



ELSEVIER

Journal of Molecular Catalysis A: Chemical 107 (1996) 273–279

JOURNAL OF
MOLECULAR
CATALYSIS
A: CHEMICAL

Immobilized catalysts for enantioselective hydrogenation: The effect of site-isolation

B. Pugin

Central Research Services, Ciba, R-1055.629, CH-4002 Basle, Switzerland

Abstract

Functionalized PPM (PPM: (2*S*,4*S*)-4-diphenylphosphino-2-(diphenylphosphino-methyl) pyrrolidine), a chiral diphosphine ligand, was bound to silica gel with different loadings [mmol ligand/g support] and used as model to detect possible effects of site isolation in the enantioselective hydrogenation of methyl-acetamidocinnamate (MAC) with cationic and with neutral Rh-catalysts and of *N*-(2-methyl-6-ethylphen-1-yl)methoxymethylmethylketimin (MEI) with an Ir-catalyst. To investigate the influence of high local catalyst concentration in absence of a support, two new bis-PPM ligands with spacers of different length were prepared and tested. The results indicate that site isolation effects occur with two of the catalytic systems used: Whereas immobilized cationic Rh-catalysts are practically not affected, the neutral Rh-catalysts lose most of their activity with increasing catalyst loading. Probably, this is due to the formation of chloride-bridged Rh-dimers which is favored by high catalyst concentration as indicated by experiments with the bis-PPM-ligands. Immobilization has a spectacular effect with the Ir-system. It is known that Ir-complexes in presence of hydrogen can form stable hydrogen-bridged dimers that are catalytically inactive. The fact that the activity (and also productivity) of the immobilized catalysts increases with decreasing catalyst loading indicates, that the formation of these dimers can be prevented by immobilization.

Keywords: Enantioselectivity; Hydrogenation; Immobilization; Diphosphine; Rhodium; Iridium; Alkene; Imine

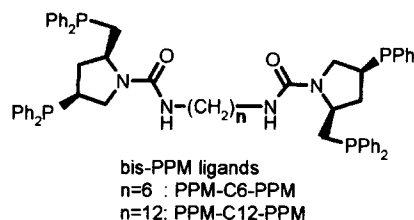
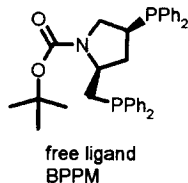
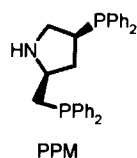
1. Introduction

Rh, Ru and Ir diphosphine complexes belong to the most developed class of homogeneous enantioselective catalysts. Although many of these catalysts are highly active and selective in the hydrogenation of a large variety of unsaturated prochiral substrates, only few have been used on an industrial scale. Among others, one important technical problem is the separation and recovery of the soluble catalyst. Much effort has been made to solve this problem by anchoring such catalysts on a support [1]. However, in most cases immobilization has caused severe reduction of the catalytic activity. Only few investigations on

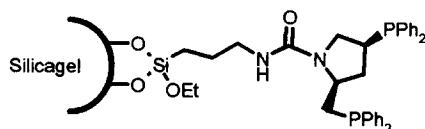
possible causes have been made. There are indications that besides the preparation method, other factors like e.g. the pore size of insoluble supports [2] or, when working with organic polymer supports, the choice of solvent plays a major role [3]. So far, only very little attention has been paid to possible effects of catalyst loading [mmol catalyst/g support] with this important class of catalysts.

With different types of immobilized catalysts it has been shown that catalyst loading can indeed have important effects on catalyst performance [4]. The most prominent example is the hydrogenation of alkenes with titanocene-catalysts [5–8]. These homogeneous catalysts have a strong

Soluble ligands:



Immobilized ligands



Ligand	Support	Loading [mmol ligand / g support]
Si-PPM-1	Grace 332	0.016
Si-PPM-2	"	0.058
Si-PPM-3	"	0.092
Si-PPM-4	"	0.19
Si-PPM-5	Merck 100	0.11
Si-PPM-6	"	0.20

Fig. 1. Ligands used for the preparation of the catalysts.

tendency to react irreversibly, forming dimers that are no more catalytically active. *Site isolation*, that is attaching these catalysts to a support in such a way that they can no more interact with each other, prevents their deactivation and enhances their activity and productivity. A mathematical model that describes the observed reaction rate in function of catalyst loading was proposed and shown to match very well with the experimental results [6].

