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New, efficient, heterogenized catalysts for asymmetric hydrogenation of dehydroamino acid derivatives

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New, efficient and highly active Rh complexes have heterogenized and applied in the asymmetric hydrogenation of (*Z*)-α-acetamidocinnamic acid and its methyl ester. The prepared catalysts show excellent activity and selectivity, similar to the homogeneous analogs and at the same time they show all the advantages of the heterogeneous catalysts: the easy handling, the possibility to filter out from the reaction mixture and to reuse in several subsequent runs.

KEY WORDS: heterogenized catalyst; asymmetric hydrogenation; Rh complex.

1. Introduction

An increasing need has recently been emerged towards selective synthesis in the production of fine chemicals, due to environmental and economical demands. Among these processes selective hydrogenations, especially asymmetric hydrogenations have become more and more important. Soluble complexes are widely used for the above purpose with excellent activity and selectivity [1]. However, the inability to recover and recycle the catalyst limits their practical application. The heterogenization of these complexes could be a solution to overcome the above mentioned problems. The heterogenized versions of these complexes can be expected to have the advantages of the heterogeneous catalysts and at the same time they could reserve the excellent performance of the homogeneous system. Consequently, an increasing demand has developed towards the heterogenization of these complexes, which is represented by the large number of recent publications [2].

A new, efficient method for heterogenization of homogeneous hydrogenation catalysts has been recently introduced by Augustine *et al.* [3]. The procedure involves two steps: (i) the adsorption of the heteropoly acid, (HPA: phosphotungstic, phosphomolybdenic or silicotungstic acids) to the support, (ii) the attachment of a preformed metal complex to the HPA. The heteropoly acids are attached to the support by the reaction of the basic sites of the support with the acidic protons. The attachment of the complex occurs *via* a bond, which is forming between the surface oxygen atoms of the HPA and the metal center of the complex. The nature of this bond is not clear yet, either ion-pairing or direct bonds have been suggested. However, the resulting catalyst is at least as active as the homogeneous one, and it has the advantages of a heterogeneous system [4].

Chiral monophosphanes have been used as chiral modifiers for asymmetric enantioselective hydrogenation [5,6]. However shortly after it was demonstrated that the performance of the Rh complexes with diphosphanes surpass the performance of the monophosphanes in the hydrogenation reaction [7]. A new, simple method was introduced to prepare enantiomerically pure (2*R*, 4*R*)- and (2*S*, 4*S*)-bis(diphenylphosphino)pentane (BDPP) isomers starting from acetylacetone [8]. A Rh complex of this chiral ligand, the [Rh(NBD)(2*R*,4*R*)-BDPP]ClO_4 was successfully applied in the hydrogenation of methyl (*Z*)-α-acetamidocinnamate with excellent activity and selectivity [8]. An even higher activity was found using dimethylated derivatives of BDPP in the hydrogenation reaction [9]. Full potential of this remarkable catalytic system can be applied if the above catalyst will be heterogenized. Heterogenized homogeneous complexes provide new features for catalysis what can not be realized neither with traditional homogeneous nor with heterogeneous catalysts. The heterogenized homogeneous complexes are expected to combine the best features from both field of catalysis. These features are the excellent activity and selectivity, like the homogeneous complexes together with the easy separation and the possibility to recycle. In this paper, we report our effort to heterogenize the above mentioned complexes and to apply the

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heterogenized catalysts in the asymmetric hydrogenation of methyl (*Z*)-α-acetamidocinnamate.

2. Experimental

Preparation of the catalysts. [Rh(NBD)(2*S*,4*S*)-BDPP]PF_6 and [Rh(NBD)(2*S*,4*S*)-3,5-diMe-BDPP]PF_6 complexes were prepared according to a published process [9]. (*Z*)-α-acetamidocinnamic acid was purchased from Aldrich and methylester was prepared by a standard procedure [10].

Anchoring the soluble complexes. 1.5 g of Al_2O_3 (CAMAG, basic) was suspended in 30 mL of methanol. 288.0 mg (0.1 mmol) of phosphotungstic acid hydrate (PTA) was dissolved in 25 mL of methanol and this solution was added dropwise into the alumina suspension with efficient stirring. The stirring was continued for 2 days at room temperature, under an Ar atmosphere. The mixture was filtered and the solid residue was suspended in 30 mL of methanol. 78.0 mg (0.1 mmol) of [Rh(NBD)(*2S,4S*)-BDPP]PF_6 (catalyst 1) or 89.3 mg (0.1 mmol) [Rh(NBD)(*2S,4S*)-3,5-diMe-BDPP]PF_6 (catalyst 2) complex (NBD = 2,5-norborna-diene, Bicyclo[2.2.1]hepta-2,5-diene) was dissolved in 40 mL of deoxygenated methanol and this solution was dropped slowly with stirring to the suspension. The stirring was continued for another two days. The mixture was filtered and washed with methanol, until a colorless solution was obtained. The light yellow solid material was dried at 30 °C for 2 h in vacuum and for 1 day under argon. 1.45 and 1.40 g of catalysts were obtained with 12.04 μmol/g (catalyst 1) or 11.66 μmol/g (catalyst 2) Rh content, respectively.

