International Journal of Science and Research (IJSR)
ISSN (Online): 2319-7064
Index Copernicus Value (2015): 78.96 | Impact Factor (2015): 6.391

Enantioselective Hydrogenations of C=O (Carbon-Oxygen Double Bonds) Catalysed by Immobilized Rh Complexes

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Abstract: ***Using a modified Augustine's method different Rh complexes were anchored on Al_2O_3 support. The prepared catalysts were characterized by usual spectroscopic methods and were applied in the hydrogenation of several acetophenone derivatives (p-CF_3-acetophenone, acetophenone, p-NH_2-acetophenone). Enantioselective C=O hydrogenations were observed with reasonable activity and selectivity on all heterogenized complexes, e.e. up to 80 % was observed. Meanwhile the immobilized samples showed all the advantages of the heterogeneous systems: easy handling and recyclability.***

Keywords: Anchored Rh complexes, hydrogenations, alcoholic solution, enantio selective, catalyst.

1. Introduction

An increasing demand has developed during the last couple of decades towards the use of enantiomericaly pure products, especially in pharmaceutical and agrochemical industry [1]. The most attractive method to produce a single enantiomer is the enantioselective catalysis, which is able to produce a large amount of chiral product with a relatively small amount of chiral ligand. Currently the most widely used and versatile enantioselective catalysts are the homogeneous metal complexes with chiral ligands. From industrial point of wiev, however catalysts which are not soluable in the same phase as organic reactants have several advantages over the homogeneous ones. They have more easily handling properties and easier to separate them from the reaction mixture. These catalysts can be truly heterogeneous ones i.e. insoluable like modified metal complexes [2] or they can be soluable in different solvents such as water [3]. An other approach to have a heterogeneous metal complex to immobilize the complex onto a support [4].

This strategy – the heterogenation of metal complexes – has about 30 years of history but the increasing importance of selectivity results a new reneissance of this field. Several research groups investigate the new possibilities to anchore homogeneous complexes [4,5]. A new heterogenization method was introduce by Augustine and coworkers, which are using a HPA as an anchoring agent [6,7]. The method involves two steps, first the HPA anchored onto the support and after the metal complex from alcoholic solution. Spectroscopic data proved that metal – oxygen bond is forming during the second step, meanwhile the HPA is thought to react with the basic sites of the support. Nevertheless the resulting catalyst is at least as active as the homogeneous one and has the advantages of the heterogeneous systems [8].

The asymmetric reduction of the C=O group for the production of enantiomerically pure secondary alcohols has a fundamental importance in modern synthetic chemistry [9]. The Noyori's catalyst, Ru(BINAP) opened the way to the efficient asymmetric hydrogenation of C=O group of functionalised ketons, which had an other binding group capable of coordinating the reactive metal centre. The second generation" of Noyori's catalyst, which is a ruthenium metal centre having a chiral diphospine and a chiral diamine ligand made possible the asymmetric hydrogenation of unfunctionalised ketones [10]. Aromatic, heteroaromatic and unsatureted ketons could be reduced with excellent productivity and enantioselectivity; however aliphatic ketones were reduced only with moderate selectivity. Símilarly substituted acetophenone derivatives were hydrogenated with cinchona modified Pt/Al_2O_3 catalyst with low and moderate enantioselectivity [11].

