Catalysis Today 138 (2008) 104–109

Contents lists available at ScienceDirect

Catalysis Today

journal homepage: www.elsevier.com/locate/cattod

Efficient new supported catalyst for asymmetric reductions

Jeremy Yune, Karine Molvinger *, Françoise Quignard

Institut Charles Gerhardt, UMR 5253 CNRS/ENSCM/UM2/UM1, Matériaux Avancés pour la Catalyse et la Santé, ≪MACS≫ - 8, rue de l'Ecole Normale, 34296 Montpellier cedex 5, France

ARTICLE INFO

Article history:
Available online 26 July 2008

Keywords:
Oxazaborolidine
Silica
Supported catalyst
Enantioselective reduction

ABSTRACT

Heterogeneous catalysis is important for fine chemistry, especially for the synthesis of optically active molecules. Here, we present a new supported catalyst: the oxazaborolidine immobilised on silica. These molecules are well known in homogeneous conditions and provide excellent activity and selectivity for the reduction of ketones. The problems of the separation of the catalyst and product and the difficult recovery of the catalyst lead us to heterogenize this system.

1. Introduction

Heterogeneous catalysis is important in many fields of chemistry, there are now numerous examples of this technique in the production of optically active molecules [1]. 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 surface directly or via a spacer [2].

Synthesizing optically active secondary alcohols has become a great challenge in organic chemistry [3]. Since their discovery by Itsuno, the oxazaborolidines [4] have become a powerful tool for the enantioselective borane reduction of ketones into chiral secondary alcohols. The mechanism has been elucitated by Corey [5]: in fact oxazaborolidine (synthesized from amino alcohol) forms a complex with the borane and this complex reduces rapidly the ketones with excellent yields and enantiomeric excesses. Excellent results have been reported by Quallich using (1*S*, 2*R*)-2-amino-1,2-diphenylethanol, since one face of the catalyst is shielded due the orthogonal arrangement of the phenyl substituents [6]. As it has been shown, the major problems of this system are the difficult separation of the catalyst/product and the re-use of this catalyst. In order to solve this problem, Itsuno synthesized polymer-bound β-amino-alcohols [7]. Later, Stone [8] and Caze [9] immobilised oxazaborolidines on polyethylene. Good enantiomeric excesses were obtained but the mechanical resistance of the support was deficient. Molvinger et al. [10] grafted the oxazaborolidines on metallic surface (nickel). The system was efficient and presented a great mechanical resistance. The only disadvantage was the small surface area of the support (110 m^2/g). The use of silica can provide a higher surface area and lead to better catalytic results.

Here we describe the immobilisation of oxazaborolidines on silica and its use for the enantioselective reduction of acetophenone.

2. Experimental

2.1. Materials

Amino silica was purchased to Fluka, 4-formylphenylboronic acid, (1*S*,2*R*)-(+)-2-amino-1,2-diphenylethanol, acetophenone, dodecane, borane were purchased from Aldrich and used as received.

