Rationale on the Abnormal Effect of Temperature on the Enantioselectivity in the Asymmetric Borane Reduction of Ketones Catalyzed by L-Prolinol

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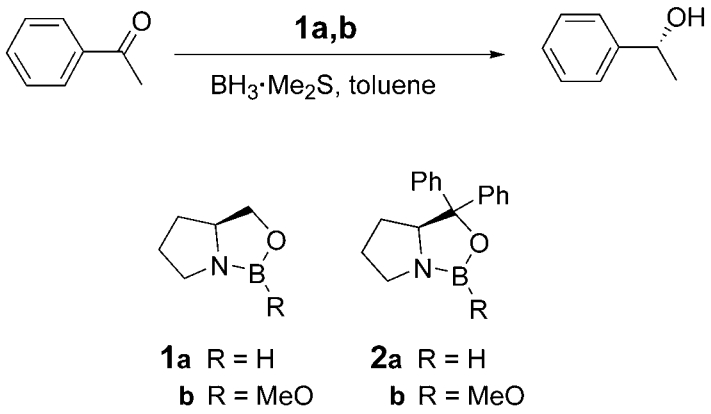
The effect of temperature on the enantioselectivity of the oxazaborolidine-catalyzed asymmetric borane reduction of ketones was investigated in the presence of (5*S*)-3-oxa-1-aza-2-borabicyclo[3.3.0]octane (=(3a*S*)-tetrahydro-1*H*,3*H*-pyrolo[1,2-*c*][1,3,2]oxazaborole; **1a**) and its 2-methoxy derivative (**1b**) as catalysts, which were synthesized from L-prolinol with borane and trimethyl borate, respectively. The results indicate that the two catalysts induce a different temperature-dependent enantioselectivity. The enantioselectivity of the *B*-unsubstituted (5*S*)-3-oxa-1-aza-borabicyclo[3.3.0]octane (**1a**) increases with increasing temperature, while its *B*-methoxy-substituted derivative **1b** shows the highest enantioselectivity at *ca.* 50°. (5*S*)-3-Oxa-1-aza-2-borabicyclo[3.3.0]octane (**1a**) is more likely to dimerize than its 2-methoxy derivative **1b**. The conversion rates of L-proline to L-prolinol in the presence of different amounts of borane were also determined in this study.

1. Introduction. – Enantioselective 1,3,2-oxazaborolidine-catalyzed borane reduction of prochiral ketones to chiral secondary alcohols is one of the most-often applied reactions in asymmetric syntheses and has been widely used in the preparation of various secondary alcohols during the past two decades (for recent reviews, see [1]). Numerous new efficient oxazaborolidines have been developed and applied until now. In comparison with the numerous attempts to search for new catalysts, in only some of the papers was attention paid to the factors that affect enantioselectivity in the asymmetric reduction, such as the structure [1][2] and stability [3] (including dimerization) of the catalyst, the borane source [4], the reduction of temperature [5], the solvent [3a][4c], the additive [6], the electronic effect [7], *etc.* Although a few papers have reported the effects of temperature on enantioselectivity, different 1,3,2-oxazaborolidines seem to show obviously different effects on the enantioselectivity, and the effect of *B*-unsubstituted 1,3,2-oxazaborolidine has not been investigated in detail. Herein, we wish to report our observations and rationale on the effects of prolinol-derived, *B*-unsubstituted and *B*-methoxy-substituted 1,3,2-oxazaborolidine catalysts in the asymmetric borane reduction of acetophenone.

2. Results and Discussion. – Many chiral 1,3,2-oxazaborolidines derived from chiral vicinal amino alcohols have been prepared and evaluated in the asymmetric borane reduction of ketones, and some excellent enantioselectivities have been achieved with them [1]. (5*S*)-3-Oxa-1-aza-2-borabicyclo[3.3.0]octane (=(3a*S*)-tetrahydro-1*H*,3*H*-pyrrolo[1,2-*c*][1,3,2]oxazaborol; **1a**), derived from (2*S*)-pyrrolidine-2-methanol (=L-

