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The Oxazaborolidine-Borane Reduction Of Ketones: Identification and Reactivity of Transient Intermediates

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Abstract: An investigation of the reaction pathway for oxazaborolidine - borane reduction of ketones has revealed a transient intermediate which can competitively reduce ketones. Copyright © 1996 Elsevier Science Ltd

Introduction

The asymmetric reduction of ketones is a valuable tool in synthetic organic chemistry. Of the methods available to carry out this transformation, the oxazaborolidine-borane reagents have shown great utility.[1] These types of asymmetric catalysts were originally pioneered by Itsuno and Corey and further developed by others.[2] There are numerous examples in the literature for the chiral synthesis of alcohols, amines and amino alcohols.[3,4,5] In general, these reagents provide excellent enantioselectivity for the asymmetric reduction of most aromatic ketones. However, in our experience, the optimum experimental conditions for chiral reduction is somewhat substrate specific and requires considerable fine tuning. It has become obvious that the choice of catalyst, borane source, order and rate of addition and reaction temperature are all crucial to achieving high degrees of enantioselectivity. Other parameters, such as additives, can also influence the stereoselectivity.[6] We desired a better understanding of the intricate details of these reactions in order to more effectively predict optimal conditions for reduction of a given substrate. By careful investigation of this reaction, we have gained valuable insight into the mechanism of this complex reaction. Herein we describe some evidence which offers support for the mechanism originally proposed in part by Corey [2] (Scheme 1).

Results and Discussion

The mechanism shown in Scheme 1 is supported by *in situ* NMR experiments as well as other chemical studies. In an attempt to identify early intermediates **3** or **4**, we undertook extensive variable temperature NMR studies. Multinuclear NMR studies were conducted using several different ketones. Reacting stochiometric quantities of the oxazaborolidine borane complex **1** (OAB-BH_3) at low temperature (between -40 °C and -100 °C) with simple ketones such as acetone (**a**), or p-methoxyacetophenone (**b**) rapidly generates a species such as **4** . ^{13}C NMR data shown in Table 1 is consistent with the structures **4a** and **4b**.

Scheme 1

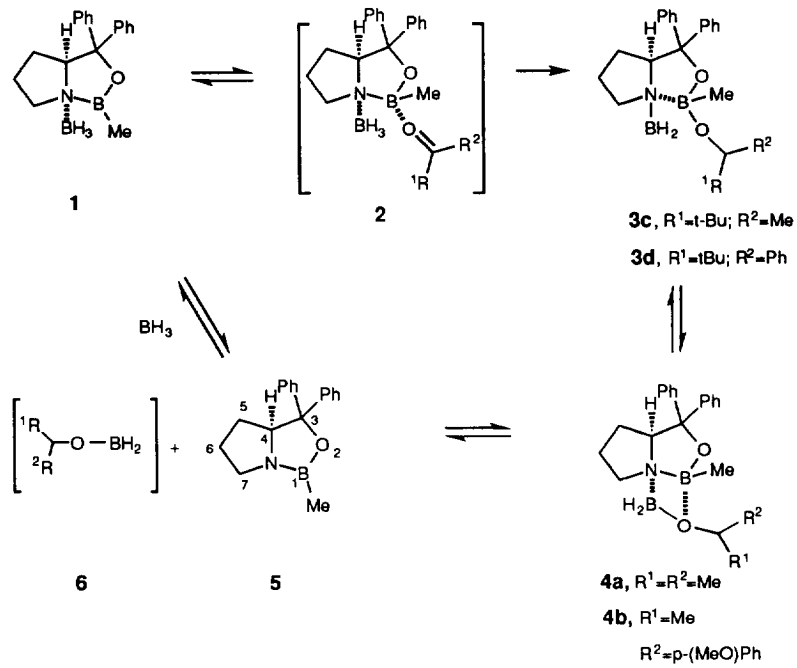


Table 1

^{13}C Chemical Shifts (ppm) in **1**, **5** and Adduct **4** at -100°C

	C_3	C_4	C_5	C_6	C_7	BMe	*Ipso*	OCH	Other
1	89.3	75.5	31.3	23.9	57.0	-4.4	142.7 144.6	----	----
5	86.3	71.2	29.5	24.9	42.3	-5.9	143.3 147.1	----	----
4a	85.3	70.7	31.5	24.7	53.2	-2.3	146.4 147.1	70.4	20.0 21.5
4b	85.5	70.7	31.6	24.7	53.3	-2.6	146.3 147.4	76.5	23.8 132.3

