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New heterogeneous catalyst for enantioselective borane reduction of ketones: phosphinamide anchored to nickel boride

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Abstract

A new example of heterogenization of a homogeneous catalyst by anchoring the chiral molecule to nickel boride is reported. The enantioselectivity in the reduction of acetophenone reaches that reported under homogeneous conditions.

While heterogeneous catalysis is important in many fields of chemistry, there are only a few examples of this technique in the production of optically active molecules. Heterogenization of a homogeneous catalyst is an approach which attempts to combine high enantioselectivity (homogeneous catalysis) and the ease of separation (heterogeneous catalysis). One strategy involves tethering the homogeneous catalyst to an inorganic or organic surface directly or via a spacer. Recently, we prepared nanoparticles of nickel boride (NiB_2) by reducing nickel iodide with lithium borohydride[1] and we showed that β-aminoalcohols react with boron to afford an oxazaborolidine which is strongly anchored to the surface of the particles. The chiral 1,3,2-oxazaborolidines built on the surface are highly effective catalysts[2] for the enantioselective reduction of ketones to chiral secondary alcohols by borane, as is well known under homogeneous conditions.[3]

A recent review[4] highlights the interest in asymmetric catalysis of phosphinamides and related materials containing the N–P=O structural unit. These catalysts were used in the asymmetric reduction of ketones by borane and in the asymmetric C–C bond forming reaction. Below we describe the fixation of a phosphinamide on nickel boride, which gives a high surface area, using elemental boron as an anchoring agent. We also report the catalytic properties of these solids in the borane reduction of acetophenone.

We took the (*R*)-(+)-*N*-(1-phenylethyl) *P*,*P*-diphenylphosphinamide **1** (Scheme 1) as a model since the properties of this homogeneous catalyst in the enantioselective reduction of ketones have been described in detail by Wills et al.[5–7] This compound dramatically accelerates the reduction of acetophenone but with moderate enantioselectivity (ee = 26%).

We anticipate that the amino function would act as an anchor by reacting with elemental boron on the NiB_2 surface, since we observed previously that the hydroxy group and the amino

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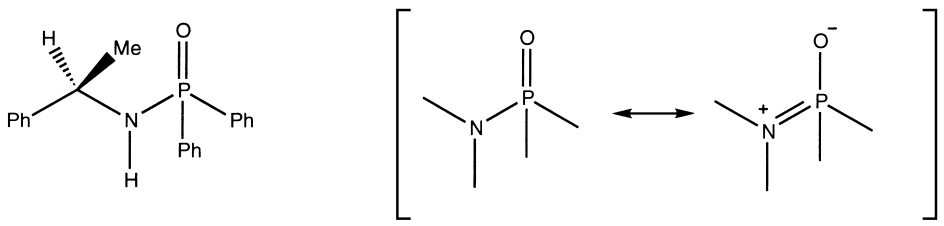

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Scheme 1.

group of β-aminoalcohol react with boron atoms, evolving 1 mol of hydrogen for each mol of aminoalcohol to afford an oxazaborolidine strongly anchored at the surface of the particles.[1] However, the oxygen atom might be a second anchoring site since its electron donor character (Scheme 1) is well established.[4,5]

No hydrogen evolution was observed either by adding a solution of **1** in THF to the stirred suspension of NiB_2 or by heating the reaction mixture under reflux. G.l.c. showed no traces of the phosphinamide could be detected in the solvent, provided that the molar ratio phosphinamide/boron was 0.0225 or lower.[8,9] Therefore, **1** is chemisorbed on NiB_2 and a strong interaction of the electron rich oxygen atom with a boron atom is the most likely explanation.

As a catalyst for the reduction of acetophenone by borane,[10] the solid thus obtained affords enantiomeric excesses close to those reported in homogeneous conditions (Table 1). The phosphinamide is strongly bonded to the particles. Two observations sustain this assertion:

- first, no traces of **1** could be detected in the liquid phase after reduction; and
- second, the catalyst can be recycled with little or no loss of performance.

Table 1
Heterogeneous asymmetric reduction of acetophenone over phosphinamide anchored on NiB_2

Entry	Ph./B[1] (mol %)	Cat/ketone (mol %)	T (K)	Solvent[2]	Borane reagent	BH_3/ketone	Enantiomeric excess (%)[4] 1st red.	2nd red.	3rd red.
1	2.25	5	293	THF	BH_3,THF	0.6	19.7	17.1	13
2	2.25	5	273	THF	BH_3,THF	0.6	19	13.9	
3	2.25	5	323	THF	BH_3,THF	0.6	10.7	8.5	
4	2.25	10	293	THF	BH_3,THF	0.6	19.5	15.9	11.8
5	2.25	2	293	THF	BH_3,THF	0.6	10.2	8.9	5.3
6	2.25	10	293	THF	BH_3,SMe_2	0.6	14.1	11.5	
7	2.25	10	293	THF	BH_3,DEA[3]	1.3	26.2	24.6	20.8
8	2.25	10	293	DCM	BH_3,THF	0.6	18.3	14.8	15.4
9	4.50	10	293	DCM	BH_3,THF	0.6	18.9	17	18.4

1 Phosphinamide / boron

2 The same solvent was used for the anchoring of the chiral molecule and for the reduction

3 BH_3, diethylaniline

4 The reduction led to the alcohol of predominantly S configuration.

A variety of reactions were carried out in order to determine the effect of various parameters on the stereochemical course of the reaction, and the results are summarized in Table 1.

