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In situ NMR study of asymmetric borane reduction reaction—an abnormal factor in the temperature effect on the bis-oxazaborolidine catalyst and the relationship between the catalyst structure and selectivity

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Abstract

The relationship between the structure of the catalyst and the selectivity in the asymmetric borane reduction reaction of prochiral ketones is discussed. The variation of the catalyst itself at low temperature is observed by the in situ NMR method and the origin of the temperature effect of the reaction is proposed. It is concluded that the amount of the effective component of the catalyst present has an important effect on the enantioselectivity.

1. Introduction

The enantioselective reduction of prochiral ketones is an important method for the synthesis of optically active secondary alcohols, which are key intermediates for medicines and pesticides, etc. Some of the best enantioselectivities have been achieved with systems derived from chiral vicinal amino alcohols, which were pioneered by Itsuno,[1] and then developed by Corey's group[2] and are well known as the CBS reduction. Comparing the numerous attempts to improve the enantiomeric excess, few papers have concentrated on the mechanistic aspects of the catalytic reaction, and many phenomena are still difficult to explain.

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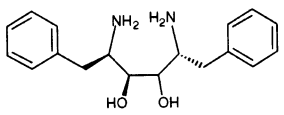
During the course of studies of borane reductions of ketones catalyzed by oxazaborolidine, many papers have reported the effect of temperature on selectivity.[3] In one of the first paper concerning this reaction, Corey and co-workers[2] stated that enantioselectivity often decreases somewhat with decreasing temperature. Stone studied this effect in detail and improved the selectivity by adjusting the temperature that was dependent on the substrate.[4] Corey summarized this effect in his recent comprehensive review[5] and stated that the coordination of Me_2S, THF etc. to borane generally did not affect the level of enantioselection except at temperatures below 243 K. They attributed this effect to the alteration of the equilibrium between borane, the coordinated ligand, the oxazaboralidine catalyst and the ketone at this temperature, and this allowed the intervention of the competing reduction pathways. It has been observed that certain catalysts exist in a temperature dependent equilibrium with their dimeric form. Buono et al.[6] reported that with increasing temperature the equilibrium was shifted towards the monomeric form. The dimer is certainly less active as a catalyst due to more steric hindrance and a decreased reactivity of B towards the ketone because of the strong donation of O and N. Thus the amount of catalyst dimer present has a negative effect on the selectivity. These elucidations may be reasonable but there are still no definite conclusion and convincing proof, so we tried to study the temperature effect with our bis-oxazaborolidine catalyst by in situ NMR method in the hope of gaining insight into the effect.

Recently, good enantioselectivities of the C_2-symmetric ligand **1** applied in the asymmetric borane reduction of prochiral ketones have been found and the important intermediate responsible for the enantioselectivity was shown to be **2** by in situ NMR method.[7]



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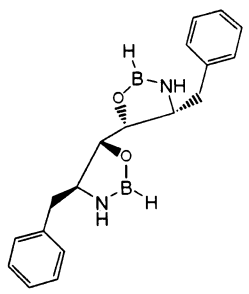

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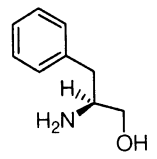

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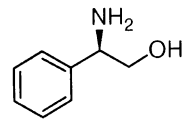

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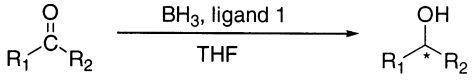
During the study of the asymmetric borane reduction of ketones catalyzed by the ligand **1**, a dramatic temperature effect on enantioselectivity was observed (Table 1). With the increase of the temperature from 243 to 308 K, the chemical yield and the enantioselectivities were greatly improved (Fig. 1).

These results stimulated our interest to study the 'equilibrium' described by Corey et al. Another problem that concerned us most is why so simple and less rigid a molecule (compound **1**) can induce so high an enantioselectivity? Herein we try to provide some evidence for this problem.

Table 1
Asymmetric stoichiometric borane reduction of prochiral ketones by ligand **1** at different temperatures



Entry	R1	R2	Temperature (K)	Yield (%)	Ee (%)[a]	Configuration[b]
1	Ph	Me	243	55	33.8	*S*
2	Ph	Me	303	95	60.6	*S*
3	Ph	Me	308	95	65.5	*S*
4	Ph	Me	318	94	64.8	*S*
5	Ph	CH_2Cl	308	92	84.7	*R*
6	Ph	CH_2Br	308	91	88.1	*R*
7	β-Naphthyl	Me	308	95	69.6	*S*

[a] Values of % ee were obtained by a HPLC chiral column OD, OJ.
[b] Configurations of the products $[\alpha]_D$ were gained by comparing with the standard compound.