The ^{11}B shifts for **4a** and **4b** also support these assignments (Table 2). The methylated boron shifts near 13-14 ppm are significantly different from the shifts in either **1** or **5** (34.5 and 34.3 ppm respectively).[3] Shielding by ~20 ppm is acceptable for a tetracoordinated BMe such as **4** .[7]

Interestingly, experiments with more bulky ketones such as pinacolone (**c**), phenyl t-butyl ketone (**d**), and diisopropyl ketone (**e**) have provided evidence for the early reaction intermediate **3**. This intermediate has

been previously proposed by Corey[2] and others, however, to our knowledge, this is the first evidence to support its existence.

Table 2

^{11}B Chemical Shifts (ppm) in Adduct **4** at Low Temperature

	T, °C	BH_2	B-Me
4a	-60	2.9	13.3
4b	-45	3.7	14.3

The adducts **3** (**c**, **d**, **e**) form relatively slowly at -75°C ($t_{1/2}$~1-2 h) and are reasonably stable at these temperatures (< -70°C). Intermediate **3** appears as two interconverting forms which we believe is due to hindered rotation around the N-B-O bonds. Some of the NMR data which supports these structures is shown in Table 3.

Table 3

^{13}C Chemical Shifts (ppm) in Adduct **3** at Reduced Temperature

Adduct *	T °C	C_3	C_4	C_5	C_6	C_7	BMe	*Ipso*	OCH	Other
3c (6)	-100	82.0	64.2	28.7	24.8	53.5	-2.2	143.4, 145.9	77.3	15.8, 33.9
(1)	-100	81.4	66.7	28.7	24.0	52.9	0.6	143.8, 144.9	74.9	16.4, 33.9
3d	-75	82.4	64.2	29.2	24.9	53.9	-1.0	143.8, 146.0	84.9	25.8, 35.0, 141.7
3e (8)	-75	82.8	64.6	28.7	24.2	53.5	-1.4	143.0, 144.8	84.3	14.6, 18.1, 18.8, 20.1, 28.6, 30.3
(1)	-75	82.8	64.6	28.7	24.2	53.5	1.0	143.0, 144.8	80.3	16.7, 17.4, 19.5, 19.7, 29.5

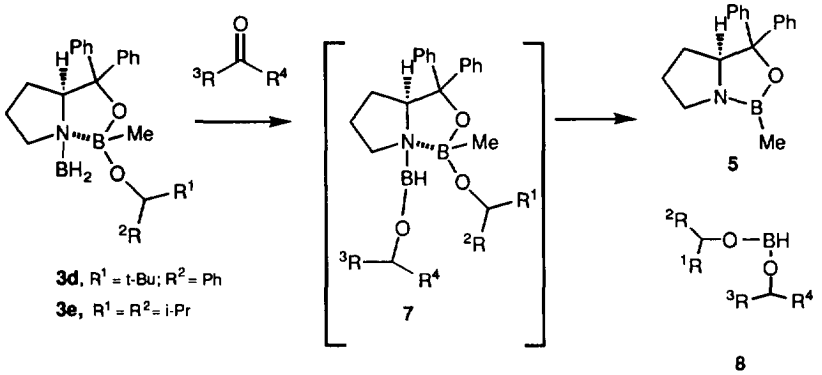
* Relative amounts of two interconverting forms are indicated in ( ). **3d** shows only one form.