Catalyst characterization. FT-IR spectra of the support, the Rh complexes and the heterogenized samples were recorded on a Bio-Rad FTS-65 A spectrophotometer, in the range of 400–4000 cm^{-1}, in KBr pellets. Solid state ^{31} P NMR spectra of the heterogenized sample was taken on a BRUKER AVANCE DRX 500 MHz instrument. The metal content of the anchored catalysts was determined using a JOBIN YVON 24 type ICP-AES instrument; samples were dissolved in cc. HNO_3.

Hydrogenation experiments. Methyl (*Z*)-α-acetamidocinnamate or (*Z*)-α-acetamidocinnamic acid were hydrogenated in a batch reactor of 30 mL capacity, at 25 °C and 0.2 MPa hydrogen pressure. 5 μmol (3.9 or 4.5 mg) homogeneous and 100 mg heterogenized complexes were prehydrogenated for 10 min at 0.5 MPa hydrogen pressure. Then 51.75 mg (250 μmol) of methyl (*Z*)-α-acetamidocinnamate, dissolved in 2 mL of methanol was injected, the reactor was pressurized with H_2 and then the reaction was started with stirring. Samples were taken every 10 min from the reaction mixture, and the products were analyzed by capillary gas chromatography. The enantiomeric excess was determined on Permabond®-CHIRASIL-L-VAL column (25 m, internal diameter 0.25 mm, film thickness 0.25 μm, carrier gas: He, F.I.D. detector; the retention times of the enantiomers are 40.7 min (*R*), 40.9 min (*S*), temperature program 100– 170 °C (2 °C/min).

Catalysts recycling. The heterogenized catalysts were used in several subsequent runs. After the reactions the catalyst was recovered by filtration under Ar, washed with ethanol, dried in Ar and then reused.

3. Results and discussion

With the final goal of developing active, enantioselective, heterogeneous catalysts, we have prepared the anchored [Rh(NBD)(*2S,4S*)BDPP]PF_6 and [Rh(NBD)(*2S,4S*)-3,5-diMe-BDPP]PF_6 catalysts, with the method developed by Augustine *et al*. [3]. The heterogenization was carried out using phosphotungstic acid (PTA) as anchoring material. The heterogenized complexes were characterized by spectroscopic methods and applied as catalysts in the asymmetric hydrogenation of (*Z*)-α-acetamidocinnamic acid and methyl (*Z*)-α-acetamidocinnamate.

3.1. Catalysts characterization

The heterogenized catalysts were characterized by means of IR spectroscopy. The FT-IR spectra of the support (PTA/Al_2O_3), the [Rh(NBD)((*2S,4S*)BDPP]PF_6 and the [Rh(NBD)(*2S,4S*)-3,5-diMe-BDPP]PF_6 complexes and the heterogenized samples were all taken.

The comparison of these spectra (figure 1) shows that several vibrational modes of [Rh(NBD)(*2S,4S*)-BDPP]PF_6 (1380, 1440, and 1590 cm^{-1}) were found to be present on the [Rh(NBD)(*2S,4S*)BDPP]PF_6/Al_2O_3 sample.

Similar spectra were obtained in the case of [Rh(NBD)(*2S,4S*)-3,5-diMe-BDPP] PF_6 complex and its heterogenized analog. The comparison of these spectra leads to a similar conclusion, as formerly.

Solid state ^{31} P NMR spectra of the heterogenized sample show similar resonances like the complexes in liquid phase. The resonances between 33–40 ppm are broader than in liquid phase (30 ppm) which can be a sign of the attachment to the support.

The concentration of the metal complex in the heterogenized catalysts was determined by ICP-AES method, after dissolving the samples in cc. HNO_3. The metal loading of the catalysts were 12.04 μmol/g (catalyst 1) and 11.66 μmol/g (catalyst 2), respectively.