prolinol), was reported by *Buono* and co-workers to be an effective catalyst in the asymmetric reduction of ketones in refluxing toluene, giving excellent yields and enantioselectivities [5a]. However, a year later, *Martens* and co-workers found that only moderate enantioselectivities were obtained under the same conditions and argued against the results of *Buono* and co-workers [8]. According to [5], the effect of temperature on the enantioselectivity of *B*-unsubstituted chiral 1,3,2-oxazaborolidines has not been investigated in detail at temperatures $> 55°$. Recently, we found that (5*S*)-2-methoxy-4,4-diphenyl-3-oxa-1-aza-2-borabicyclo[3.3.0]octane (**2b**) is a better catalyst than the *B*-unsubstituted (5*S*)-4,4-diphenyl-3-oxa-1-aza-2-borabicyclo[3.3.0]octane (**2a**) [9]. Employing (5*S*)-3-oxa-1-aza-2-borabicyclo[3.3.0]octane (**1a**) as a simple catalyst easily prepared from L-prolinol, even *in situ* from L-proline, we now investigated the effects of temperature on the enantioselectivity of acetophenone reduction in the presence of **1a** or of its 2-methoxy derivative **1b**, aiming at finding a simple and efficient catalyst (*Scheme 1*) and at settling the argument on the enantioselectivity in refluxing toluene.

Scheme 1. *Asymmetric Borane Reduction of Acetophenone Catalyzed by* L-*Prolinol*



In our asymmetric reduction, catalyst **1a** (0.1 equiv. rel. to acetophenone) was prepared first by addition of borane · dimethyl sulfide ($BH_3 \cdot Me_2S$; 1.5 equiv. rel. to L-prolinol) to a solution of L-prolinol in toluene and heating at 45° for 14 h or at 110° for 15 min. After adjustment to the desired temperature and after addition of an additional amount of $BH_3 \cdot Me_2S$ (1.0 equiv. rel. to acetophenone), acetophenone (1.0 equiv.) was added dropwise within 0.5 h[1]). Catalyst **1b** was prepared *in situ* by addition of trimethyl borate to a solution of L-prolinol in toluene and stirred at 25° for 2 h. Then, at the desired temperature and after addition of $BH_3 \cdot Me_2S$ (1.0 equiv. rel. to acetophenone), acetophenone (1 equiv.) was added dropwise within 0.5 h. The enantiomer excesses were determined after usual workup (see *Exper. Part*) by means of HPLC on a *chiral OD* column. The results revealed different temperature-dependent enantioselectivities

[1]) The experimental results established that no obvious difference in enantioselectivity was observed between the two modes used for the preparation of catalyst **1a**.

for the two catalysts (see *Figs. 1* and *2*). With catalyst **1b**, the highest enantioselectivity (60%) in the asymmetric reduction of acetophenone was achieved at *ca.* 50° (*Fig. 2*), similarly to catalyst **2b** reported previously [5b,g]. In contrast, with catalyst **1a**, the enantioselectivities increased almost linearly ($r^2 = 0.98$) with increasing temperature (*Fig. 1*). Compared with the traditional dependence of enantioselectivity on temperature, the results with catalyst **1a** are abnormal.