We have developed an efficient method for the immobilization of chiral diphosphine ligands and are now studying factors that may have an effect on catalytic performance [2]. Using free and immobilized (2*S*,4*S*)-4-diphenylphosphino-2-(diphenylphosphino-methyl) pyrrolidine (PPM) as model-ligands (Fig. 1) we herein describe the influence of catalyst loading in the enantioselective hydrogenation of methyl-acetamidocinnamate (MAC) with cationic Rh-complexes (with BF_4^- as a non coordinating anion) and neutral Rh-complexes (with Cl^- , an anion that forms covalent bonds) and the hydrogenation of *N*-(2-methyl-6-ethylphen-1-yl) methoxymethylmethylketimin (MEI) with an Ir-complex. In addition, the influence of high local catalyst concentration as it occurs with immobilized catalysts

is simulated by using new bis-PPM-ligands, that is, PPM-ligands that are linked together with spacers of different length.

2. Experimental

All reactions involving phosphines and the manipulations in the hydrogenation experiments were carried out under an argon or nitrogen atmosphere and with deoxygenated solvents. *N*-(2-methyl-6-ethylphen-1-yl) methoxymethylmethylketimin (MEI) was prepared by condensation of 2-methyl-6-ethyl-aniline with methoxyacetone and distilled before use. The immobilized PPM-ligands were prepared as described previously [2], using Merck 100 silicagel ($S_{\text{BET}} = 322 \text{ m}^2/\text{g}$; particle size = 200–500 μm ; mean pore diameter = 14 nm) and Grace 332 silicagel ($S_{\text{BET}} = 325 \text{ m}^2/\text{g}$; particle size = 35–70 μm ; mean pore diameter = 19 nm) as supports.

2.1. Preparation of PPM-C6-PPM

89 μl (0.55 mmol) 1,6-diisocyanatohexane and a catalytic amount of dibutyltin-dilaurate (5 mg) were slowly added to 497 mg (1.1 mmol)

PPM in 10 ml dichloromethane and the solution stirred at room temperature overnight. Evaporation of the solvent followed by column chromatography (Silicagel Merck 60, diethyl ether) gave 560 mg (87% yield) of PPM-C6-PPM as a white solid. $^1\text{H-NMR}$ (CDCl_3): ρ (ppm) 1.1–1.5 (m, 8H, $-(\text{CH}_2)_4-$), 1.75–2.4 (m, $2 \times 3\text{H}$, PPM), 2.7–4.0 (m, $2 \times 8\text{H}$, PPM and $-\text{CH}_2-\text{NH}-\text{CO}-$), 7.2–7.6 (m, $2 \times 10\text{H}$, $\text{P}(\text{C}_6\text{H}_5)_2$). $^{31}\text{P-NMR}$ (CDCl_3): ρ (ppm) –22.95, –8.85. Elemental analysis (%), found: C, 73.38; H, 6.71; N, 5.24; P, 11.35. Calc. for $\text{C}_{66}\text{H}_{70}\text{N}_4\text{O}_2\text{P}_4$: C, 73.73; H, 6.56; N, 5.21; P, 11.52.

2.2. Preparation of PPM-C12-PPM

PPM-C12-PPM was prepared as PPM-C6-PPM except that 1,12-diisocyanatododecane was used instead of 1,6-diisocyanatohexane. and was obtained in a 85% yield. $^1\text{H-NMR}$ (CDCl_3): ρ (ppm) 1.1–1.5 (m, 20H, $-(\text{CH}_2)_{10}-$), 1.75–2.4 (m, $2 \times 3\text{H}$, PPM), 2.7–4.0 (m, $2 \times 8\text{H}$, PPM and $-\text{CH}_2-\text{NH}-\text{CO}-$), 7.2–7.6 (m, $2 \times 10\text{H}$, $\text{P}(\text{C}_6\text{H}_5)_2$). $^{31}\text{P-NMR}$ (CDCl_3): ρ (ppm) –22.99, –8.88. Elemental analysis (%), found: C, 74.18; H, 7.22; N, 4.85; P, 10.40. Calc. for $\text{C}_{72}\text{H}_{82}\text{N}_4\text{O}_2\text{P}_4$: C, 74.59; H, 7.13; N, 4.83; P, 10.69.

2.3. Hydrogenation of MAC with cationic Rh-catalysts

1.25 equivalents of ligand were gently stirred in a round bottom flask with a solution of 12.5 μmol $[\text{Rh}(\text{cod})_2]\text{BF}_4$ (cod: 1,5-cyclooctadiene) in 2.5 ml methanol. In the case of supported catalysts a deeply orange catalyst and a colorless solution was obtained within less than 5 min. After 10 min. a solution of MAC (2.5 mmol) in 15 ml methanol and 5 ml THF was added, the atmosphere of Argon was changed to hydrogen and the hydrogenation started by switching on the magnetic stirrer with 1000 rpm. The hydrogenations were carried out at 25°C and a hydrogen pressure of 1 bar. Gas chromatography was used to monitor the reaction (column: SE 54, 15 m) and to deter-

mine the ee (column: Chirasil-L-val). The leaching of Rh was found to be in the range of 4%–6% in the first reactions and about 1% with reused catalysts [2].