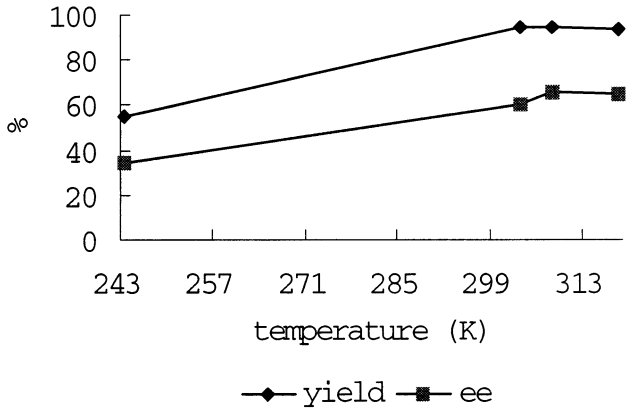


Figure 1. Plot of temperature versus yield and % ee of the asymmetric borane reduction of acetophenone (Table 1, entry 1–4)

2. Experimental

2.1. Sample preparation

Compound **1** was synthesized from L-tartaric acid, as described elsewhere.[3] Ligand **3** and another compound **4** were prepared from the reduction products of their corresponding amino acids by $LiAlH_4$.

For preparing the coordinated compounds, 50 mg of the ligand (1*R*,4*R*,2*S*,3*S*)-1,4-dibenzyldiamino-2,3-butanediol **1** (0.17 mmol) was put in the pretreated NMR sample tube, and 0.3 ml of 2 M borane (0.6 mmol) in THF was dropped in at 203 K, and the temperature was increased gradually to 308 K. The sample tube was sealed and kept for more than 12 h at 308 K, when compound **2** was the main component in the system.

Other samples with different ligand concentrations were also prepared by this method.

2.2. NMR experiments

NMR experiments were performed on a Bruker DRX 400 spectrometer with a 5 mm BBI probehead. ^{1}H, ^{13}C and ^{11}B NMR experiments were carried out at room temperature or at a predetermined temperature. ^{1}H, ^{13}C and ^{11}B NMR spectra were recorded at 400.1, 100.6 and 128.4 MHz, respectively. The 90° pulses for ^{1}H, ^{13}C and ^{11}B NMR spectra were 10, 10.1 and 10 μs, respectively. Their spectral widths were 4807.7, 25062.7 and 25641.0 Hz with data points at 16, 16 and 8 K, respectively.

The ^{11}B NMR background from the probehead was deducted from the ^{11}B NMR spectrum and the peak at δ −20 for $BH_3{\cdot}Me_2S$ was chosen as the internal standard in order to eliminate the effect of temperature on the chemical shift.

2.3. In situ NMR tests

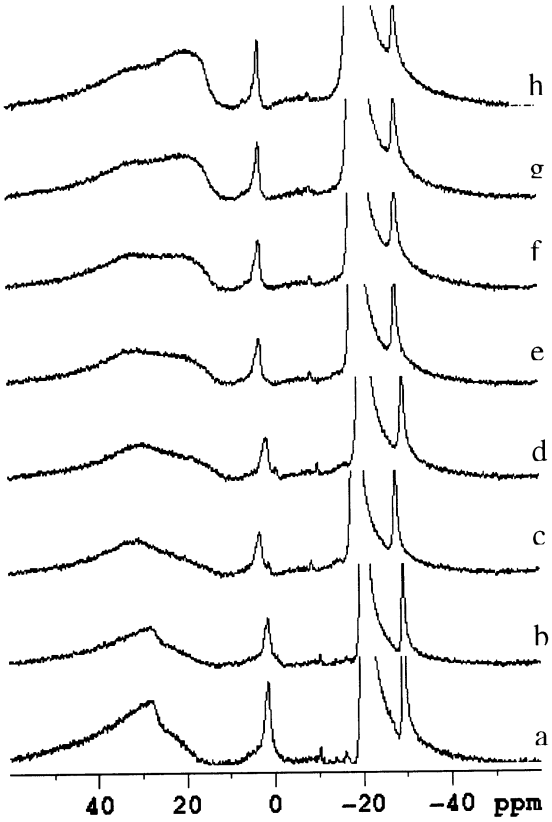
An in situ NMR method was employed to decide the structure of the coordinated catalysts. The NMR sample tube was evacuated and filled with argon gas before the sample was introduced, and a small tube filled with D_2O or acetone-d_6 was put in the NMR sample tube as the lock signal. The sample was transferred from the reaction system to the NMR sample tube under an argon atmosphere, then the tube was sealed and moved to the magnet for continuous NMR detection immediately.

