Pergamon

Tetrahedron: *Asymmetry* 11 (2000) 2263–2266

TETRAHEDRON:
*ASYMMETRY*

# Asymmetric reduction of acetophenone over heterogeneous oxazaborolidine catalysts

Karine Molvinger, Monique Lopez and Jean Court*

*LEDSS.CNRS (UMR 5616) et Université Joseph Fourier, BP 53, 38041 Grenoble, France*

Received 26 April 2000; accepted 11 May 2000

---

**Abstract**

The reduction of acetophenone over the heterogeneous catalyst $NiB_{2-0.1}$(oxazaborolidine)$_{0.1}$ by borane in THF at 273 K is quicker than in homogeneous phase. The catalyst presented high enantioselectivity (ee $\geq$90%) at low molar ratio provided the ketone was added very slowly to the catalyst and borane complex.

---

The borane reduction of ketones catalyzed by 1,3,2-oxazaborolidines is a very efficient homogeneous process for the preparation of secondary alcohols with very high enantiomeric excesses.[1] Excellent results have been reported by Quallich[2] using (1*S*,2*R*)-2-amino-1,2-diphenylethanol, since one face of the catalyst is shielded due to the orthogonal arrangement of the phenyl substituents. After hydrolysis the separation of the alcohol product from the catalyst precursor can be difficult. In order to solve this problem, some researchers have described the synthesis of polymer-bound β-amino alcohols,[3] polymer-supported boron-bound oxazaborolidines[4,5] and polymer enlarged oxazaborolidines in a membrane reactor.[6] In an approach to combining the advantages of heterogeneous and homogeneous catalysis, i.e. the ease of separation and the high stereoselectivity, we prepared oxazaborolidines supported on nickel-boride particles. The heterogeneous catalysts $NiB_{2-0.1}$(oxaza)$_{0.1}$ were obtained by reacting nickel-boride $NiB_2$[7] with 0.1 mol of (1*S*,2*R*)-(+)-2-amino-1,2-diphenylethanol (catalyst A) or with 0.1 mol (1*R*,2*S*)-(–)-norephedrine (catalyst B). The catalysts A and C were prepared by the same procedure but, whereas the catalyst A was obtained starting from $NiI_2{\cdot}6H_2O$, $NiCl_2{\cdot}6H_2O$[8] was used for the catalyst C.

In a previous communication[9] we showed that the reduction of substituted acetophenones using borane–THF as the reducing agent in the presence of 1 equivalent of nickel-bound oxazaborolidine, i.e. in stoichiometric conditions, proceeds with high enantioselectivity. Here we report the reduction of acetophenone in catalytic conditions and some kinetic points in order to show that we have got a real heterogeneous catalyst.

---

* Corresponding author.

PII: S0957-4166(00)00191-9

We assume that the oxazaborolidine is strongly bound to the nickel-boride nano-particles, since by TLC, no traces of the amino alcohol could be detected in the liquid phase after reduction. However, the nature of the bond between the oxazaborolidine and the nano-particle is not known and the scission of this bond, resulting in a homogeneous reaction, cannot be excluded, whereupon the reduction would be homogeneous. In order to shed light on the nature of the reduction (heterogeneous or homogeneous) we carried out two reductions in the same conditions (solvent, amino alcohol, ratio oxazaborolidine/acetophenone, ratio $BH_3$/acetophenone, temperature, etc.).[10] The measured acetophenone and 1-phenylethanol concentration plotted against time is given in Fig. 1.

The first graph (Fig. 1(a)) shows the reduction of acetophenone by borane and the 4,5-diphenyl-1,3,2-oxazaborolidine in homogeneous phase in THF at 273 K under inert atmosphere.

The second (Fig. 1(b)) shows the same experiment in the same conditions but in heterogeneous phase. The heterogeneous reduction is much quicker. Even a second utilization of the same catalyst after three THF washings is quicker than in the homogeneous phase.

The oxazaborolidine formed initially at the surface of the particle cannot be totally dissolved during the first use since the catalyst can be reused; thus, if the oxazaborolidine particle bond was broken, the oxazaborolidine concentration in THF would be lower in the heterogeneous reduction than in the homogeneous one and the rate would be smaller in the heterogeneous reduction than in the homogeneous one. We observed exactly the opposite, thereby demonstrating the heterogeneous nature of our catalyst system.