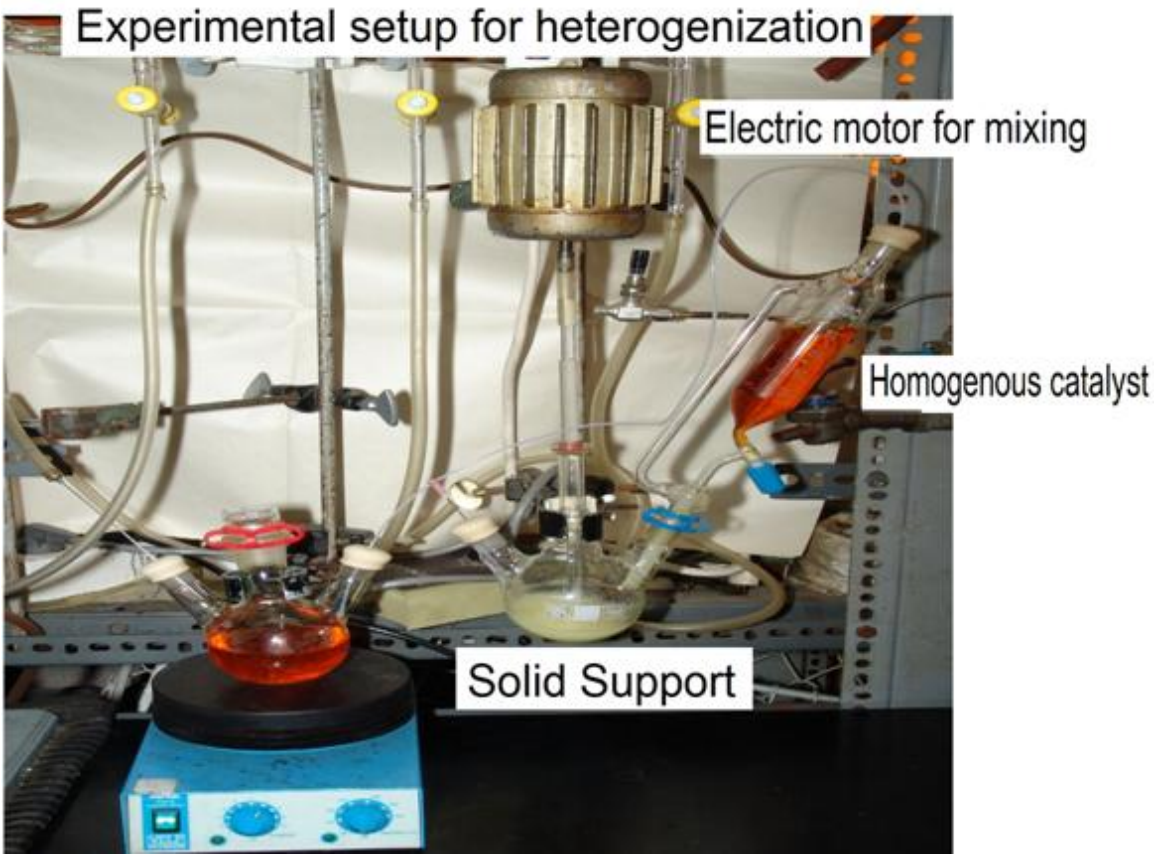
Using the Augustine's method several anchored $[Rh(NBD)(2S,4S)(BDPP)]BF_4$ complexes were prepared recently [12]. The prepared catalysts were succesfully applied in the asymmetric hydrogenation of (*Z*)-α-acetamidocinnamic acid and its methyl ester. Phosphine basicity was varied by using different substituents, like p-CH_3O, p-CF_3, 3,5-$(CH_3)_2$ on the diphenyl-phosphine moieties. An increasing activity and selectivity was observed with increasing phosphinite basicity in the hydrogenation of methyl (Z)-α-acetamidocinnamate. Having the above results it was interesting to study the asymmetric hydrogenation of C=O bond, catalysed by the same anchored complexes. The selected materials for the hydrogenation were differently substituted acetophenones derivatives to study the effect of substituents on the activity and selectivity. We have also applied differently substituted Rh complexes, to study the substituent effect on the complexes, as well.

2. Experimental

2.1. Preparation of the Catalysts

[Rh(NBD)(2*S*,4*S*)-BDPP]PF_6 (1), [Rh(NBD)(2*S*,4*S*)-3,5-$(CH_3)_2$-BDPP]PF_6 (2)and [Rh(NBD)(1,3-diPh-1,3-BDPPr)] PF_6 (1, 3-diPh-1,3-BDPPr = 1,3-diphenyl-1,3-bis (diphenylphosphino) propane) (3) complexes were prepared according to a published procedure [13,14]. Acetophenone and it's substituted derivaties were purchased from Aldrich and used as received.

The anchoring of the soluble complexes was done following the Augustine's method, as described in our former publication [12].



2.2. Catalyst characterization

The catalysts characterization was done by usual spectroscopic methods:
The identification of the complexes was done by FT-IR and by ^{31}P NMR spectroscopy. 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. The NMR spectra were recorded at room temperature using a Bruker Avance spectrometer operating at 11.7 Tesla magnetic field (31P: 202.46 MHz).

The metal content of the anchored catalysts was determined using an ICP-AES instrument after dissolving the samples in cc. HNO_3. The metal loading of the catalysts were 12.04 µmol/g (Catalyst 1), 11.66 µmol/g (Catalyst 2), and 12.00 µmol/g (Catalyst 3) respectively.