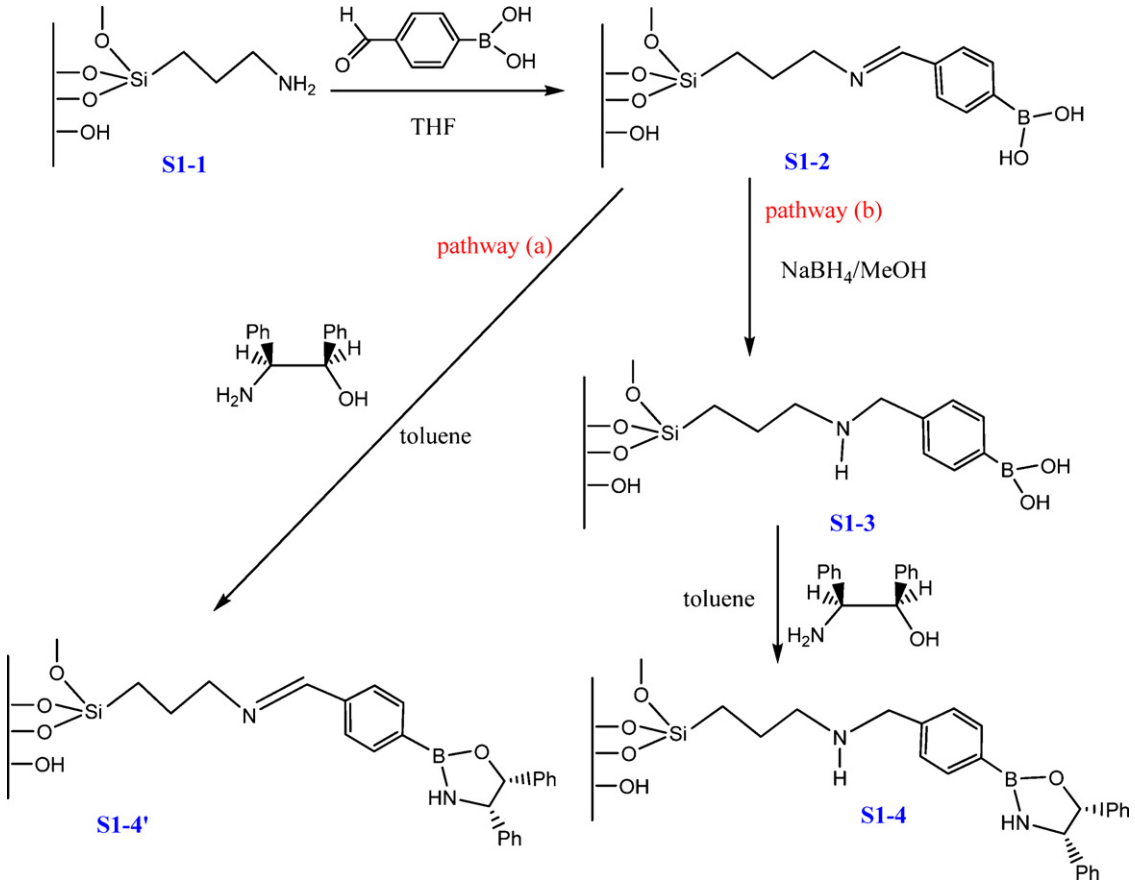
THF was distilled under argon on sodium/benzophenone. Toluene was distilled under argon on sodium.

2.2. Techniques

- Nitrogen sorption isotherms at 77 K were obtained with a Micromeritics ASAP 2010 apparatus. The surface areas (S_{BET}) were determined using BET equation. Prior to measurement, the samples were outgassed for 8 h at 120 °C. The *C* parameter is obtained by the mathematical treatment of the BET equation.
- DRIFT spectra were performed on Bruker vector 22.

* Corresponding author. Tel.: +33 467163443; fax: +33 467163470.
E-mail address: karine.molvinger@enscm.fr (K. Molvinger).

0920-5861/$ – see front matter © 2008 Elsevier B.V. All rights reserved.
doi:10.1016/j.cattod.2008.06.009



Scheme 1. The two pathways to synthesize the supported oxazaborolidine.

2.3. Preparation of the catalysts

The supported catalysts were prepared in several steps, by two pathways (Scheme 1).

Step 1: 1 g of amino silica (1.8 mmol of NH_2/g of silica) is activated at 120 °C under vacuum for 3 h. After cooling the silica under nitrogen flux, 0.271 g of 4-formylphenylboronic acid (1.8 mmol) dissolved in THF (50 mL) is added and heated to reflux for 24 h. Then the solid is filtered with THF (3× 20 mL), CH_2Cl_2 (3× 20 mL) and then with diethylether (3× 20 mL). The solid is washed with a soxhlet apparatus for 24 h (dichloromethane/diethylether = 1/1). Then, the solid is dried at 70 °C for 3 h (S1-2).

For pathway (a), the imine (S1-2) formed is not reduced and is directly used to form the oxazaborolidine (S1-4′).

Step 2: Reduction of the imine. 1 g of S1-2 (0.578 mmol/g of silica) is activated at 120 °C under vacuum for 3 h. After cooling the silica under nitrogen flux, 0.239 g of $NaBH_4$ (5.78 mmol) dissolved in methanol (50 mL) in an ice bath is added and stirred for 12 h. The mixture is hydrolysed by adding ice. The solid is filtered and washed with methanol (2× 100 mL), with dichloromethane (2× 100 mL) and then with diethylether (2× 100 mL) and washed in a soxhlet apparatus (dichloromethane/diethylether = 1/1) for 24 h. Then, the solid is dried at 70 °C for 3 h (S1-3).