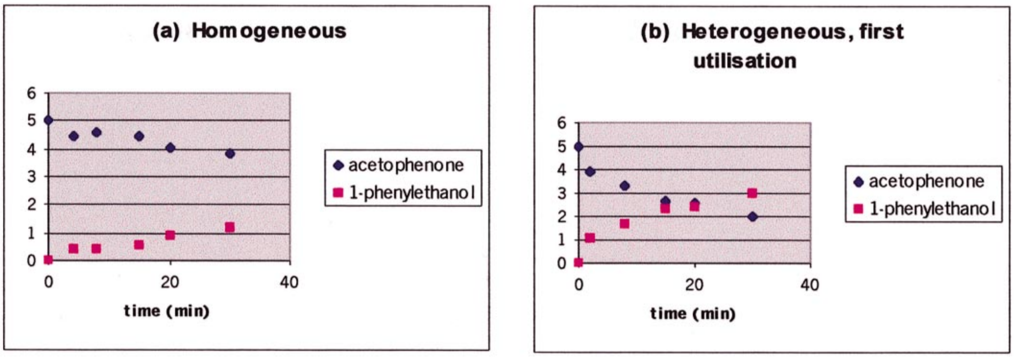

Figure 1. Product distribution versus time for the reduction of acetophenone (◆) by borane–THF into 1-phenylethanol (●) catalyzed by the oxazaborolidine in THF (a) and by the catalyst $NiB_{2-0.1}(oxaza)_{0.1}$ in suspension in THF (b)

The catalytic reduction (reaction procedure II)[11] was carried out at 323 K, by adding the ketone very slowly to the catalyst and borane complex. No acetophenone was detected by GLC analysis of samples withdrawn from the reaction mixture during the addition and at the end of the addition. Thus, despite of the presence of 'free $BH_3$', i.e. not complexed with the oxazaborolidine catalyst, the uncatalyzed reduction was minimized and the ees observed for the first and second reduction are as high as those obtained in stoichiometric conditions (Table 1). The influence of adding the ketone very slowly to the catalyst and borane source is known in homogeneous reduction.[12]

It has been shown[6] that using polymer-enlarged oxazaborolidines which are homogeneously soluble, the catalyzed reduction shows Michaelis–Menten type kinetics for the ketone ($K_M = 2.8$ mmol/$L^{-1}$) whereas the uncatalyzed reaction proceeds in the first order with respect to ketone and

Table 1
Enantioselectivity in the reduction of acetophenone by $BH_3$ and the nickel–oxazaborolidine catalyst and reuse of this catalyst

| Catalyst | Mol % of catalyst | Reaction procedure | alcohol | ee 1st reduction | ee 2nd reduction | ee 3rd reduction |
|---|---|---|---|---|---|---|
| A | 100 | I | *S* | 94 | 91 | 91 |
| A | 10 | II | *S* | 94 | 91 | 82 |
| B | 100 | I | *R* | 92 | 90 | 90 |
| B | 10 | II | *R* | 91 | 89 | 81 |
| C | 10 | II | *S* | 93 | 91 | 83 |

Catalyst A: $NiI_2$, $6H_2O$ → $NiI_2$ + $LiBH_4$ → $NiB_2$ + (1*S*, 2*R*)-(+)-2-amino-1,2-diphenylethanol → A

Catalyst B: $NiI_2$, $6H_2O$ → $NiI_2$ + $LiBH_4$ → $NiB_2$+(1*R*, 2*S*)-(-)-norephedrine → B

Catalyst C: $NiCl_2$, $6H_2O$ → $NiCl_2$+$LiBH_4$ → $NiB_2$+(1*S*,2*R*)-(+)-2-amino-1,2-diphenylethanol → C

borane; i.e. the catalyzed initial rate is almost constant when the acetophenone concentration is $\geq 30$ mmol $L^{-1}$ while the rate of the uncatalyzed reaction increases with the acetophenone concentration. Thus, the lower the acetophenone concentration is, the better the resulting ee is. Since the heterogeneous reduction is quicker than in homogeneous phase, the competing uncatalyzed reduction yielding the racemate is less important, and the observed ee with the catalyst A is higher than in homogeneous reduction[13] (94 and 91% versus 89%). The enantioselectivity observed with the oxazaborolidine derived from norephedrine is also higher in the heterogeneous condition than in the homogeneous one: ee = 91 and 89% versus 86% obtained with 30 mol% of catalyst.[4] This observation is important for an application in a larger scale since norephedrine is ten times cheaper than (1*S*,2*R*)-(+)-2-amino-1,2-diphenylethanol. The catalysts A and C prepared from $NiI_2 \cdot 6H_2O$ and $NiCl_2 \cdot 6H_2O$ present the same catalytic properties.