2.3 Hydrogenation experiments

Acetophenone and it's substituted derivatives [methyl-(4-trifluoromethylphenyl)-ketone: (*p*-trifluormethyl)acetophenone and (4-aminophenyl)-methyl-ketone: (*p*-amino)acetophenone] were hydrogenated in a batch reactor of 20 mL capacity, at 50 ºC and 2.5 MPa hydrogen pressure. 5 µmol (3.9 mg, 4.5 mg, and 4.5 mg) homogeneous and 250 mg heterogenized complexes were prehydrogenated in 5 ml of methanol for 10 minutes at 1.0 MPa hydrogen pressure at room temperature. Then 250 µmol starting material (47.0 mg of acetophenone, 30.5 mg 4-CF_3-acetophenone or 33.8 mg 4-NH_2-acetophenone) was dissolved in 5 mL of methanol and was injected into the reactor. The reactor was pressurized with H_2 and then the reaction was started with stirring. Every reaction was run for 6 hours and the products were analyzed by capillary gas chromatography. The enantiomeric excess was determined on Cyclodex-B column, using Helium (He) as a carrier gas: F.I.D. detector; at isoterm temperature 120 ºC.

2.4. Catalysts recycling

The heterogenized catalysts were successfully reused in several subsequent runs. After the reactions the reaction mixture was removed from the catalyst, it was dried under vacuum and Ar, then reused.

3. Results and discussion

With the aim of extenting the application of our heterogenized samples we have anchored several Rh complexes on Al_2O_3 support, using a method developed by Augustine [6]. The immobilized catalysts were characterized by usual spectroscopic methods and were applied in the hydrogenation of several acetophenone derivetives.

Catalysts characterization

The immobilized catalysts were characterized by IR and ^{31}P NMR spectroscopy. The FT-IR spectra of the support PTA/Al_2O_3, the neat complexes [Rh(NBD)(2*S*,4*S*)-BDPP]PF_6, [Rh(NBD)(2*S*,4*S*)-3,5-$(CH_3)_2$-BDPP]PF_6, [Rh(NBD)(1,3-diPh-BDPPr]PF_6, and the heterogenized samples were all taken. The comparison of the spectra of [Rh(NBD)(2*S*,4*S*)-BDPP]PF_6 complex and the heterogenized analog shows several similar bands (1380,1410 and1480 cm^{-1}), indicating the anchoring of the same complex. A similar observation was found comparing the spectra of the two other complexes and their heterogenized analogs.

Data obtained from the solid state ^{31}P NMR spectroscopy has also supported the assumption, anchoring the same complex on the surface. 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 amount of catalytically active metal complex was determined by measuring the metal content of the heterogenized samples. This value 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 , 11.66 µmol/g and 12.00 µmol/g respectively.

The effect of substituents on the hydrogenation of acetophenone derivatives

Recently we have reported the effect of substituents of the diferent Rh complexes on the hydrogenation of methyl (*Z*)-α-acetamidocinnamate [12].The ligand basicity was varied by using *p*-CH_3O-,3,5-$(CH_3)_2$ and *p*-CH_3O-3,5-$(CH_3)_2$ substituents on the diphenyl-phosphine moities of the molecule. The results of the hydrogenation experiments showed an increase in enentioselectivity and activity with increasing basicity. So, the electronic tuning of the ligand gave a chance to improve the selectivity and activity.

A similar substituent effect was also studied in this work, but in the case of asymmetric C=O hydrogenation. The selected strating materials were differently substituted acetophenone derivatives, namely: (*p*-trifluormethyl)acetophenone, acetophenone and (*p*-amino)acetophenone. The study was done systematicaly on both homogeneous and heterogenized [Rh(NBD)(2*S*,4*S*)-BDPP]PF_6 (complex **1**), [Rh(NBD) (2*S*,4*S*)-3,5-$(CH_3)_2$-BDPP]PF_6 (complex **2**), [Rh(NBD)(1,3-diPh-BDPPr]PF_6 (complex **3**) complexes. To have the fair comparison we have used the same protocoll for all of the studied starting materials.

The investigation was strarted with the hydrogenation of (*p*-trifluormethyl)acetophenone and the observed results can be seen in Table 1.

Table 1: The products distribution in the hydrogenation of (*p*-trifluormethyl)acetophenone.