Step 3: Formation of the oxazaborolidine. 1 g of S1-3 (0.285 mmol/g of silica) is activated at 120 °C under vacuum for 3 h. Under inert atmosphere, 20 mL of toluene and 0.06 g of (1*S*,2*R*)-(+)-2-amino-1,2-diphenylethanol (0.285 mmol) dissolved in toluene (5 mL) are added to the silica and left 4 days at reflux temperature. The apparatus is equipped with a Dean–Stark in order to recover the water formed during the reaction. The solid is filtered under argon and washed with reflux toluene for 1 h for removing the excess of amino alcohol. These filtration and washing are done three times. A last washing is done by dry THF (S1-4). For pathway (a), no toluene washing is done, just a washing by THF has been done (S1-4′).

2.4. Catalytic test

0.31 g of catalyst S1-4 (0.073 mmol of oxazaborolidine grafted) is activated at 120 °C for 3 h. Under argon atmosphere, 20 mL of THF is added, followed by 0.5 mL (0.5 mmol) of BH_3 (1 M in THF). Acetophenone (85 μL, 0.73 mmol) is added slowly to the mixture. At the end of the reaction, the liquid phase is recovered after filtration under inert atmosphere, diluted with 2 M HCl and extracted with ethyl acetate. The enantiomeric excess is determined by gas chromatography (GC) with a varian 3900 equipped with a chiral column Restek Rt-βDEX (length 30 m, diameter 0.32 mm, film thickness 0.25 μm). A pre-column SGE (length 2 m, diameter 0.32 mm) is installed. The injector and detector temperatures are 200 °C and 220 °C. The temperature program is 90 °C for 3 min followed by a ramp from 90 °C to 120 °C (1 °C min^{-1}) then to 150 °C (10 °C min^{-1}), then a plateau for 3 min at 150 °C.

Table 1
Textural properties of the materials

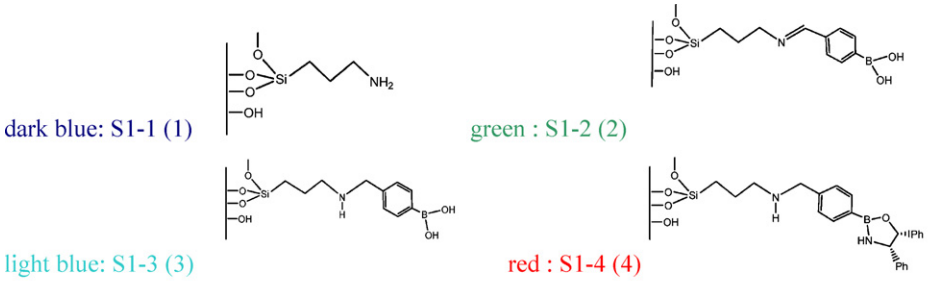
Samples	S_{BET} (m^2/g)	V_{pore} (cm^3/g)	C parameter
S1-1	366	0.5	37
S1-2	284	0.41	42
S1-3	279	0.42	41
S1-4	151	0.23	33
S1-4′	128	0.25	38

3. Results and discussion

The immobilisation of oxazaborolidine on silica is performed by two ways, including 2 or 3 steps. Firstly, 4-formylphenyl boronic acid reacts on a commercial amino-silica S1-1 to form an imine bond S1-2, eventually reduced by sodium borohydride to give S1-3 (pathway (b)). The supported oxazaborolidine S1-4′ and S1-4 are synthesized from the reaction of boronic acid with the amino alcohol S1-2 (pathway (a)) and with the amino alcohol S1-3 (pathway (b)) respectively (Scheme 1).

The solids obtained after each step of the synthesis are characterized by nitrogen adsorption/desorption, DRIFT and elementary analysis.

For both pathways, the surface area of the solids, determined by nitrogen adsorption/desorption isotherms, decreases after each step as the amount of the organic species grafted on the silica increases. For the same reason, a decrease in the pore volume is



