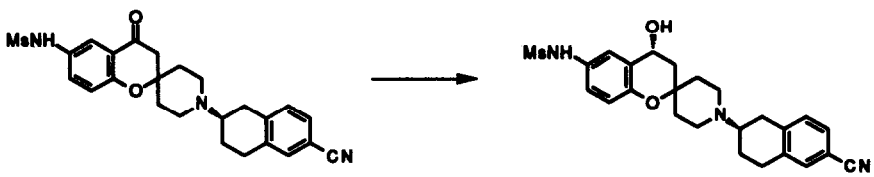
Abstract: In the presence of triethylamine, the reduction of ketones using stoichiometric amounts of oxazaborolidine-borane complex (OAB·BH_3) shows increased enantioselectivity.

During the course of our synthetic studies we required an efficient asymmetric reduction of ketone **1** to alcohol **2** (MK-499)[1].



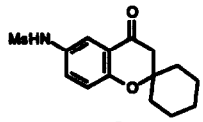
1 **2**

While there are several literature methods for chiral reduction of ketones,[2] we chose to explore the highly acclaimed oxazaborolidine (OAB) reagents discovered by Corey and Itsuno.[3,4] Although there are numerous literature examples describing application of this method, there remains uncertainty with regard to the mechanistic details.

Previous work from our laboratories indicated that the borane complex OAB·BH_3 is a stable reagent.[5] This reagent was found to reduce aromatic ketones with good to excellent stereoselectivities. Previous experience also indicated that one mole of OAB·BH_3 is capable of reducing 2 moles of simple ketones rapidly at 0 °C. However, treatment of 2 moles of ketone **1** with 1 mole of OAB·BH_3 led to only a 50% conversion. The addition of a second mole of OAB·BH_3 led to complete consumption of the ketone **1** and provided the desired alcohol **2** in 99.6% ee. Our speculation that the tertiary amine functionality within ketone **1** was preventing the second hydride transfer was substantiated by precomplexation of the tertiary amine of compound **1** with 1 mole of borane prior to reaction with the OAB·BH_3 reagent. Thus, treatment of ketone **1** with 1 mole equivalent of borane methyl sulfide led to a stable 1:1 borane amine complex which was isolated and characterized by NMR.[6] Treatment of this complex with 0.5 mole OAB·BH_3 led to complete conversion

to the desired alcohol **2**. Interestingly however, we noted that the enantioselectivity of this reaction was significantly lower (92% ee).

To investigate this further, we studied the reduction of model ketones (**3** to **7**) using 0.6 ~ 0.7 equivalent of OAB·BH_3, and compared these results with the asymmetric reduction of the ketones in the presence of 1 equivalent of tertiary amine (triethylamine) using 1.2 ~ 1.5 equivalent of OAB·BH_3 reagent. The results which are shown in Table 1 indicate that the enantioselectivity of the reduction is significantly enhanced by the addition of 1 equivalent of triethylamine.



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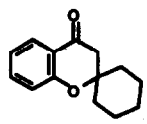

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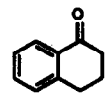

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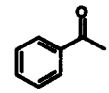

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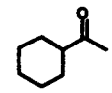

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Table 1

Ketones	3	4	5	6	7
OAB·BH_3, % ee	90	91	90	96	67
OAB·BH_3 and Et_3N, % ee	99.1	99.4	99.4	99.2	87

All reactions were run at -15 °C, OAB·BH_3 was added either as a solid or a solution to a solution of ketone or ketone with triethylamine. The alcohols were isolated by silica gel flash chromatography and characterized by NMR, and enantioselectivities were determined by making the Mosher esters of resulting alcohols and racemic alcohols and assayed by HPLC using normal phase Zorbax silica column.

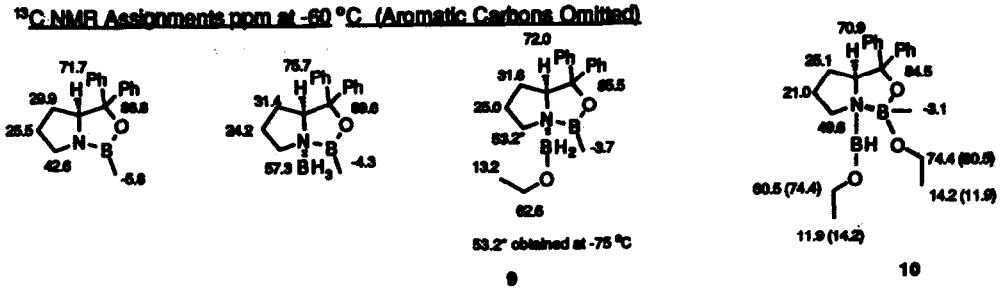
Reacting acetophenone and triethylamine with OAB·BH_3 at room temperature led to the formation of monoalkoxyborane triethylamine complex **8** [7] as identified by NMR (^1H, ^{13}C, ^{11}B) (Scheme 1). This explains why only one hydride was transferred from OAB·BH_3.

Scheme 1

8

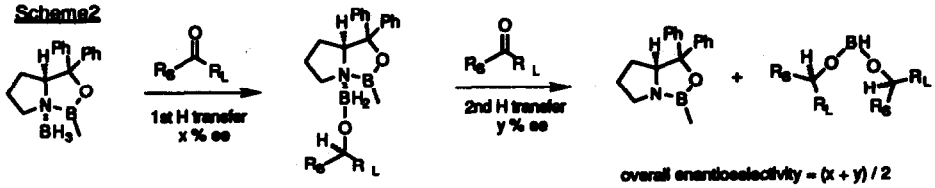
In order to learn more about the reduction of ketones by OAB·BH_3, we undertook a low temperature ^1H and ^{13}C NMR study.[8] Using NMR to monitor the reaction of acetone with OAB·BH_3 at -80 °C indicated an extremely rapid transfer of one hydride resulting in a monoisopropoxyborane oxazaborolidine complex (1:1 adduct) which was quite stable at -80 °C. When the reaction temperature was raised to -40 °C, there was indication of a small amount of a second intermediate being generated, but it reacted almost as quickly as it was formed to give diisopropoxyborane and thus remained at a low concentration. Interestingly, when acetone was replaced with the more reactive acetaldehyde, the second hydride transfer occurred readily even at -75 °C and we observed both intermediates **9**, and **10** (1:1 adduct and 2:1 adduct) by NMR.

^{13}C NMR Assignments ppm at -60 °C (Aromatic Carbons Omitted)



Although our NMR studies do not indicate any free monoalkoxyborane formation, we can not rule out the possibility that it is present in low concentration and may cause uncatalyzed reduction of the ketone.[9,10] Based on our NMR results, however, we believe a second hydride can be transferred from the resulting monoalkoxyborane-oxazaborolidine complex **11** to the ketone with different enantioselectivity (Scheme 2).

Scheme2



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In summary, by trapping the reactive intermediate free monoalkoxyborane or monoalkoxyborane-oxazaborolidine complex with triethylamine, the enantioselectivity of the asymmetric reduction was significantly improved.

Acknowledgments: We thank Dr. D. J. Mathre for helpful discussion.

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