3. Results and discussion

Study of the catalyst **2** at different temperatures disclosed some abnormal information (Fig. 2). With a decrease in temperature the component of the catalytic system changes. The broad peaks at $\delta \sim 29$ and $\delta \sim 1.6$ in Fig. 2(a) are assigned to the monomer and dimer (N–B–O in the ring) of ligand **1**, respectively. The peak at $\delta \sim 5.6$ is the incompletely transformed catalyst (–O–B–O–) according to our previous work.[7] The upfield peaks from δ −10 to −30 came from the solution of borane complex such as $BH_3{\cdot}Me_2S$ and $BH_3{\cdot}THF$, etc. When the catalyst was investigated from 308 to 223 K (Fig. 2(a–h)), the broad peak at δ 29 decreased greatly and another broad peak at δ 16 appeared gradually from 263 to 223 K. These two peaks in the ^{11}B NMR spectrum (Fig. 2(f)) can be well resolved by deconvolution using the Bruker software WINNMR, as shown in Fig. 3. The other ^{11}B NMR spectra in Fig. 2 were also deconvoluted and the data are collected in Table 2.

These results show that with a decrease in temperature the peak at δ 29 was still the main component, in spite of the fact that the other peaks at δ 19 and δ 16 were formed (Fig. 4). When the sample was diluted with 0.5 ml deuterated THF this variation became dramatic. As indicated in Fig. 5, three peaks in the spectrum detected at 223 K (Fig. 5, (1)) can be well resolved by deconvolution and the ratio of the three peaks is 49/36/14. Generally, as it becomes more dilute in the real catalytic system, it can be reasonably assumed that the transformations would become more dramatic.

Considering the mechanism proposed by Corey[2] and the reaction results, which were greatly affected by the temperature, it could be concluded that component 'a' at δ 29 in Fig. 3 was the effective catalyst for the borane reduction reaction, and the chiral induction ability for components b and c were not so satisfactory. Components b and c were assumed to be the



a: 308K b: 303K c: 273K d: 263K

e: 253K f: 243K g: 233K h: 223K

Figure 2. ^{11}B NMR spectra with decoupling of the coordinated compound of ligand **1** with borane at different temperatures

complex of the catalyst and the solvent. As the flexibility of the solvent decreases at low temperatures, so it is easy to interact with the catalyst. It has been proved that components b and c have the ability to interact with the substrate. Furthermore, they can affect the reaction.[8] The complexes are certainly less active as catalysts due to more steric hindrance and a decreased reactivity of B towards the ketone, caused by strong donation of O (THF) or S (Me_2S) in the solvent molecule.

As indicated in Figs. 2 and 3, the temperature-dependent equilibrium of the catalysts with their dimeric forms was not obviously observed. But several novel species were found at low temperatures and the catalytic system at low temperatures became a more complicated mixed system, thus the amount of effective catalyst was decreased. From our point of view the decreased amount of effective catalyst (oxazaborolidine) was the main reason for the diminished enantioselectivity and this was in accord with the conclusions of the literature.