Effect of the temperature: An increase in temperature results in a decrease in enantioselectivity (Entries 1 and 3) as observed in homogeneous conditions.[5] The ee remains the same when the temperature is reduced to 273 K (entry 2), whereas in homogeneous catalysis, at this temperature, the phosphinamide partially precipitates from the solution; as a result the reaction rate and the enantioselectivity decrease.[5]

Percentage of catalyst used: The results using 5 and 10 mol% of catalyst are the same, but a decrease to 2 mol% halves the enantiomeric excess (entries 1, 4 and 5). Thus, at this catalyst level, the uncatalyzed reduction is significant despite the rate acceleration of the acetophenone reduction by **1**.

Borane source (entries 4, 6 and 7): As compared with the borane–tetrahydro complex, the reduction with the borane–methylsulfide complex is much slower and less enantioselective. The best results are obtained using the borane-*N*,*N*-diethylaniline complex (entry 7, ee = 26%). Furthermore, the enantioselective properties remain high even for the third reduction. This borane source has been successfully used in oxazaborolidine-catalyzed reductions of prochiral ketones.[11] It is important to note that the uncatalyzed rate of reduction of ketones with this borane source is particularly low,[12] thus in competition with the catalyzed reaction, the unselective reduction is minimized. Furthermore, in oxazaborolidine catalyzed reductions, amines have been added to reaction mixtures to enhance the enantioselectivity, the transfer of the second hydride, which is less enantioselective, being suppressed.[13] An analogous effect might be attributed to the presence of *N*,*N*-diethylaniline. Note that the molar ratio BH_3/ketone was 1.3 instead of 0.6 for the other borane sources.

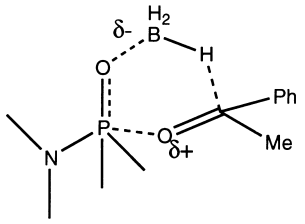
Solvent effect: Substituting dichloromethane (DCM) for THF as solvent for the anchoring of the chiral molecule and for the reduction has two beneficial effects (entries 8 and 9):

- first, twice as much phosphinamide can be anchored from DCM solution; and
- second, for the highest phosphinamide/boron ratio, the enantioselectivity obtained in the third reduction is as high as that obtained in the first reduction.

We observed previously that in the reduction of nickel iodide with sodium naphthalene, THF was strongly chemisorbed on nickel particles. Thus, we assume that the lower limit of the phosphinamide boron ratio observed in THF results from the competitive chemisorption of phosphinamide with the solvent.

As a result of the study on the effect of the parameters, it appears that the enantioselectivity under heterogeneous conditions may reach that reported in homogeneous conditions (ee = 26%). Thus, the strong interaction of the phosphinamide oxygen atom with a boron atom has little influence on the enantioselective properties of **1**. Furthermore, since the reduction gave predominantly the *S* enantiomer of 1-phenylethanol, as reported under homogeneous conditions, we assume that the Wills mechanism[5] may also stand for the heterogeneous reduction (Scheme 2).

An improvement to the phosphinamide-catalyzed reduction, through the incorporation of a proximal hydroxyl group in the catalyst, has been reported.[14–16] This hydroxyl group reacts with a NiB_2 boron atom and may be a second anchoring site for the substituted phosphinamide as reported for β-aminoalcohol[1,2] and as observed with (2*R*,3*R*)-2,3-dihydroxybutane.[17]



Scheme 2.

Heterogenization of the homogeneous reduction of ketones catalyzed with phosphinamide has been achieved: the catalyst can be easily separated from the alcohol by settling and decanting, it can be reused with almost the same performance, and furthermore its enantioselective properties are maintained even at low temperature. In conclusion, the whole study (β-aminoalcohol, phosphinamide, diol) demonstrates the great potential of the readily available nickel boride for heterogenization of enantioselective homogeneous catalysts.

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8. The phosphinamide was prepared by the reaction of (*R*)-(+)-α-methylbenzylamine with diphenylphosphine chloride (triethylamine, dichloromethane, room temperature) according to the procedure used by Wills et al.[5]
9. The phosphinamide (0.45 mmol) in solution in 5 ml of THF was added to the stirred suspension of NiB_2 (10 mmol) in THF (80 ml). After 16 h at reflux, the THF was decanted and removed. The catalyst was then washed with 80 ml of THF before use. No trace of the phosphinamide was detected by g.l.c. analysis of the solvent.
10. Borane–THF (0.6 equivalent) was added to a stirred suspension of phosphinamide bound to nickel boride in 40 ml of THF at room temperature under nitrogen. After 1 min, 1 equivalent of acetophenone was added. The mixture was stirred at room temperature until the reaction was complete (g.l.c. analysis). 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. Before reuse, the solids were washed with 80 ml of solvent. 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 product was determined by capillary GC with a chiral column (hydrodex β cyclodextrin, 25 m–0.25 mm Macherey–Nagel).
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17. (2*R*,3*R*)-2,3-Dihydroxybutane (0.45 mmol in 2 ml DCM) was added to the stirred suspension of NiB_2 (10 mmol in 80 ml DCM). After 16 h at room temperature, 0.45 mmol of hydrogen was obtained. The solid was washed with 80 ml DCM before use in the experimental conditions described for the phosphinamide.With the borane-*N*,*N*-diethylaniline as reducing agent, the catalyst gives (*S*)-1-phenylethanol with ee = 6%. The ee is low, since both oxygen atoms have similar coordinating capability to the borane. However, the catalyst can be recycled two times with no loss of performance, thus the diol is strongly bound to the nickel boride suggesting the formation of a dioxaborolidine.