Catalysts	Products		Conversion (%)	e.e. (%)
	R	*S*		
complex 1	8.9	43.0	61.9	70.0
complex 1/HPA/Al_2O_3	9.9	29.4	39.0	51.0
complex 2	17.2	77.6	93.8	60.0
complex 2/HPA/Al_2O_3	10.6	37.5	48.1	58.1
complex 3	16.0	81.0	97.8	80.0
complex 3/HPA/Al_2O_3	7.9	26.0	34.0	60.0

Reaction conditions: 5 µmol complex or 250 mg anchored complex, 10 ml EtOH, 6µl Et_3N, 250 µmol (*p*-trifluormethyl)acetophenone, 2.5 MPa H_2 pressure, 50 ^oC, 6 hr

Data in Table 1 show that all the catalysts were active in the hydrogenation of (*p*-trifluormethyl)acetophenone with slightly different activity and selectivity. Complex 2 and 3 had about the same activity and selectivity, meanwhile complex 1 was a little bit less active and selective. Comparing the homogeneous and heterogenized complexes an interesting observation can be found. The heterogenized complexes were slightly less reactive than the homogeneous ones. This observation is in contrast to our earlier results, since sofar we always had a higher activity on the heterogenized samples.

To check the effect of substituents on the hydrogenation of acetophenone derivatives we have studied the hydrogenation of unsubstituted and NH_2 substituted acetopheno derivaties , too. The same protocoll was used to get a fair comparison and the obtained results can be seen in Table 2 and 3.

Table 2: The activity and selectivity of hydrogenation of acetophenone on Rh complexes.

Catalysts	Products		Conversion (%)	e.e. (%)
	R	*S*		
complex 1	9.2	41.5	50.9	75.0
complex 1/HPA/Al_2O_3	2.5	31.1	33.6	73.3
complex 2	13.5	62.3	75.8	68.2
complex 2/HPA/Al_2O_3	10.3	37.5	47.8	67.1
complex 3	6.9	66.2	75.1	88.0
complex 3/HPA/Al_2O_3	12.5	33.2	45.8	64.0

Reaction conditions: see Table 1.

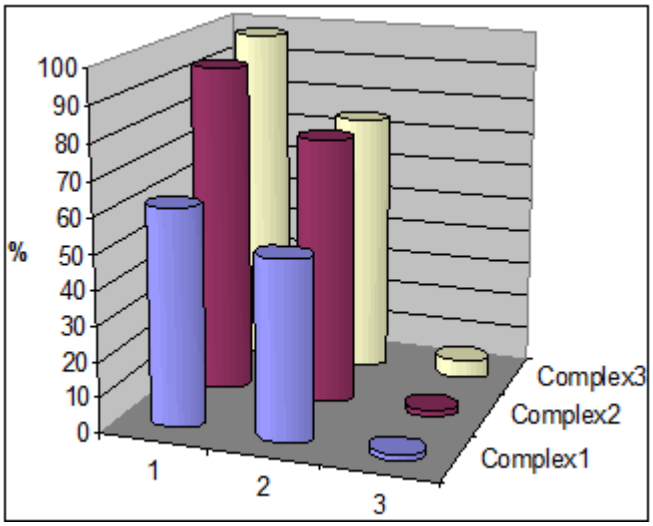
Table 3: The activity and selectivity of hydrogenation of 4-NH_2-acetophenone on Rh complexes

catalysts	products		Conversion (%)	e.e. (%)
	R	*S*		
complex 1	0.2	1.3	1.5	75.0
complex 1/HPA/Al_2O_3	0.1	0.8	0.9	75.6
complex 2	0.1	1.8	1.8	88.0
complex 2/HPA/Al_2O_3	0.1	0.5	0.6	78.2
complex 3	0.7	4.0	5.2	72.0
complex 3/HPA/Al_2O_3	0.3	2.8	3.1	80.0

Reaction conditions: see Table 1.

Experimental data in Table 2 and 3 show that all of our Rh complexes were active in the hydrogenation of the two other acetophenone derivatives. Comparing the different complexes they had about the same activity and selectivity in each of the starting material respectively. The same is holds for the comparison of the homogeneous and the heterogenized samples.

Considering the differently substituted acetophenone derivatives data show a definite substituent effect regarding the hydrogenation activities. As it is well known the two applied substituents CF_3 and NH_2 have the opposite tendency in the electronic effect. The obtained data for the hydrogenation of these derivatives are in a good correlation with this tendency, which can be seen on Figure 1.



(**1:** (*p*-trifluormethyl)acetophenone, **2**: acetophenone, **3**: *p*-NH_2-acetophenone)

Figure 1: The effect of substituents in the hydrogenation of acetophenone derivetives on different Rh complexes

The slowest activities were observed in the case of *p*-NH_2-acetophenone, which can be rationalised by the strong electron withdrawing capability of the NH_2 group. Consequently the highest activity and selectivity was observed in the hydrogenation of *p*-trifluormethyl)acetophenone.