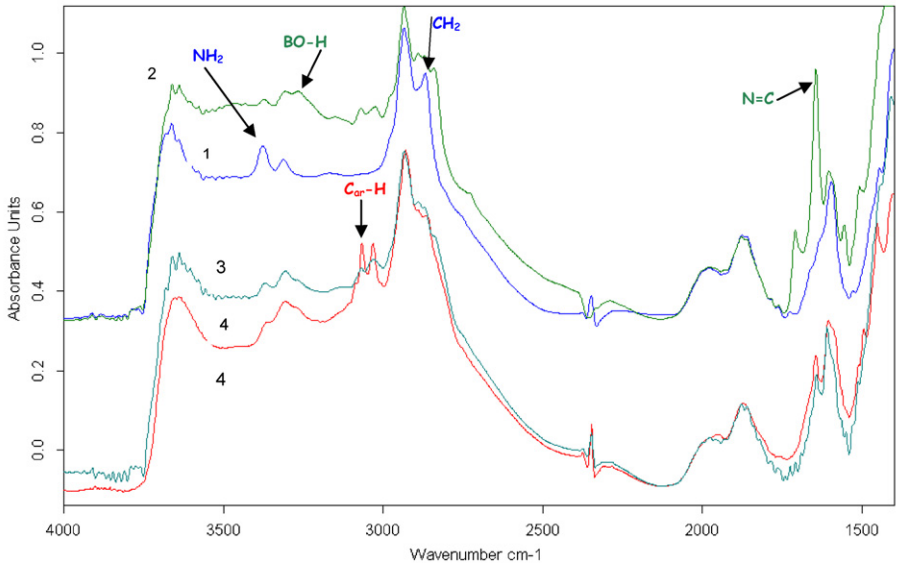
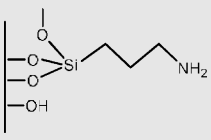
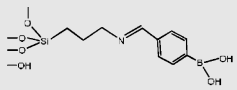
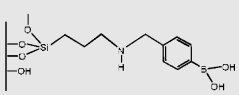
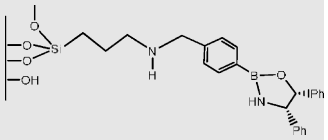
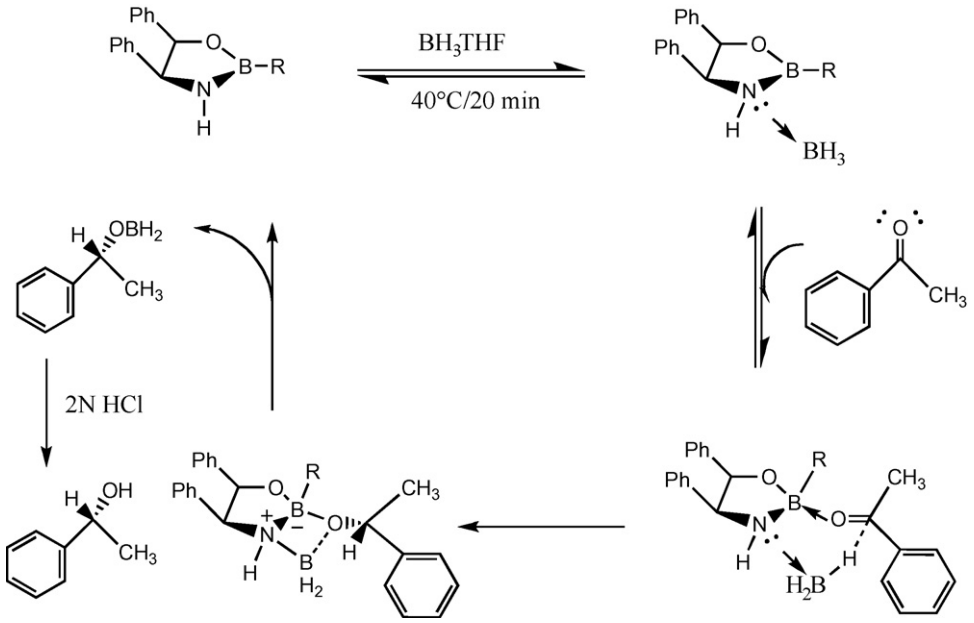


Fig. 1. DRIFT of the four solids (pathway b). For interpretation of the references to colour in this figure legend, the reader is referred to the web version of the article.

Table 2
Loading of each step of the synthesis determined by elementary analyses

Samples	Species on the surface		
		 	
S1-1	1.26 mmol/g		
S1-2	0.47 mmol/g (37%)[a]	0.79 mmol/g (63%)[a]	
S1-3	0.42 mmol/g (37%)[a]	0.73 mmol/g (63%)[a]	
S1-4	0.42 mmol/g (37%)[a]	0.5 mmol/g (43%)[a]	0.23 mmol/g (20%)[a]

[a] yield of the reaction.