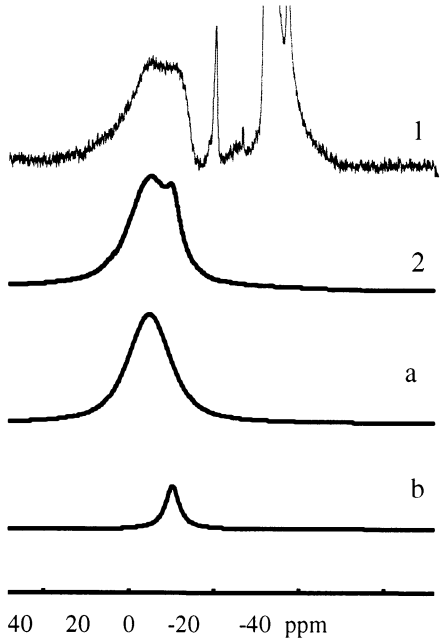


Figure 3. ^{11}B NMR and their partly deconvoluted spectra of catalyst **1** at 243 K in Fig. 2(f) (a and b are the deconvoluted peaks and the integration of the peaks a and b equals 2). (1) The original spectrum; (2) the deconvoluted spectrum

Besides the temperature effect on the novel catalyst, another interesting phenomenon was also noticed. The structure of compound **1** can be regarded as a combination of two molecules of compound **3**, but the efficiency of compound **3** was proven to be not so satisfactory and only a 37% ee was obtained in the quantitative reaction[1] (Scheme 1).

However, a 63.9% ee can be obtained using only a catalytic amount of ligand **1** (0.1 equiv.) in the same reaction. This means that the chiral induction ability of ligand **1** was greatly improved after the combination of two molecules in ligand **3**.

Table 2
Variation of the catalyst monomer at different temperatures

Temperature (K)	% ee	%		
		δ 29	δ 19	δ 16
308	65.5	100	0	0
303	60.6	100	0	0
273		100	0	0
263		96.5	3.5	0
253		93.1	6.9	0
243	33.8	87.0	13.0	0
233		85.0	15.0	0
223		77.6	20.4	2.0

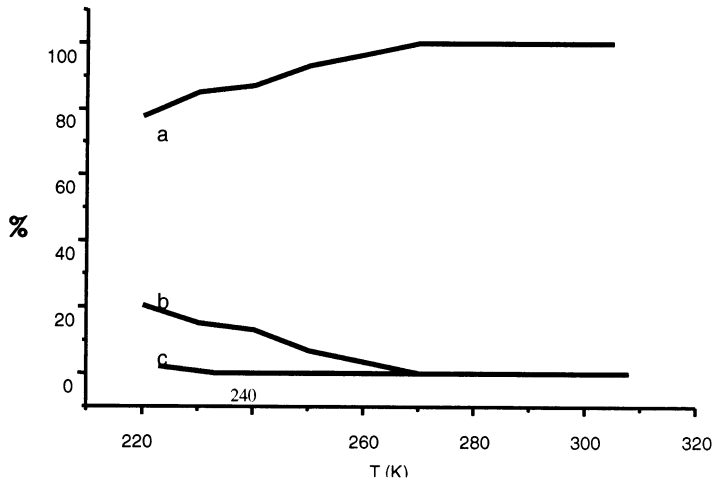
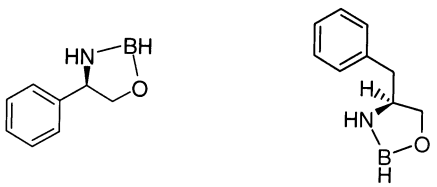


Figure 4. A plot of temperature versus variation of the catalyst monomer. (a) The peak at δ 29; (b) the peak at δ 19; (c) the peak at δ 16

The primary reaction product of amino alcohol with borane would be the oxazaborolidines (**2**, **5** and **6**, respectively), which was the key intermediate for the enantioselective borane reduction. Due to the similarity of the structure, compound **4** was chosen for comparison of the spectroscopic properties of compound **3** after coordination with borane.



5 **6**

The existence of **2** was detected in our previous work (Fig. 2(a and b)), but similar experiments for **3** and **4** give a surprising result. The in situ NMR test of the coordinated compounds of **3** and **4** with borane showed that the systems of the two coordinated ligands are quite complicated and there were several boron compounds in the mixture (Fig. 6). The ^{11}B NMR spectra of the coordinated system of **3** and **4** are quite similar, which indicates a similar reactivity of the two amino alcohols with borane.