3.2. Hydrogenation of methyl (*Z*)-α-acetamidocinnamate

The [Rh(NBD)(*2S,4S*)-BDPP]PF_6 and [Rh(NBD)(*2S,4S*)-3,5-diMe-BDPP]PF_6 complexes were successfully applied in the hydrogenation of (*Z*)-α-acetamidocinnamic

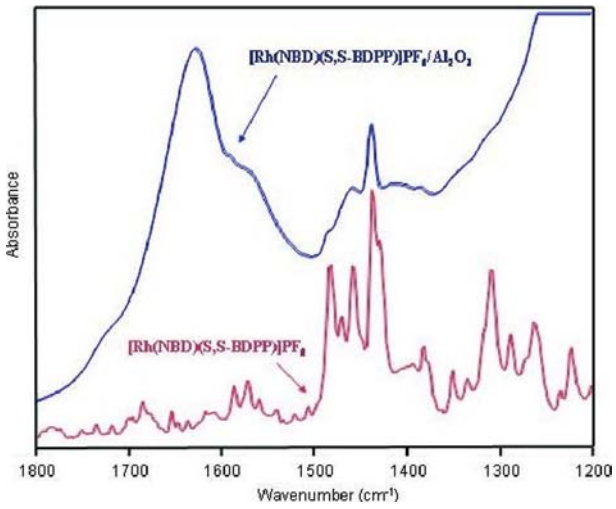


Figure 1. The FT-IR spectra of the [Rh(NBD)(*2S,4S*)BDPP]PF_6 complex and the heterogenized sample.

acid and methyl (*Z*)-α-acetamidocinnamate (scheme 1) with excellent activity and selectivity [8].

In order to evaluate the performance of our heterogenized samples, we have studied the hydrogenation in homogeneous and heterogeneous conditions, too. For the best comparison, we have used the same protocol for both reactions (except the amount of catalyst).

Tables 1 and 2 show the results obtained in the hydrogenation of (*Z*)-α-acetamidocinnamic acid and methyl-(*Z*)-α-acetamidocinnamate, respectively.

As the above tables shows all of the catalysts were active in the hydrogenation of both starting materials. Among the two starting materials, the hydrogenation of methyl (*Z*)-α-acetamidocinnamate was a slightly slower on all catalysts, as it was expected.

Our data prove that all the heterogenized catalysts were active in the studied reactions. As a matter of fact, the specific activity (calculated at 5 min) of the heterogenized catalysts were higher than the same values of the homogeneous catalysts. For both substrates, the Rh complex modified by dimethyl substituted BDPP had higher specific activity than the unsubstituted one. The enantioselectivity of the heterogenized catalysts almost the same as the homogeneous complexes, in the case of dimethyl substituted analogs it is even better. Our heterogenized samples have about the same performance as the homogeneous analogs.

A the major advantage of using heterogeneous catalyst is the possibility to recycle. The heterogenized catalysts were filtered out from the reaction mixture and were applied in several subsequent runs in the hydrogenation of methyl (*Z*)-α-acetamidocinnamate (figure 2.)

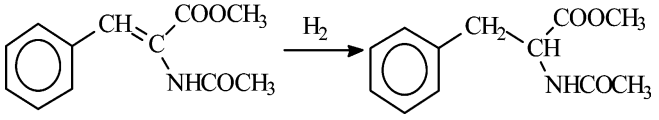
As figure 2 shows the heterogenized catalyst was active in three subsequent runs, the activity did not decrease at all. The enantioselectivity has decreased some extent, but the difference is not high and the reason for this is not clear.

It is also possible to recycle the anchored [Rh(NBD)((*2S,4S*)-BDPP]PF_6 catalyst. Figure 3 shows the obtained results studying the hydrogenation of methyl (*Z*)-α-acetamidocinnamate in three subsequent runs.

The recycling experiments show that our heterogenized complexes can be used in several subsequent runs without any significant change in their performances.

4. Conclusion

We have prepared the anchored [Rh(NBD)((*2S,4S*)-BDPP)]PF_6 and [Rh(NBD)(*2S,4S*) −3,5-diMe-BDPP]PF_6 complexes, using phosphotungstic acid as anchoring agent. Our heterogenized catalyts were applied in the asymmetric hydrogenation of methyl (*Z*)-α-acetamidocinnamate and (*Z*)-α-acetamidocinnamic acid. Both catalysts were active in these hydrogenation reactions. They show similar activity and selectivity as their homogeneous analogs and all the advantages what



Scheme 1. The hydrogenation of methyl (*Z*)-α-acetamidocinnamate.

Table 1
The activity and the selectivity of the [Rh(NBD)(*2S,4S*)-BDPP)]/PF_6 complexes and their heterogenized analogs in the asymmetric hydrogenation of (*Z*)-α-acetamidocinnamic acid[a]

Catalyst precursors	Ee[b] (%)	Conversion[c] (%)	TOF[c] (h^{-1})
[Rh(NBD)(*2S,4S*)-BDPP]/PF_6	99.0 (*R*)	30	180
[Rh(NBD)(*2S,4S*)-BDPP]/PF_6/Al_2O_3	89.0 (*R*)	55	1250
[Rh(NBD)(*2S,4S*)-3,5-diMe-BDPP]/PF_6	96.0 (*R*)	90	540
[Rh(NBD)(*2S,4S*)-3,5-diMe-BDPP]/PF_6/Al_2O_3	96.4 (*R*)	70	1800

[a]Reaction conditions: 5 μmol homogeneous complex or 100 mg heterogenized sample, 250 μmol substrate, 25 °C, 0.2 MPa H_2 pressure. Reaction time: 30 min, conversion: 100%.
[b]Ee was determined by GC analysis, Permabond®-L-Chirasil-Val column, using temperature program 100–170 °C (2 °C/min).
[c]Calculated at a reaction time of 5 min.