Since **3** is unstable at higher temperatures (> -50°C), direct ^{11}B NMR spectroscopy was not possible due to rapid ^{11}B quadrupolar relaxation at low temperatures. However, coarse ^{11}B chemical shift data could be obtained from a series of single-frequency ^{11}B decoupled proton difference NMR experiments. A broad two proton singlet at 4.39 ppm for **3d** at -75°C was narrowest in the difference spectrum for ^{11}B cw irradiation positioned near 40 ppm (BF_3-OEt_2 = 0.0 ppm).[8,9] Although coarse steps (20 ppm from 0 to 80 ppm) were used in the ^{11}B regime, a boron shift near 40 ppm (rather than near 0 ppm) supports a free BH_2 group as depicted in **3**.[10]

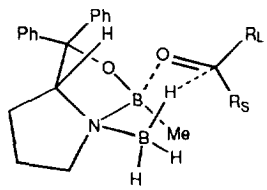
While the detailed mechanism by which **3** and /or **4** are ultimately recycled back to active catalyst is still not clear, we have made some interesting observations regarding the reactivity of these intermediates. Preforming intermediate **3d** at low temperature (-75°C) and subsequent treatment with p-methoxyacetophenone (R^3 = p-MeOPh, R^4 = Me) and warming to -50°C results in the consumption of both **3d** and p-methoxyacetophenone. Low temperature NMR analysis of the mixture indicates that **5** and the mixed dialkoxy borane **8** are the products (Scheme 2). Most notable about this result is the fact that the enantioselectivity of the p-methoxyacetophenone reduction by the intermediate **3d** is significantly lower as

compared with p-methoxyacetophenone reacting directly with OAB-BH_3 (85% vs. 98% ee).[11] We have not observed an intermediate such as **7** nor do we detect any free monoalkoxyborane **6**. Several laboratory scale experiments using this sequential addition of different ketones have all provided similar results.

Scheme 2



In each example, the ketone which is added to the preformed intermediate **3** is reduced with lower enantioselectivity. Experiments using preformed **3e** (R^1 = R^2 = i-Pr) and subsequent treatment with acetophenone (R^3 = Ph, R^4 = Me) also indicated lower enantioselectivity for the 2nd reduction (i.e. ~85%). This experiment was designed to rule out the possibility that nondetectable concentrations of free monoalkoxyborane **6** might be the 2nd hydride source. The fact that the ee (~85%) was lower, but still significant, argues against hydride transfer from the achiral monoalkoxyborane **6** (R^1 = R^2 = i-Pr).[12] We have previously noted different enantioselectivities for the two hydride transfers. Based on these most recent results, we have modified our earlier proposal regarding the 2nd hydride transfer.[6c] This new data strongly suggests that **3** is a reactive intermediate which can competitively reduce ketones. It is not surprising that ketone reduction by a species such as **3** provides lower enantioselectivity. The alkoxy group coordinated to the ring boron precludes complexation of the second ketone to this boron and therefore prevents hydride transfer via a highly organized six membered transition state such as **9**.[13]



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The discovery that intermediates **3** /**4** along the reaction pathway can adversely compete with the catalyst explains several observations about these reactions. For example, the beneficial effect of slow addition techniques, which is well documented, can now be rationalized. Aside from effectively keeping low concentrations of the borane source (i.e. BH_3 or BMS) and ketone, slow addition techniques allow adequate

time for intermediates such as **3** to "decompose" and regenerate the desired catalyst OAB-BH_3. The same rationale can be used to explain the beneficial effects observed (for some substrates) at higher temperatures.[14] At higher temperature, the rate of catalyst recycle from the reaction intermediates is accelerated. Obviously, the rate of competing reduction by the borane source at a higher temperature also has to be considered. More recently we have also demonstrated enhanced enantioselectivities by the use of additives which effectively accelerate the decomposition of the reactive intermediates.[6] We have evidence that the intermediates **3/4** react rapidly with isopropanol thus precluding their reaction with the ketone.