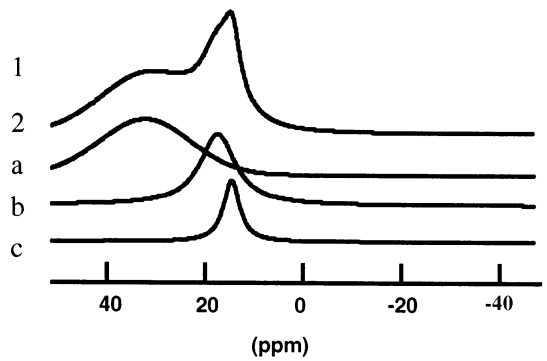
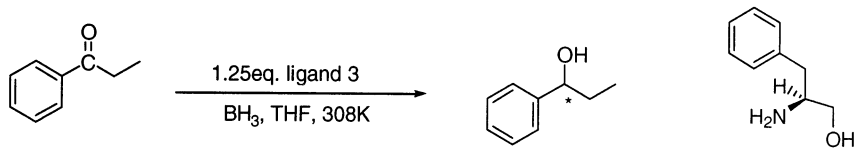


Figure 5. ^{11}B NMR and their partly deconvoluted spectra of the diluted catalyst **1** at 223 K in Fig. 2(f) (a, b and c are the deconvoluted peaks and the integration of the peaks a, b and c equals 2)



(R) 37%ee **3**

Scheme 1. Asymmetric borane reduction of phenylacetone

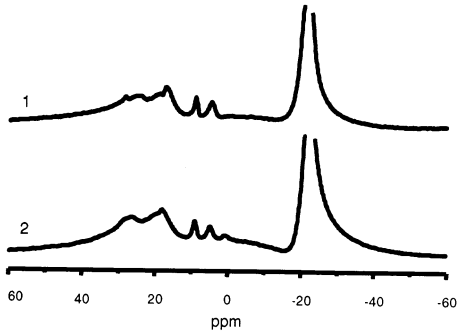


Figure 6. ^{11}B NMR spectra with decoupling of the coordinated ligands **3** and **4** at room temperature. (1) Coordination of **4** with borane; (2) coordination of **3** with borane

The peak at about δ 28 is assigned to the monomer of the catalyst, which was intermediate **6**, but the dimer is difficult to assign as there are three peaks in the range of δ 1–10 (Fig. 6, (2)). The spectrum for the coordinated compound **4** with borane is relatively sophisticated and the small peak at about 28 is assumed to be the intermediate **5**. From Fig. 6 it is easy to deduce that the amount of intermediate **5** or **6** at δ 28 is quite low. The ^{1}H and ^{13}C NMR spectra (not shown) of the two ligands and their coordinated compounds also manifested a mixed system after coordination. The chemical shift of the spectral line of the carbon connected to the amino group proceeds downfield to about 6 ppm. About 3 ppm upfield shift for the spectral line of the carbon connected to the hydroxyl group was found in the ^{13}C NMR spectra after coordination of **3** and **4** with borane. These results show that the main component of ligands **3** and **4** coordinated with borane were the complexes of their amino group with borane. Their hydroxyl group may be surrounded by the solvent molecules, thus hampering the combination of borane with the hydroxyl group. Combining the real reaction conditions and the above results, it can be concluded that the amount of effective components of the catalyst (**5** and **6**), which are responsible for the enantioselectivities, is relatively low, thus causing a low efficiency of the catalysts. Of course, another unnegligible factor accounting for the high enantioselectivity of **1** is the C_2 symmetric properties of the ligand and the catalyst, which has been discussed earlier[7] and did not exist in compound **3**.

At the beginning of the study of the CBS reduction, the importance of the preparation of chiral oxazaborolidines in pure form was realized, as catalyst purity is essential for the attainment of high enantioselectivity and reproducibility in the reduction of ketones. Considerable effort has been extended towards the development of effective procedures for the generation of pure oxazaborolidines without the need of a purification step.[9] However, it is realized now that the catalyst itself can be transformed into other species under appropriate conditions. It is possible to find proper ways to obtain pure catalyst, but it is not easy to limit the transformation of the catalyst itself in the system under some conditions. Thus it is possible to find an optimum condition for every catalyst such that the catalyst can be used to the utmost extent.

Although the effect of temperature on the selectivity has been described many times in the literature, no complete explanation has been reported. It is difficult to provide a straightforward explanation, as the selectivity of this reduction is likely to be a result of many complex factors. Our observations just add another aspect of the reaction and hope to gain insight into the origin of temperature effects on the borane reduction reaction catalyzed by dual-centered oxazaborolidines.

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