In summary, the reaction of β-amino alcohol with nickel-boride ($NiB_2$) affords oxazaborolidine anchored to nano-particles, which is an example of a heterogenized homogeneous catalyst with heterogeneous rate exceeding homogeneous value and at least equal enantioselectivity. Both enantiomers of the two amino alcohols used are commercially available and are comparably priced, thus both enantiomeric alcohols can be obtained.

## Acknowledgements

We thank Region Rhone Alpes for support.

## References

1. Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 1986.
2. Quallich, G. J.; Woodall, T. M. *Tetrahedron Lett.* **1993**, *34*, 4145.
3. Itsuno, S.; Ito, K.; Hirao, A.; Nakahama, S. *J. Chem. Soc., Perkin Trans. 1* **1984**, 2887.

4. Caze, C., El Moualij, N., Hadge, P., Lock, C. J., Ma, J. *J. Chem. Soc., Perkin Trans. 1* **1995**, 345.
5. Franot, C.; Stone, G. B.; Engeli, P.; Spondlin, C.; Waldvogel, E. *Tetrahedron: Asymmetry* **1995**, *6*, 2755.
6. Giffels, G.; Beliczey, J.; Felder, M.; Kragl, U. *Tetrahedron: Asymmetry* **1998**, *9*, 691.
7. Molvinger, K.; Lopez, M.; Court, J. *J. Mol. Catal.* **1999**, *150*, 267.
8. Nickel chloride ($NiCl_2 \cdot 6H_2O$) cannot be totally dried in a desiccator for 48 h at room temperature under vacuum over zeolite 4 Å freshly dehydrated at 600 K as observed with $NiI_2 \cdot 6H_2O$; a further heating at 353 K under vacuum for 12 h was necessary. Note that commercial $NiI_2$, even 'dried' before use, does not afford as good results as $NiI_2 \cdot 6H_2O$ after drying. We attribute this observation to a texture difference as, after drying, $NiI_2 \cdot 6H_2O$ is a pulverulent powder which is more easily dissolved in THF than $NiI_2$.
9. Molvinger, K.; Lopez, M.; Court, J. *Tetrahedron Lett.* **1999**, *40*, 8375.
10. Reactions were carried out at 273 K. Borane–THF (1 M, 5 mmol) was added to a stirred suspension of $NiB_{2-0.1}(oxaza)_{0.1}$ (0.6 mmol) in 15 mL of THF or to a solution of 4,5-diphenyl-1,3,2-oxazaborolidine (0.6 mmol) in 15 mL THF. After 1 min, acetophenone (5 mmol) was added at once. From time to time, samples (0.2 mL each) were taken, transferred to test tubes, immediately quenched with methanol (1 mL) stirred for 2 h and analyzed by gas chromatography. The conditions for the measurements were as follows: a packed column (4 m×1/8 in) with OV 210 10%+XE 60 5% on chromosorb WHP 80/100 under a temperature of 383 K. Tetradecane was used as internal standard.
11. Procedure II: Borane–THF (1 M, 9 mmol) was added to the stirred suspension of $NiB_{2-0.1}(oxaza)_{0.1}$ (9 mmol) in 100 mL of THF at 323 K under nitrogen. After 30 min the ketone (0.9 mol $L^{-1}$ in THF; 10 mL, 9 mmol) was added very slowly (0.083 mL $min^{-1}$). Five minutes after the end of the addition the solids were allowed to settle and the liquid phase was removed through a transfer tube by means of a pressure differential, the catalyst being left in the flask for reuse, after three washings with THF. The liquid phase was diluted with 2 M HCl and extracted with ethyl acetate, which was then washed with saturated aqueous NaCl, dried, and evaporated. The enantiomeric purity of the 1-phenylethanol was determined by capillary GC with a chiral column (hydrodex β cyclodextrin, 25 m×0.25 mm (Machery–Nagel)). Procedure I: Borane–THF (1 M, 0.9 mmol) was added to a stirred suspension of $NiB_{2-0.1}(oxaza)_{0.1}$ (9 mmol) in 100 mL of THF at room temperature under nitrogen. After 30 min the ketone (0.9 mmol) was added at once and stirring was continued at room temperature until the reaction was complete (GLC analysis usually 2–2.5 h). The work-up is the same as in procedure II.
12. Mathre, D. J.; Thompson, A. S.; Douglas, A. W.; Hoogsteen, K.; Carroll, J. D.; Corley, E. G.; Grabowski, E. J. J. *J. Org. Chem.* **1993**, *58*, 2880.
13. Jiang, Y.; Qin, Y.; Mi, A.; Huang, Z. *Tetrahedron: Asymmetry* **1994**, *5*, 1211.