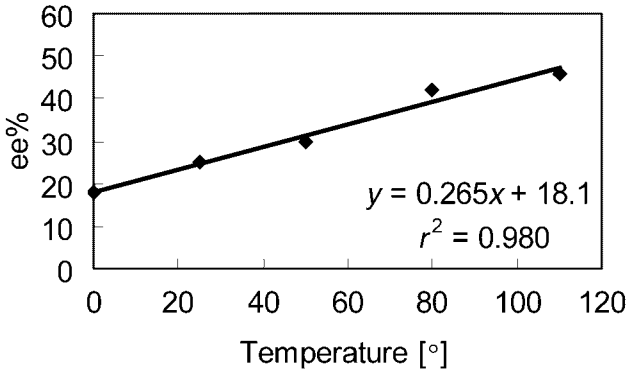


Fig. 1. *The effect of temperature on the enantioselectivity of catalyst* **1a**

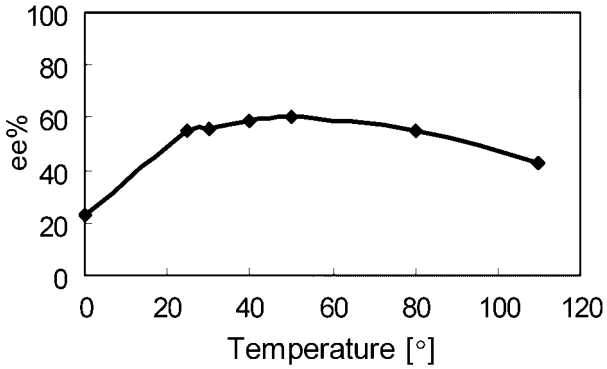


Fig. 2. *The effect of temperature on the enantioselectivity of catalyst* **1b**

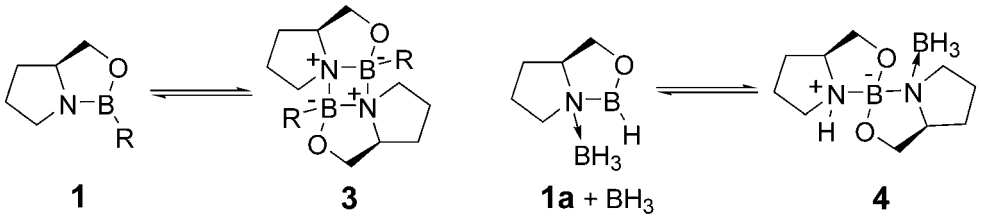
As we suggested previously [5g], dimerization is an important factor in temperature-dependent enantioselectivities for *B*-unsubstituted catalysts, while noncatalytic reduction is a non-negligible factor for *B*-substituted catalysts.

Based on literature data [5] and our results, the different temperature-dependent enantioselectivities can be rationalized by the dimerization of catalyst **1a** at lower temperatures and the formation of the monomer with increasing temperature. Thus, the monomer/dimer ratio is highest at 110°, close to the boiling point of toluene. We suggest that catalyst **1a** tends to dimerize more easily than catalyst **1b** because of the different substituents at the B-atom. The electron-donating MeO group in **1b** decreases the *Lewis* acidity of the B-atom so that it cannot coordinate with the N-atom of another molecule, thus preventing **1b** from dimerizing. That is the reason why chiral 1,3,2-

oxazaborolidines substituted at the B-atom by an electron-rich alkyl, aryl, or alkoxy group usually show better enantioselectivities than the corresponding *B*-unsubstituted chiral 1,3,2-oxazaborolidines under reduction conditions (*cf.* also [3]).

Thus, we presumed that, energetically, the dimer **3**, as suggested by *Nevalainen* on the basis of quantum-chemical calculations [10], should be the most-favored one of the possible dimers, rather than dimer **4** (*Scheme 2*), which is still a chiral reducing reagent and could also reduce ketones asymmetrically. Thus, **3** should be one of the active species in the asymmetric reduction. The equilibrium between monomer **1** (monomer-borane complex) and the postulated dimer **3** (dimer-borane complex) in the reduction system is shown in *Scheme 2*.

Scheme 2. *Equilibrium between the Monomer* (monomer-borane complex) *and the Postulated Dimer* (dimer-borane complex)



To interpret the abnormal effect of temperature on the enantioselectivity in the reduction, we decided to determine the monomer/dimer ratios for catalysts **1a** and **1b** at different temperatures. ^{11}B-NMR Tracing experiments were designed and carried out at different temperatures; unfortunately, we could not observe clear monomer/dimer ratios for **1a** at different temperatures (25–110°) due to the complexity of the ^{11}B-NMR spectrum. Moreover, the EI-MS of **1a** showed a monomer peak at *m*/*z* 111 and a dimer peak at *m*/*z* 222. For catalyst (**1b**), only one ^{11}B-NMR signal was observed at 8.13 ppm, which should arise from monomeric **1b**; no dimer was detected in the reducing system. The ^{11}B-NMR results are in accordance with our rationale mentioned above.

Buono and co-workers reported that L-proline could also be used as a catalyst in asymmetric borane reduction of ketones and found that enantioselectivity increased with increasing reduction temperature [5a]. These authors and the *Martens* group also found that L-proline always gave lower enantioselectivities than L-prolinol in the asymmetric reduction [5a][8]. Another factor affecting the enantioselectivity is the amount of catalyst in the reduction mixture, which depends on the amount of L-prolinol. The latter is related to the conversion of L-proline in the reduction system. Thus, we determined the conversion rate of L-proline to L-prolinol at different temperatures in the presence of 1.5 or 10 equiv. of borane, which are related to the amounts of borane in the preparation of catalysts and reduction of ketone, respectively (*Figs. 3* and *4*). The results established increasing conversion rates with increasing temperature or amount of borane. L-Proline seems to be an inactive species in the catalytic reduction but L-proline could also be used as a catalyst in the asymmetric borane reduction of ketones because it is reduced to L-prolinol. However, L-proline always gave lower enantioselectivity than L-prolinol in asymmetric reductions, due to

its incomplete reduction. Nevertheless, its induced enantioselectivity increased with increasing reduction temperature because the reduction rate of L-proline increased with increasing temperature.