Conclusion

As with any reaction, definitive proof of the mechanism of the oxazaborolidine-borane reduction is not possible. This work offers some insight into the complex nature of this particular chemistry. From a practical standpoint, it offers a working model to explain the wealth of data currently known about these reactions. This should allow the scope of this chemistry to become even more general. In addition, these results might be useful for the development of new and more selective reagents. Catalysts, which by design do not have a second hydride available, may offer improved enantioselectivities.[15]

Experimental

General: NMR spectra (^1H, ^{13}C , ^{11}B) were recorded at various temperatures using Bruker WM-250, AM-400 or AMX-400 spectrometers. Internal referencing of ^1H and ^{13}C spectra for all temperatures was performed relative to $CHDCl_2$ at 5.32 ppm and CD_2Cl_2 at 53.8ppm, respectively. Boron-11 shifts were referenced to a seperately prepared BF_3-OEt_2-CD_2Cl_2 mixture. APT [16] and DEPT [17] techniques were employed throughout to distinguish proton populations.

(A) Two-step mixed ketone reductions (NMR study):

A typical NMR experiment utilized 62.3 mg (0.21mmol) of OAB-BH_3 **1**, 0.5mL CD_2Cl_2 and 64.5mL (0.45 mmol) di-isopropyl ketone. The mixture was aged at -75°C for 2 h and complete consumption of **1** was verified by ^1H NMR. The second ketone, (16mg , 0.1 mmol of p-methoxyacetophenone) was then added and the mixture was warmed to -40°C and monitored by NMR for consumption of the ketone. The solutions were quenched into methanol and the carbinols were purified by silica gel chromatography and analyzed by HPLC using a Chiralcel -OD column.

(B) A general procedure for the sequential mixed ketone reductions:

To a solution of OAB-BH_3 (**1**) (276.5 mg, 0.95 mmol, 2.5 ml of CH_2Cl_2) was slowly added phenyl t-butyl ketone (**d**) (0.155 ml, 0.95 mmol) at -75 °C via a microsyringe. The resulting solution was stirred at -75 °C for 1.5 h. p-Methoxyacetophenone (**b**) (160 mg, 1.07 mmol) was added as a solid in one portion at -75 °C. After the reaction mixture was kept at -75 °C for 4.5 h, it was quenched with MeOH at -75 °C and then warmed to room temperature. The solvents were removed under vacuum and the crude mixture was chromatographed on silica gel and eluted with EtOAc/Hexane (10/90). HPLC assay for alcohol (**d**) was performed on a Chiralcell OD column and eluted with i-PrOH/Hexane (5/95 volume, flow rate = 0.50 ml/min) and indicated 97.5% ee. The chiral assay of alcohol (**b**) was performed on a Chiralcell OB column eluting with i-PrOH/Hexane (15:85) and provided 85.7% ee.

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8. Although the complexity of many reaction mixtures prevented useful ^{1}H NMR interpretation, the relatively stable **3d** and **3e** allowed selected ^{1}H NMR assignments as follows: **3d** (CD_2Cl_2, 400 MHz, -75° C) δ 8.00 (d, J= 8 Hz, 1H), 6.51 (d, J=8 Hz, 1H), 5.25 (m, 1H), 5.08 (br, 1H), 4.41 (s) & 4.39 (br s) (total 3H), 3.04 (t, J=9 Hz, 1H), 2.52(m, 1H), 2.07 (m, 1H), 1.89 (m, 1H), 1.46(m, 1H), 0.78 (br s, 9H), 0.05 (s, 3H); **3e** (CD_2Cl_2, 400 MHz, -75° C) δ 7.96 (br s, 1H), 6.63 (br s, 1H), 5.10 (br dd, J= 8, 5 Hz, 1H), 4.33 (br, 1H), 4.24 (br m, 1H), 3.06 (d, J=8.8 Hz, 1H), 2.89 (m, 1H), 2.38 (m, 1H) 1.92 (m, 1H), 1.70 (m, 1H), 1.42 (m, 2H), 1.12 (m, 1H), 0.85 (d, J=6 Hz, 3H), 0.74 (d, J =6 Hz, 3H), 0.51 (d, J=6Hz, 3H), 0.13 (s, 3H), -0.16(d, J=6Hz, 3H). COSY and HETCOR 2D NMR results confirmed ^{1}H and ^{13}C assignments.

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