Scheme 2. Mechanism of the ketone reduction by the system oxazaborolidine/BH_3 in homogeneous conditions.

observed. The values of the *C* parameter of these materials are given in Table 1. C_{BET} parameter, was calculated using the Brunauer–Emmett–Teller model [11] in which $C_{BET} = \alpha \exp[(E_1 - E_L)/RT]$, where E_1 is the interaction energy between the surface and the first adsorbed layered of polarizable nitrogen molecule and E_L is the adsorption energy of nitrogen on the follower layers estimated to be the nitrogen liquefaction energy. Hence, C_{BET} coefficient has been associated to the surface polarity considering the interaction energy E_1 between the surface and the first adsorbed layered of polarizable nitrogen molecule, but without taking into account the lateral intermolecular interaction [12]. The values of the *C* parameters increase for S1-2 and S1-3, probably due to the polarity of the grafted organic species (B-OH) and decrease for S1-4 and S1-4′ which are less polar (Table 1).

The DRIFT analysis allows a rapid and easy way to obtain qualitative informations about the formation of grafted species for each step of the synthesis. Fig. 1 shows the spectra of the 4 products.

The bands at 3378 and 3317 cm^{-1}, characteristic of $\nu(NH_2)$ are present on the spectra of the amino silica (dark blue) and are still visible after the grafting of the organic species, certified the presence of residual amine groups on the surface. The bands at 3300 and 3262 cm^{-1}, characteristic of ν(B-OH) appear on the spectra of S1-2 (green) proving the grafting of the formylphenylboronic acid and disappear on S1-3 and S1-4. The bands at 3070 and 3028 cm^{-1} on the spectra of S1-4 (red), characteristic of ν(C-H aromatic) attest the grafting of the 2-amino-1,2-diphenylethanol. The band at 1646 cm^{-1} proves the formation of the imine bound during the first step. We can note that even after reduction of the imine, a small quantity of imine remains. The IR spectra show bands at 1708 and 2730 cm^{-1} corresponding to $\nu(C=O)$ of the formylphenylboronic acid. After washing by the soxhlet apparatus, these two bands disappear, confirming that the formylphenylboronic acid was physisorbed on the silica surface. The DRIFT proves that some amino groups remain after the formation of the imine. The formation of the oxazaborolidine is confirmed by the presence of a band at 1452 cm^{-1} characteristic of ν(B-N).

The loading of each solid is determined by elementary analyses (Table 2). The successive reactions are not completed although many attempts were performed in order to optimize each step of the synthesis. The yields are reported in Table 2.

In order to test the efficiency of the supported oxazaborolidine material, the asymmetric reduction of acetophenone is considered. In homogeneous condition, the mechanism has been elucidated by Corey [5] (Scheme 2). The key points of this mechanism are:

- the complexation of the borane on the nitrogen of the oxazaborolidine,
- the complexation of the carbonyl of the ketone on the bore of the oxazaborolidine. This is oriented by two factors:
  - o the two phenyl groups prevent the approach of the ketone on this side,
  - o the R group on the bore of the oxazaborolidine constitutes a steric hindrance, so the prochiral ketone approach on the side where the interactions are minimized.

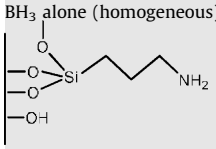
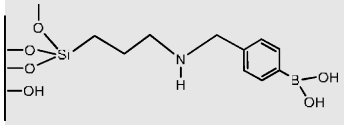
In agreement with this mechanism, the borane is first introduced on the supported oxazaborolidine for 20 min, in order

Table 3
Catalytic results for the reduction of acetophenone

Run	Species involved in the catalysis	Oxazaborolidine /BH_3/ketone	Time (min)	Conversion (%)	Yield (%)	Selectivity (%)	ee (%)
1	S1-4′	0.1[a]/0.7/1	120	50	50	100	65
3	S1-4′	0.1/0.7/1	60	100	50	50	54
1	S1-4	0.1[b]/0.7/1	1140	0	0	0	0
		0.1/1.4/1 (0.7 mmol of borane added)	100	84	56.2	67	77.8
		0.1/2.1/1	120	100	100	100	75

[a] 0.8 mmol of oxazaborolidine/g of silica determined by TGA.
[b] 0.234 mmol of oxazaborolidine/g silica determined by elementary analysis.