Our results established that the enantioselectivities reported by *Martens* and co-workers are reliable, and (5*S*)-2-methoxy-3-oxa-1-aza-2-borabicyclo[3.3.0]octane (**1b**) shows indeed a better enantioselectivity than (5*S*)-3-oxa-1-aza-3-borabicyclo[3.3.0]octane (**1a**). However, the enantioselectivities induced by both **1a** and **1b** are not as good as those reported by *Buono* and co-workers [5a].

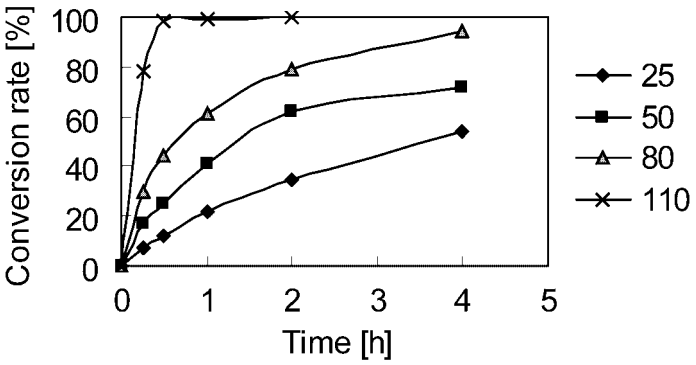


Fig. 3. *Conversion of* L-*proline to* L-*prolinol with 1.5 equiv. of borane at different temperatures*

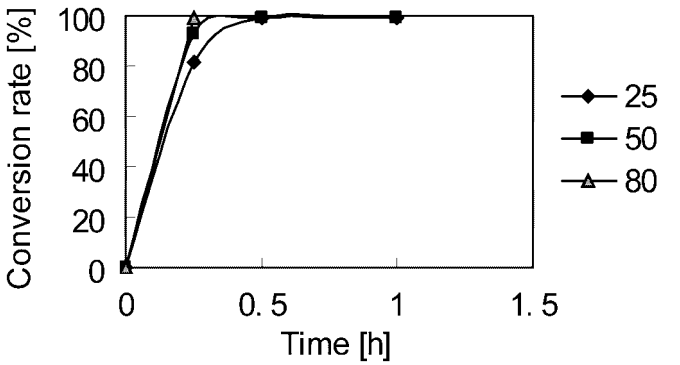


Fig. 4. *Conversion of* L-*proline to* L-*prolinol with 10 equiv. of borane at different temperatures*

3. Conclusions. – In conclusion, the effect of temperature on the enantioselectivity of the asymmetric borane reduction of acetophenone catalyzed by the *B*-unsubstituted (5*S*)-3-oxa-1-aza-2-borabicyclo[3.3.0]octane (**1a**) and its *B*-methoxy-substituted derivative **1b**, which are derived from L-prolinol with borane and trimethyl borate, respectively, was investigated. The results indicate that the enantioselectivity in the presence of **1a** increases with increasing temperature, which represents an abnormal effect of temperature on the enantioselectivity, while that of **1b** shows the highest enantioselectivity around 50°. The different temperature-dependent enantioselectiv-

ities were caused by the different substituents at the B-atom of the catalysts. The *B*-unsubstituted **1a** tends to dimerization, which is not observed for the *B*-methoxy-substituted **1b**.

