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Oxazaborolidine Catalyzed Borane Reductions of Ketones: A Significant Effect of Temperature on Selectivity

Guy B. Stone

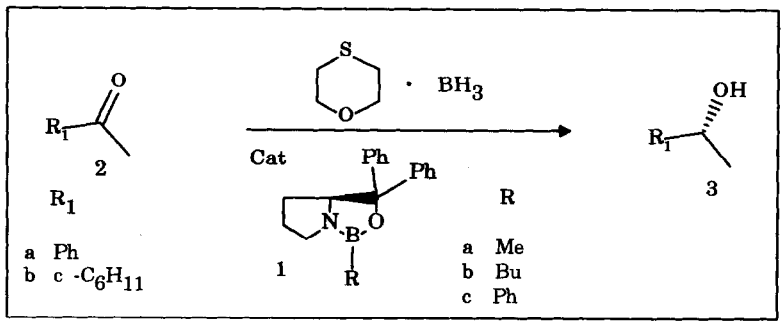
SANDOZ PHARMA AG, Chemical Process Research and Development Department, CH-4002 Basel, Switzerland

Abstract - The effect of temperature on the selectivity of oxazaborolidine catalyzed borane reductions of ketones has been studied. For two model ketones, acetophenone (**2a**) and cyclohexylmethyl ketone (**2b**), and two different oxazaborolidine catalysts [derived from *n-butyl-* and *phenyl*boronic acids with (S)-diphenylprolinol], these reductions were carried out over a range of temperatures in THF and toluene. Our results show that in general there is an increase in selectivity with increasing temperature until 30-50 °C where the selectivity then begins to decrease. As a result of these findings, the amount of catalyst for the reduction of acetophenone was reduced from 10 % to 1 % with only a small decrease in selectivity (96 % and 94 % respectively). We obtained the highest selectivity ever reported for the reduction of acetophenone by a borane-phenyl substituted diphenylprolinol derived catalyst (98 % ee using the catalyst **1c** at 40°C). In addition, we obtained the highest reported selectivity for the reduction of cyclohexylmethyl ketone by a diphenylprolinol derived catalyst (89 % ee using n-butyl-substituted borane catalyst **1b** at 50 °C).

During the course of our studies in the area of oxazaborolidine catalyzed borane reductions of ketones,[1] we observed an effect of temperature on selectivity. While this has been mentioned several times in the literature, a more detailed study has not yet been published to our knowledge. In one of the first papers concerning this reaction, published by Corey[2] and co-workers, it was stated: "Enantioselectivity often decreases somewhat with...decreasing temperature..." Several other authors[3] have found this to be true as similar statements can be found in the literature. In contrast to this, researchers from Merck write[4] "As expected, the level of enantioselectivity increased by decreasing the reaction temperature." This pertains to their studies of reduction with stoichiometric complexes of the catalyst-BH_3 where they postulate that increasing temperature liberates BH_3 from the catalyst resulting in a loss of selectivity due to uncatalyzed reduction. We have made the general observation (for model ketones **2a** and **2b**) that selectivity increases with increasing temperature until an optimal range is reached (30-50 °C) where the selectivity then begins to decrease. We wish to report here our results of a more careful study of this temperature effect.