Table 4
Reduction of acetophenone on the intermediate species and by BH_3 alone in homogeneous conditions

Solids	Time (min)	Conversion (%)	Selectivity (%)	Yield (%)	ee (%)
BH_3 alone (homogeneous)	30	100	100	100	0
	30	77	94	72	0
	45	52	50	26	0

to complex on the nitrogen atom, and then acetophenone is added very slowly. The influence of the rate of addition of the ketone to the catalyst and borane source is known in homogeneous reduction [13]. Thus, despite the presence of 'free BH_3', i.e. not complexed with the oxazaborolidine catalyst, the uncatalyzed reduction is minimized and the ees observed are higher. In order to be in catalytic conditions the ratio oxazaborolidine/BH_3/ketone is chosen as 0.1/0.7/1; the sub-stoechiometric amount of borane is justified by the fact that the borane gives two hydrides and thus, can reduce two ketones.

The results of the catalytic reduction of acetophenone by both catalysts (S1-4 and S1-4′) are reported in Table 3. The reduction by the catalyst S1-4′ obtained by the pathway (a) is incomplete for the first run. One hypothesis to explain this result is the consumption of the borane for the reduction of the imine. During the following runs, the borane only serves for the reduction of the acetophenone and a conversion of 100% is reached. A moderate ee is obtained. The selectivity is maintained even after three runs.

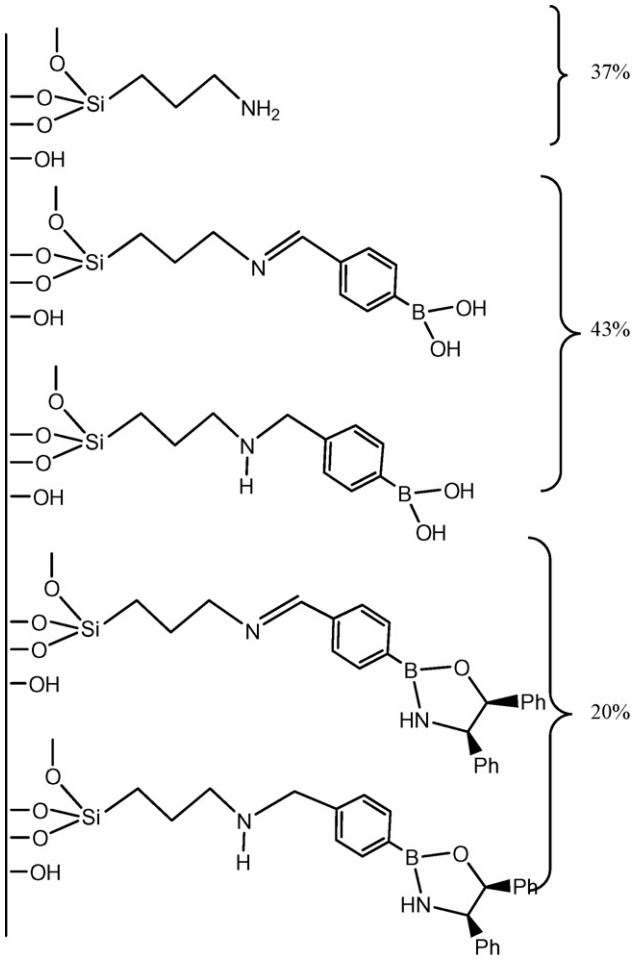
Concerning the solid S1-4 prepared by the pathway (b) surprisingly, the same kind of behaviour is observed. During the first run, no reduction occurs. A second addition of 0.7 equivalent borane allows the reduction of acetophenone but not completely, a third addition of 0.7 equivalent of borane is necessary to reach the total reduction of the acetophenone. The yield and selectivity are excellent (100%) and the enantiomeric excess is good (75%). Thus, several hypotheses can be raised to explain the great amount of borane necessary for the total reduction of acetophenone: (i) the borane can be complexed on grafted species on the surface such as amine or hydroxyl groups, (ii) the borane can reduce the residual imine. In order to clarify this phenomenon, different experiments are accomplished.

The reduction of acetophenone by the borane alone is complete in 30 min (Table 4). It seems that the solid inhibits the reaction. The reduction of acetophenone was carried out on the different solids which can represent the composition of the final catalytic solid as illustrated in Scheme 3.

The results of the reduction of acetophenone carried out with the borane in presence of the amino-silica and the acid boronic species are reported in Table 4.