Comparing the different complexes an increasing activity was observed in the order of [Rh(NBD)(2*S*,4*S*)-BDPP]PF_6 (complex **1**), [Rh(NBD)(2*S*,4*S*)-3,5-$(CH_3)_2$-BDPP]PF_6 (complex **2**), [Rh(NBD)(1,3-diPh-BDPPr]PF_6 (complex **3**), which is similar to the activity order of C=C hydrogenation, what we observed formerly [12]. Complex **3** behaves like the substituted BDPP with electron donating substituents. We have the same trend in this comparison for the different starting material, only the extent is different.

Regarding the enantioselectivities there is no such a significant trend than it was in the case of C=C hydrogenation (Figure 2.) In that case we observed an increasing activity with increasing enantioselectivity in the order of the electronic tunning.

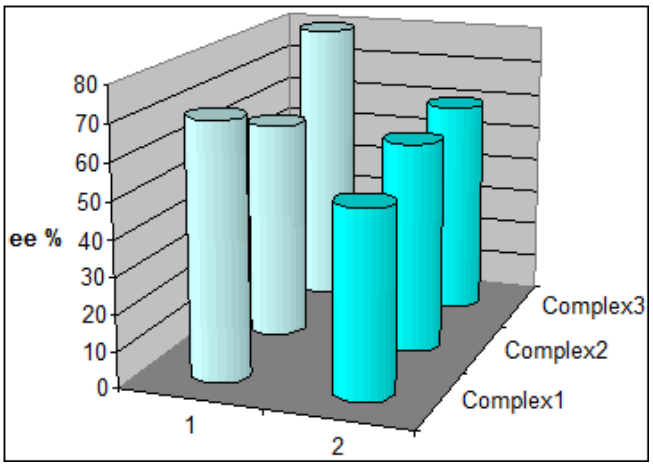


Figure 2: The comparison of the enantioselectivities of different Rh complexes in the hydrogenation of (*p* trifluormethyl) acetophenone

As Figure 2. shows only the heterogenized samples show a similar selectivity and activity order. Regarding the values of the homogeneous complexes, they are changing via a minimum curve. However the observed difference in selectivity is so small that we can not able to establish a real tendency in this change.

3.3. Catalyst recycling

The major advantage of the immobilization is the possibility to recycle the catalysts. We have applied all of our heterogenized catalysts in three subsequent runs and one example can be seen on Figure 3.

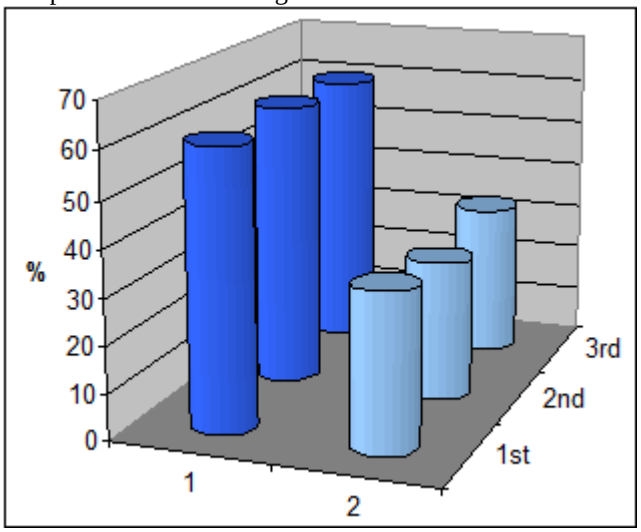


Figure 3: The activity and selectivity in three subsequent runs in the hydrogenation of (*p*-trifluormethyl) acetophenone

As it can be seen in Figure 3. The activity and the enantioselectivity have not change significantly using our catalyst in three subsequent runs. In other words our immobilized complexes behave like heterogeneous catalyst, meanwhile their activities are very close to the homogeneous analogs.

4. Conclusion

The three Rhodium complexes, [Rh(NBD)(S,S)BDPP], [Rh(NBD)(2*S*,4*S*)-3,5-$(CH_3)_2$-BDPP]PF_6 and [Rh(NBD) (1,3-diPh-BDPPr]PF_6 were anchored on Al_2O_3 support. The immobilized complexes were charaterized by spectroscopyc method and were applied in the hydrogenation of C=O bond. Differently substituted acetophenone derivatives were hydrogenate with reasonable activity and good enantioselectivity both in homogeneous and heterogenized conditions. The heterogenized complexes showed the advantages of the heterogenous systems such as easy handling and recyclability, meanwhile their activity and selectivity were same or close to the homogeneous complexes.

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