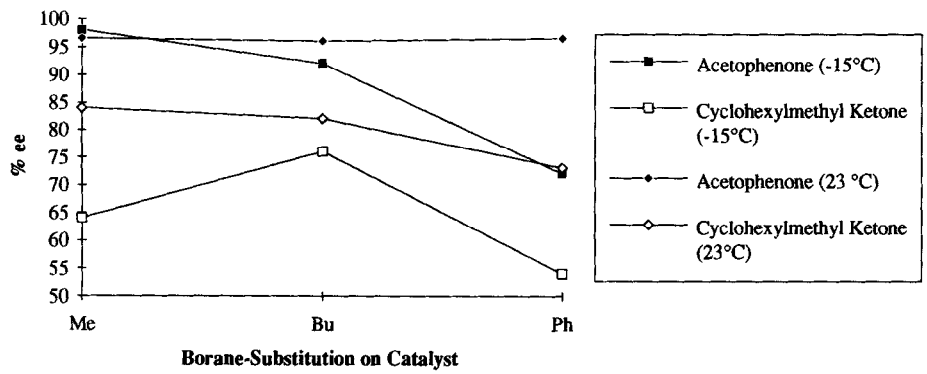
RESULTS AND DISCUSSION

Two model ketones (acetophenone **2a** and cyclohexylmethyl ketone **2b**) and two oxazaborolidine catalysts (**1b** and **1c**) were chosen for our studies. The mode of reaction usually used for these reductions was applied, that is, slow dropwise addition (ca 70 min for 0.005 mole, 1.0 M in THF) of the ketone to a THF solution of the catalyst and BH_3-complex. After considering several possibilities, we decided to use the commercially available 1,4-thioxane-BH_3 complex.[5] While this complex is known as a hydroborating reagent,[6] this appears to be its first application in oxazaborolidine catalyzed borane reductions.



A plot (**Figure 1**) of literature[7,8] data and our initial results for the reduction (10 % catalyst in THF) of **2a** and **2b** shows that the selectivity of the reaction is significantly affected by temperature for a given catalyst.

Figure 1. Oxazaborolidine Catalyzed Borane Reduction of Acetophenone and Cyclohexylmethyl Ketone: Effect of Borane-Substitution on % ee for Two Temperatures.[a]



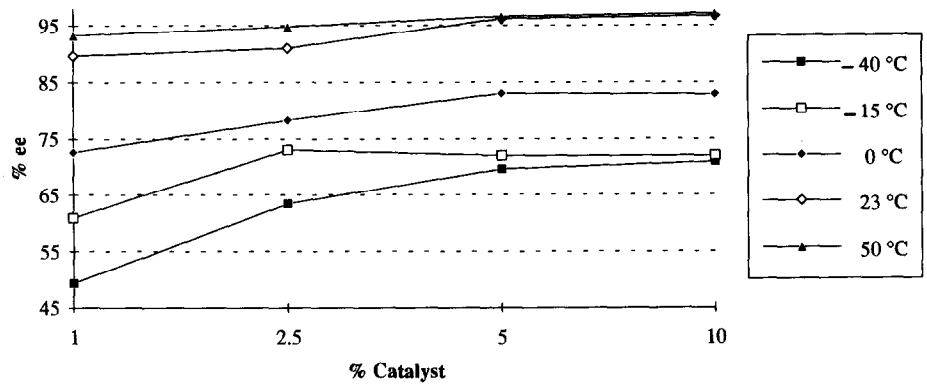
a All results are from reactions using 10 % of the indicated catalyst whereby the ketone was added to the catalyst and BH_3-complex or the BH_3-complex was added neat to the catalyst and ketone in THF. Reactions at - 15 °C are from the literature[8] and those at room temperature are results from this study as well as from the literature[7].

Furthermore, at a given temperature the use of different catalysts (varying borane-substitution, ie. Me; Bu; Ph) resulted in different selectivity. For example, in the reduction of **2a**, the selectivity was significantly effected by temperature only when the phenyl-substituted borane catalyst (**1c**) was used. Comparison of the

catalysts **1a** and **1b** at the same temperature shows not much difference as both catalyzed a highly selective reduction (ca 92 and 98 % ee respectively). However, catalyst **1c** appears to be less selective as the reduction of **2a** at -15 °C resulted in a 72 % ee. The authors[8] of this result state: "Catalysts with phenyl groups attached to the boron were not as effective for the other ketones we screened (ie. acetophenone)." In fact, we observed that the phenyl-substituted borane catalyst (**1c**) is more sensitive to temperature changes as the selectivity was increased to 96 % when the reaction was run at room temperature and the optimal temperature was found to be 40 °C at which point 98 % ee resulted. This represents the highest % ee reported for the reduction of acetophenone using the (S)-diphenylprolinol derived phenyl-substituted borane catalyst.[9] For the reduction of **2b**, the effect of temperature on selectivity was great for both catalysts **1a** and **1c** with only a slight increase for **1b**.

Secondly, it was observed that the selectivity was influenced by the amount of catalyst present in the reaction. Many literature procedures describe the use of 5-10 % catalyst in these reductions. As can be seen in **Figure 2**, for the reduction of acetophenone (**2a**), the same selectivity was observed with 5 % or 10 % catalyst and only a slight decrease was seen when 2.5 % catalyst was used. At lower temperatures there is a decrease in selectivity in going from 2.5 % to 1 % catalyst, however, the selectivity increased with increasing temperature and at 50 °C very high selectivity was achieved with 1 % catalyst (from 61 % ee at -15 °C to 90 % ee at 21 °C to 93 % ee at 50 °C).