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Experimental Part

1. *General.* Trimethyl borate and the borane·dimethyl sulfide complex were purchased from *Acros Organics*. Toluene was heated under reflux over Na and distilled prior to use. CC = Column chromatography. HPLC: *HP-1100* HPLC equipment, e.e. values: *Chiralcel OD* column (4.6 × 250 mm), eluent hexane/^{i}PrOH 9 :1, flow 0.5 ml/min, detection at 228 nm; conversion rates of L-proline to L-prolinol: *Vydac RP-C18* column (4.6 × 250 mm) eluent H_2O/MeOH 9 :1, flow 1.0 ml/min, detection at 214 nm. NMR spectra: *Mercury Plus-300* (300 MHz) spectrometer; $CDCl_3$ solns. with $SiMe_4$ as an internal standard for ^1H and ^{13}C; in toluene solns. with $BF_3 \cdot Et_2O$ (47%) as external standard for ^{11}B; chemical shifts δ in ppm.

2. *Asymmetric Reduction of Acetophenone by Using (5S)-2-Methoxy-3-oxa-1-aza-2-borabicyclo[3.3.0]octane* (**1b**): *General Procedure.* To a soln. of L-prolinol (5.1 mg, 0.05 mmol) in dry toluene (2.5 ml) was added trimethyl borate (6.0 mg, 0.06 mmol), and the mixture was stirred under N_2 at r.t. for 2 h. After the addition of 2M $BH_3 \cdot Me_2S$ in THF (0.25 ml, 0.5 mmol), a soln. of acetophenone (60 mg, 0.5 mmol) in dry toluene (2.5 ml) was added dropwise at the desired temp. with 0.5 h. The resulting mixture was stirred at the same temp. until the acetophenone was consumed (GLC monitoring). The resulting mixture was quenched with MeOH in an ice-water bath and evaporated. The residue was purified by CC (siliga gel, petroleum ether (60 – 90°/AcOEt 5 :1)): chiral α-methylbenzenemethanol. Colorless oil.

3. *Asymmetric reduction of Acetophenone by Using (5S)-3-Oxa-1-aza-2-borabicyclo[3.3.0]octane* (**1a**). *General Procedure.* To a soln. of L-prolinol (5.1 mg, 0.05 mmol) in dry toluene (2.5 ml) was added 2M $BH_3 \cdot Me_2S$ in THF (38 µl, 0.075 mmol), and the mixture was stirred under N_2 at 45° for 14 h or 110° for 15 min. After the mixture was adjusted to the desired temp. and after the addition of 2M $BH_3 \cdot Me_2S$ in THF (0.25 ml, 0.5 mmol), a soln. of acetophenone (60 mg, 0.5 mmol) in dry toluene (2.5 ml) was added dropwise within 0.5 h. The mixture was stirred until the acetophenone was consumed (GLC monitoring). Workup and purification as described in *Exper. 2:* chiral α-methylbenzenemethanol.

4. *Asymmetric reduction of Acetophenone by Using the Catalyst* **1a** *Generated from* L-*Proline. General Procedure.* L-Proline (5.75 mg, 0.05 mmol) was suspended in dry toluene (2.5 ml), and 2M $BH_3 \cdot Me_2S$ in THF (38 µl, 0.075 mmol) was added *via* syringe under N_2. The mixture was stirred at r.t. for 10 min and then heated to reflux (110°) for 0.5 h. After the mixture was cooled to the desired temp. and after the addition of 2M $BH_3 \cdot Me_2S$ in THF (0.25 ml, 0.5 mmol), a soln. of acetophenone (60 mg, 0.5 mmol) in dry toluene (2.5 ml) was added dropwise within 0.5 h. The mixture was stirred until the acetophenone was consumed (GLC monitoring). Workup and purification as described in *Exper. 2:* chiral α-methylbenzenemethanol.

5. *Conversion Rate of the Reduction of* L-*Proline by Using Borane. General Procedure.* L-Proline (5.75 mg, 0.05 mmol) was suspended in dry toluene (2.5 ml), and 2M $BH_3 \cdot Me_2S$ in THF (38 µl, 0.075 mmol; or 0.25 ml, 0.5 mmol) was added *via* a syringe under N_2. The mixture was stirred, and a sample (25 µl) of the soln. was taken periodically by syringe, quenched with MeOH (2 ml), and the resulting soln. (20 µl) analyzed by HPLC (*C18*, H_2O/MeOH 9 :1). The remaining reduction mixture was kept stirring to complete reduction. A sample (25 µl) of the final soln. was diluted with MeOH (2 ml) and analyzed as described above. The conversion rate was calculated with the following equation: Conversion rate = (absorbance of the sample at the indicated time)/(absorbance of the complete reduction sample) · 100%.

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