The reduction of acetophenone is done in the same conditions as previously with a ratio catalyst/BH_3/ketone = 0.1/0.7/1. The conversion of 77% with the amino silica proves that the amino groups complex the borane, so the amount of BH_3 is not enough to complete the reduction. Reduction of acetophenone on S1-2 (i.e the boronic species) leads to an incomplete reaction (52% of conversion). By DRIFT, a decrease of the imine band is observed, proving that the borane reduces the residual imine rather than reducing the ketone. We proved thus that the borane, introduced for the ketone reduction, concomitantly reacts with other surface functions (amine and boronic species, reduction of the residual imine). This leads to low conversion. This can be solved by adding the right amount of borane, knowing the real quantity of each species on the surface.

Another substituted acetophenone was tested, the trifluoromethylacetophenone on the catalyst S1-4. The same tendency noticed with the acetophenone is observed. The enantiomeric excess reaches 76%.



Scheme 3. Species present on the surface.

4. Conclusion

We synthesized a new heterogeneous system for enantioselective reduction of ketones. This new catalyst is well characterized and very promising. The synthesis is followed step by step by DRIFT. The elementary analyses afford the real loading of active species. The heterogeneous catalyst can be recycled several times with little loss of performance. This catalyst offers several advantages over related systems. Although the performances of the catalyst have to be improved, these first results are encouraging. Other ways of immobilisation of the oxazaborolidine with fewer steps in order to reduce the number of different species on the surface are currently under investigation.

References

[1] A. Baiker, Catal. Today 100 (1–2) (2005) 159;
G.J. Hutchings, Chem. Commun. 4 (1999) 301;
H.U. Blaser, Tetrahedron: Asymmetry 2 (9) (1991) 843.
[2] M.R. Buchmeiser, Catal. Today 105 (3,4) (2005) 612;
L.X. Dai, Angew. Chem. Int. Ed. 43 (43) (2004) 5726;
F. Quignard, A. Choplin, Compr. Coord. Chem. II 9 (2004) 445;
A. Choplin, F. Quignard, Coord. Chem. Rev. 178–180 (1998) 1679;
D. Brunel, A.C. Blanc, A. Galarneau, F. Fajula, Catal. Today 73 (1–2) (2002) 139.
[3] M. Heitbaum, F. Glorius, I. Escher, Angew. Chem. Int. Ed. 45 (2006) 4732.
[4] A. Hirao, S. Itsuno, S. Nakahama, N. Yamazaki, J. Chem. Soc., Chem. Commun. (1981) 315;
S. Itsuno, K. Ito, A. Hirao, S. Nakahama, J. Chem. Soc., Chem. Commun. (1983) 469;
S. Itsuno, M. Nakano, K. Miyazaki, H. Masuda, K. Ito, A. Hirao, S. Nakahama, J. Chem. Soc. Perkin. Trans I (1985) 2039.
[5] E.J. Corey, R.K. Bakshi, S. Shibata, J. Am. Chem. Soc. (1987) 5551.
[6] G.J. Quallich, T.M. Woodall, Tetrahedron Lett. 34 (1993) 4145.
[7] S. Itsuno, M. Nakano, K. Ito, J. Chem. Soc. Perkin. Trans I (1985) 2615;
S. Itsuno, K. Ito, A. Hirao, S. Nakahama, J. Chem. Soc. Perkin. Trans I (1984) 2887.
[8] C. Franot, G.B. Stone, P. Engeli, C. Spöndlin, E. Waldvogel, Tetrahedron: Asymmetry 6 (1995) 2755.
[9] C. Caze, N. El Moualij, P. Hodge, C.J. Lock, J. Ma, J. Chem. Soc. Perkin. Trans I (1995) 345.
[10] K. Molvinger, M. Lopez, J. Court, Tetrahedron Lett. (1999) 8375;
K. Molvinger, M. Lopez, J. Court, Tetrahedron: Asymmetry 11 (2000) 2263.
[11] S. Brunauer, P.H. Emmet, E. Teller, J. Am. Chem. Soc. 60 (1938) 309.
[12] T. Martin, A. Galarneau, D. Brunel, V. Izard, V. Hulea, A.C. Blanc, S. Abramson, F. Di Renzo, F. Fajula, Stud. Surf. Sci. Catal. 135 (2001) 4621.
[13] D.J. Mathre, A.S. Thompson, A.W. Douglas, K. Hoogsteen, J.D. Carroll, E.G. Corley, E.J.J. Grabowski, J. Org. Chem. 58 (1993) 2880.