Figure 2. Borane-Phenyl Oxazaborolidine (1c) Catalyzed Borane Reduction of Acetophenone: Effect of % Catalyst on % ee at Different Temperatures.[a]



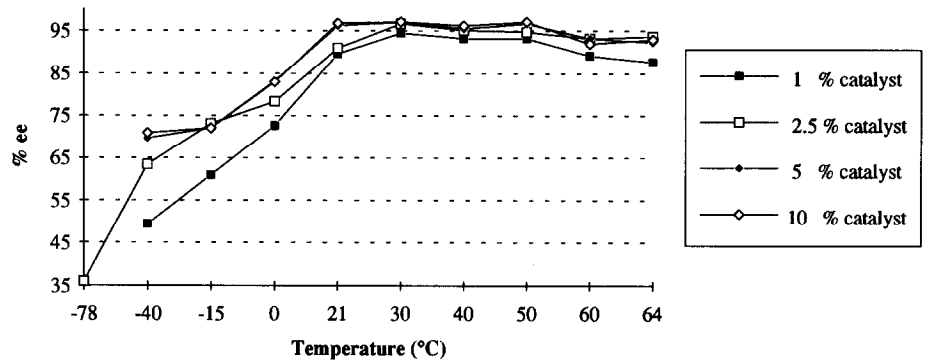
a Reaction conditions consisted of the dropwise addition of ketone in THF to a solution of the catalyst (**1c**) and BH_3-1,4-thioxane in THF at the indicated temperature (see *EXPERIMENTAL* section); % ee was determined by chiral HPLC of the crude product.

Acetophenone Reduction

A more detailed study of the effect of temperature and % catalyst on the selectivity was carried out for the reduction of **2a** using the catalyst **1c** and the results are plotted in **Figure 3**. Acetophenone is already reduced with very high selectivity therefore we wanted to find the limit of this reaction by reducing the amount

of catalyst really needed to obtain good selectivity. The reduction was carried out over a range of temperatures using four different catalyst amounts. From these results one can see that approximately the same relationship between temperature and % ee is observed for each catalyst quantity.

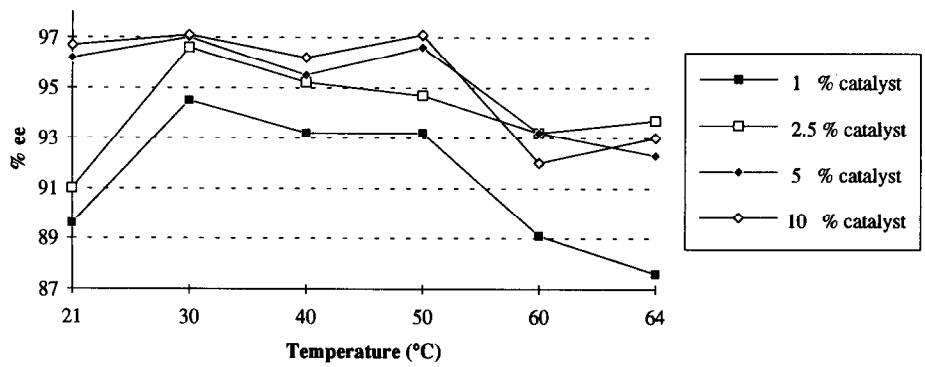
Figure 3. Borane-Phenyl Oxazaborolidine (1c) Catalyzed Borane Reduction of Acetophenone: Effect of Temperature on % ee Using Different Catalyst Quantities.[a]



a Reaction conditions consisted of the dropwise addition of ketone in THF to a solution of the catalyst (1c) and BH_3-1,4-thioxane in THF at the indicated temperature (see *EXPERIMENTAL* section); % ee was determined by chiral HPLC of the crude product.

An expansion of this chart (21-64 °C, **Figure 4**) shows that in fact the optimal temperature range for this reaction is between 30-50 °C. Application of the optimal temperature range permitted the reduction (10 % to 1 %) of the amount of catalyst needed for high selectivity. We are currently investigating the possibility of using even less than 1 % catalyst at some optimal temperature without a great loss in selectivity.