Table 2
The activity and the selectivity of the [Rh(NBD)(*2S,4S*)-BDPP]/PF_6 complexes and their heterogenized analogs in the hydrogenation of methyl-(*Z*)-α-acetamidocinnamate[a]

Catalyst precursors	Ee[b] (%)	Conversion[c] (%)	TOF[c] (h^{-1})
[Rh(NBD)(*2S,4S*)- BDPP]/PF_6	96.0 (*R*)	5	30.4
[Rh(NBD)(*2S,4S*)-BDPP]/PF_6/Al_2O_3	89.0 (*R*)	8	200
[Rh(NBD)(*2S,4S*)-(3,5-diMe-BDPP)]/PF_6	95.0(*R*)	32	194
[Rh(NBD)(*2S,4S*)-(3,5-diMe-BDPP)]/PF_6/Al_2O_3	94.6(*R*)	25	640

[a]Reaction conditions: see footnotes under table 1. Reaction time: 40 min, conversion: 100%.

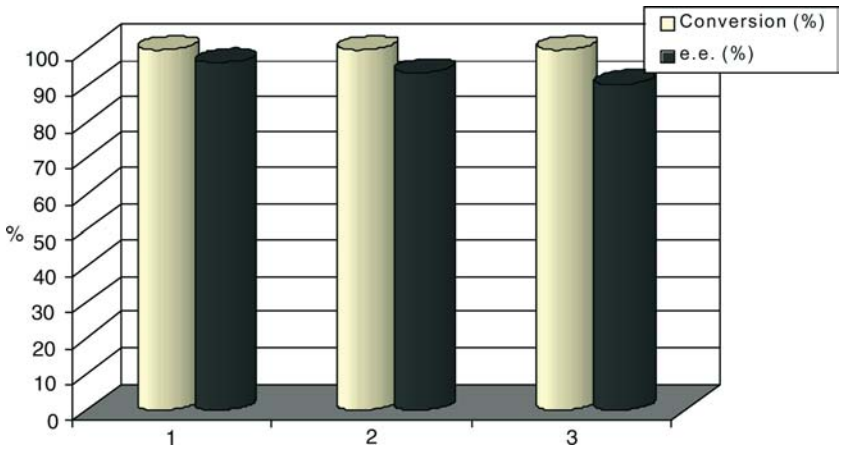


Figure 2. The activity and enantioselectivity of the anchored [Rh(NBD)(*2S,4S*)-3,5-diMe-BDPP]PF_6 complex in three subsequent runs.

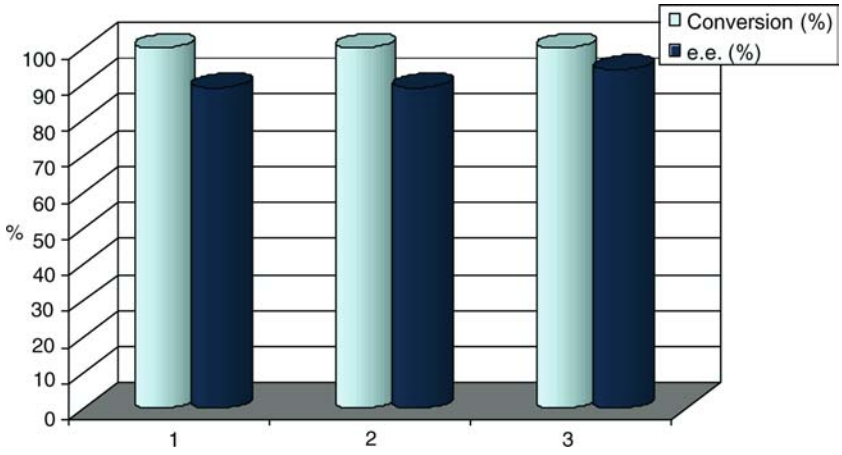


Figure 3. The activity and enantioselectivity of the anchored [Rh(NBD)(*2S,4S*)-BDPP]PF_6 complex in three subsequent runs.

we can expect from a heterogeneous system. Namely, the heterogenized catalysts can be filtered out from the reaction mixture and they can be reused in several subsequent runs without any significant loss of catalytic properties.

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