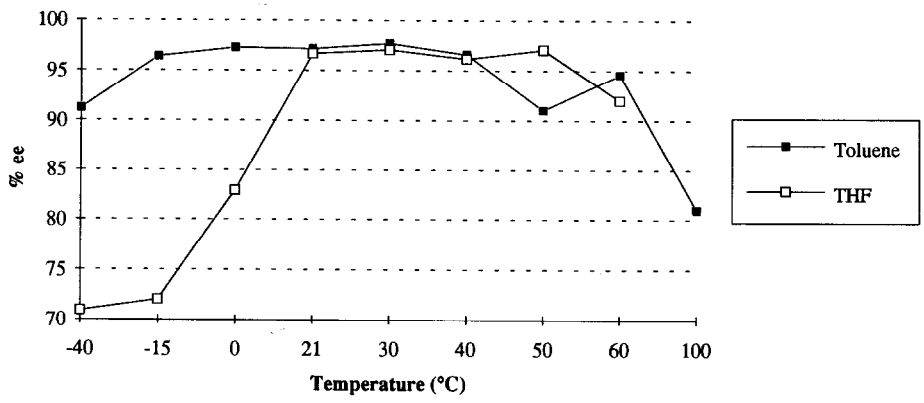
Figure 4. Borane-Phenyl Oxazaborolidine (1c) Catalyzed Borane Reduction of Acetophenone: Effect of Temperature (21 °C to 64 °C) on % ee Using Different Catalyst Quantities.[a]



a This chart is an expansion (from 21 °C to 64 °C) of **Figure 3.**

Interestingly, the effect of temperature was less great in toluene[10] (**Figure 5**) as the selectivity decreased less rapidly with decreasing temperatures when compared to reactions run in THF. These results may give some insight into explaining the temperature effect as well as the mechanism itself (see below).

Figure 5. Borane-Phenyl Oxazaborolidine (1c) Catalyzed Borane Reduction of Acetophenone: Effect of Temperature on % ee in Two Reaction solvents.[a]

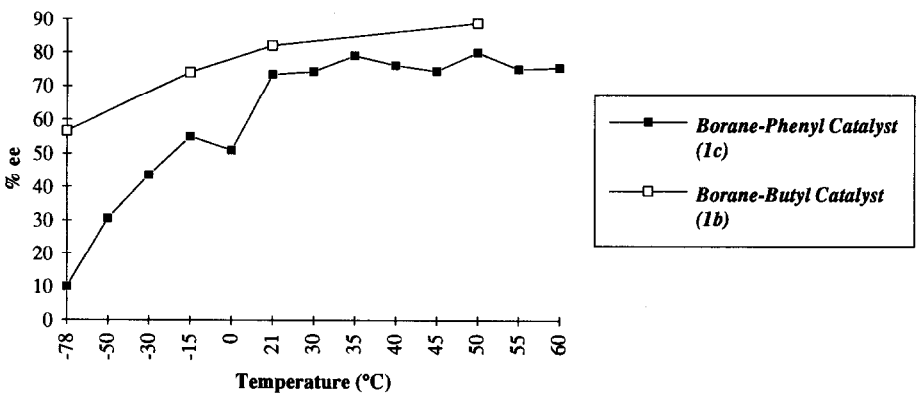


a Reaction conditions for: acetophenone (**2a**) in toluene was added dropwise to a solution of the catalyst (10 %, **1c**) and BH_3-1,4-thioxane in toluene at the indicated temperature. Work up and analysis were carried out as described in the *EXPERIMENTAL* section. Reactions in THF were as described for **Figure 3**.

Cyclohexylmethyl Ketone Reduction

As was the case for acetophenone (**Figure 1**), there is a similar temperature effect for the reduction of cyclohexylmethyl ketone. The reduction was carried out over a range of temperatures using the catalysts **1b** and **1c** (10 %, **Figure 6**). It appears that in this case the butyl catalyst is superior to the phenyl derivative.

Figure 6. Oxazaborolidine Catalyzed (10 %) Borane Reduction of Cyclohexylmethyl Ketone: Comparison of Two Catalysts (1c and 1b) Over a Range of Temperatures.[a]



a Reaction conditions: cyclohexylmethyl ketone (**2b**) in THF was added dropwise to a THF solution of the catalyst (10 % of **1b** or **1c**) and BH_3-1,4-thioxane at the indicated temperature; the crude product was converted to the phenylisocyanate derivative[14] for chiral HPLC analysis.

Acetophenone is already reduced with very high selectivity and was therefore a good system for minimizing the amount of catalyst needed in combination with the temperature effect. One of the limitations of oxazaborolidine catalyzed borane reductions is that aliphatic or less sterically biased ketones are usually reduced with less good selectivity.[1b] The second ketone examined was cyclohexylmethyl ketone (**2b**) which is typically reduced less selectively. In fact, the highest reported[7a] % ee for the reduction with a (S)-diphenylprolinol derived catalyst was 84 % (**1a**). We obtained the highest selectivity ever reported for the reduction of cyclohexylmethyl ketone (**2b**) using a (S)-diphenylprolinol derived catalyst (89 % ee using **1b** at 50 °C).

Although the effect of temperature on selectivity has been mentioned in the literature,[2-4,8,11] no systematic study or complete explanation has been presented. Interpretation of these results is not so straightforward considering that the selectivity of this reduction is likely to be a result of several different reactions.[12] It has been observed[2,4,7a,13] that certain catalysts exist in a temperature dependent equilibrium with their dimeric form. One rationale, described[11] by Bouno and co-workers, is that the amount of catalyst dimer present has an effect on the selectivity.

CONCLUSION

These results describe the observation of the effect of temperature on selectivity of oxazaborolidine catalyzed borane reductions of ketones. Most of the attempts of optimization of this reaction are usually directed towards catalyst changes instead of changes of the existing conditions. Our results indicate that there is room for improvement and that the reaction may be optimized to obtain the highest selectivity possible for a given catalyst and ketone by adjusting the temperature. It is possible that other parameters may also be adjusted for this optimization (ie. solvent, concentration, mode of addition). We believe that these results will lend insight into understanding this reaction. In addition, we hope that this optimization will improve the selectivity in some cases thus making this already powerful synthetic tool more general.

EXPERIMENTAL

Determination of enantiomeric excess was done by chiral HPLC analysis. *For (R)-1-phenyl ethanol:* analysis was carried out on the free alcohol using a Chiracel OD (DAICEL, 250 x 4.6 mm) column with Uv detection at 210 nm (flow rate was 0.5 mL/min at 40 °C). The mobile phase was 2.5 % iso-propanol in n-hexane. The column was rinsed inbetween injections with 40 % isopropanol in n-hexane during 35 min. The racemic alcohol as well as the pure antipode were tested under the same conditions as a control and the pure antipodes showed no sign of epimerization. *Analysis for (R)-1-cyclohexyl ethanol:* the crude reaction product (**3b**) was converted to the phenylisocyanate ester for analysis.[14] Column conditions were as described above with Uv detection at 235 nm and a column temperature of 25 °C. The mobile phase was 10 % isopropanol in n-hexane. The oxazaborolidine catalysts (**1b** and **1c**) were prepared according to a literature[15] procedure.

Typical procedure for ketone reductions for the temperature effect study (acetophenone ***2a*** *using 10 %* ***1c*** *as catalyst):* The reactions were run under a nitrogen atmosphere in flame dried 4-neck reaction flasks each equipped with a mechanical stirrer, a pressure equalizing addition funnel, and a thermometer. To the reaction flask was added 0.0005 mol (0.1 eq, 1.3 mL of a 0.4 M solution in toluene) of **1c**, 5 mL of THF (Merck #9731, H_2O content < 0.05 %), and 0.003 mol (0.38 mL of a 7.8 M solution in 1,4-thioxane, 0.6 eq) of BH_3-1,4-thioxane. This mixture stirred at the indicated temperature for 10 minutes before the ketone (0.6 g **2a**, 0.005 mol in 5 mL THF, 1.0 M, 1.0 eq) was added slowly dropwise via the addition funnel over 1-1.5 h. The progress of the reaction was followed by tlc and upon completion of the reaction (usually at the end of addition) the reaction flask was cooled to 0°C at which point 10 mL of MeOH was added slowly. Solvents as well as 1,4-thioxane were then removed by rotary evaporation. 8 mg of the crude oil was dissolved in 10 mL of 2.5 % isopropanol in n-hexane and analyzed directly by chiral HPLC for determination of % ee.[16] *The reaction has been run on a larger scale whereby an aqueous work-up was carried out as well as purification of the product :* 17.4 g of acetophenone (**2a**) was reduced with 5 % of **1c** as catalyst under the conditions described above. After aqueous workup, the product (**3a**) was isolated and purified by distillation (96 % yield, 99 % pure by GC). Enantiomeric purity (HPLC analysis) of the crude product was equal to that of the pure compound (96 % ee).

ACKNOWLEDGEMENTS

The author acknowledges Christoph Spöndlin and Robert Hartinger for their assistance in the determination of the % enantiomeric excess by chiral HPLC analysis of the alcohols.

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5. Available from Aldrich as a 7.8 M solution in 1,4-thioxane. This complex provides a safe alternative to BH_3-THF as sulfide complexes are known to be more stable. In comparison to Me_2S-BH_3, commonly used for these reductions, the stoichiometric liberation of 1,4-thioxane compared to dimethyl sulfide is advantageous as the former possesses a lower vapor pressure and a less obnoxious odor. It has the additional advantage of being moderately soluble in water and can therefore be washed out from organic solvents.
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8. Jones, T. K.; Mohan, J. J.; Xavier, L. C.; Blacklock, T. J.; Mathre, D. J.; Sohar, P.; Turner-Jones T.; Reamer, R. A.; Roberts, F. E.; Grabowski, J. J. *J. Org. Chem.* **1991**, *56*, 763.
9. This is interesting in terms of costs as this catalyst is considerably less expensive. Butylboronic acid is about 3 times more expensive per mole than phenylboronic acid (Fluka).
10. Toluene is an attractive solvent from an industrial point of view as it is less expensive and it is considered to be safer as it possesses a higher boiling point than THF. In addition, in-situ and one-pot catalyst generation-reaction would be possible.

11. Brunel, J. M.; Maffei, M.; Buono, G. *Tetrahedron : Asymmetry* **1993**, *4*, 2255. It is described that selective borane reductions are possible when catalyzed by (+) or (-) L-proline itself which is lacking two phenyl groups as well as a borane alkyl or aryl substituent. With increasing temperature the equilibrium is shifted towards the monomeric form. The dimer is certainly less active as a catalyst due to more steric hinderance and a decreased reactivity of B towards the ketone because of strong donation of O and N. It was stated: "due to steric effects, the influence of the temperature seems to be more important in our case than that Corey's oxazaborolidine. Indeed, the presence of two aryl groups in this latter reduces its ability to dimerize...." This could also explain why changing the substituent on borane would affect the selectivity. The dimerization is then dependent on the extent and type of substitution, on borane and on the ligand, as well as on the reaciton conditions (ie. temperature, solvent, concentration).

12. a) Corey, E. J.; Cheng, X-M.; Cimprich, K. A.; Sarshar, S. *Tetrahedron Lett.* **1991**, *32*, 6835; b) Jones, D. K.; Liotta, D. C.; Shinkai, I.; Mathre, D. J. *J. Org. Chem.* **1993**, *58*, 799.

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14. Preparation of phenylisocyanate derivative for HPLC analysis: 5 mg of the crude reaction product was dissolved in 150 µL of CH_2Cl_2 and mixed with 150 µL of phenylisocyanate. This mixture was heated at 60 °C for 30 min in a closed pressure stable vial. The solvent was removed by a stream of N_2 and the residue was dissolved in 10 % isopropanol in n-hexane to give a final volume of 10 mL.

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16. Tabular listing of results for the reduction of acetophenone (**2a**) with catalyst **1c** (from **Figure 3**) and of the reduction of cyclohexylmethyl ketone (**2b**) with catalysts **1b** and **1c** (from **Figure 6**).

Table 1. % ee Values for the Oxazaborolidine (**1c**) Catalyzed Borane Reduction of Acetophenone (see *EXPERIMENTAL* section; data also plotted in **Figure 3** and **Figure 4**).

Temp °C	1 % cat.	2.5 % cat.	5 % cat.	10 % cat.
-78	—	36	—	—
-40	49	63	70	71
-15	61	73	72	72
0	73	78	83	83
21	90	91	96	97
30	94	97	97	97
40	93	95	96	96
50	93	95	97	97
60	89	93	93	92
64	88	94	92	93

Table 2. % ee Values for the Oxazaborolidine (**1b** and **1c** at 10 %) Catalyzed Borane Reduction of Cyclohexylmethyl Ketone (data also plotted in **Figure 6**).

Temp. °C	Cat. 1c	Cat. 1b
-78	10	57
-50	31	—
-30	44	—
-15	55	74
0	51	—
21	73	82
30	74	—
35	79	—
40	76	—
45	74	—
50	80	89
55	75	—
60	75	—

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