2.4. Hydrogenation of MAC with neutral Rh-catalysts

The same procedure and the same conditions for hydrogenation were used as with cationic Rh-catalysts, except that a solution of 6.25 μmol of $[\text{Rh}(\text{cod})\text{Cl}]_2$ in 2.5 ml of toluene were used to form the catalyst precursor and that the substrate solution consisted of 2.5 mmol MAC in 20 ml methanol.

2.5. Hydrogenation of MEI with Ir-catalysts

6.5 mg (9.7 μmol) $[\text{Ir}(\text{cod})\text{Cl}]_2$, 1.2 equivalent of ligand and 2 equivalent of tetra-*n*-butylammonium iodide (NBu_4I) were gently stirred in 4 ml toluene/methanol 1/1. After 10 min, a solution of 2 g (9.8 mmol) MEI in 16 ml toluene/methanol 1/1 was added and the mixture was transferred with argon through a capillary into a 50 ml steel autoclave. The mixture was evacuated and flushed with hydrogen three times and the hydrogen pressure was finally set to 40 bar. The batch was stirred at 25°C and the course of the hydrogenation was followed by observing the drop in pressure in the autoclave. The conversion was analyzed by gas-chromatography (column: SE 54, 15 m). The supported catalysts were separated by filtration. After evaporation of the solvent, the crude product was purified by flash chromatography (silica gel Merck 60, hexane/methyl acetate 1:1) and the enantiomer excess was determined by polarimetry [9].

3. Results and discussion

3.1. Hydrogenation of MAC with cationic and with neutral Rh-catalysts

The results (Fig. 2, Table 1) show that activity and selectivity of the immobilized cationic Rh-

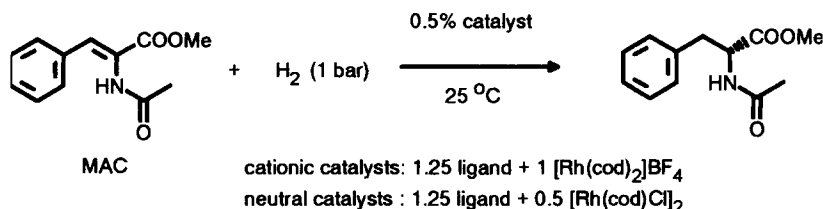


Fig. 2. Hydrogenation of MAC with cationic and with neutral Rh-catalysts.

catalysts are practically not affected by catalyst loading. We have often observed that the performance of these catalysts improves when they are reused. Therefore, the results for the first and second run are given. The reused catalysts have a very similar performance as their homogeneous counterparts, and belong to the most effective immobilized enantioselective catalysts known. As is shown with the bis-PPM ligands, variation of the local catalyst concentration has no effect on activity and selectivity. All these findings indicate that cationic diphosphine-Rh-catalysts have no tendency to interact with each other.

The neutral catalysts are about 2–3 times less active than the cationic catalysts and, in contrast to the cationic catalysts, clearly loose activity when their loading is increased. It can be ruled out, that mass-transport inhibition due e.g. to a possible reduction of the pore size by a denser coating of the pore-surface is responsible for the result, since in that case an even stronger decrease in activity should be observed with the more active

cationic catalysts. The experiments with bis-PPM show, that the activity of the neutral catalysts also decreases with increasing local concentration. Based on these results we conclude that the neutral diphosphine Rh-complexes do interact with each other in a way that is detrimental for their catalytic performance. Several observations reported in the literature indicate that less active or inactive chlorine-bridged dimers are formed: It was shown that homogeneous DIOP-Rh-chloride catalysts deactivate by a second-order process with respect to the catalytically active species. This deactivation was ascribed to the formation of chlorine-bridged dimers [10]. Also, it was found in hydrogenation and hydrosilylation reactions with neutral Rh-catalysts bound to immobilized monophosphines of the type Silicagel–Si–(CH₂)_n–PPh₂ that the catalytic activity was significantly higher with short spacers than with long ones [11,12]. This was attributed to the difference in nature of the catalytic species formed on the surface. A bimolecular structure for the catalysts of lower activity and a

Table 1

Influence of catalyst loading on the hydrogenation of MAC with cationic and neutral Rh catalysts

Ligand	Loading mmol lig/g support	Cationic catalysts				Neutral catalysts	
		1st run		2nd run		rate _{obsvd} ^a	ee
		rate _{obsvd} ^a	ee	rate _{obsvd} ^a	ee		
BPPM		18	94.8			9	93
PPM-C12-PPM		18	95.5			3.9	92.6
PPM-C6-PPM		18	95.5			1.8	92.4
Si-PPM-1	0.016					12.5	84.8
Si-PPM-2	0.058					6.7	85.2
Si-PPM-3	0.092					4.7	87.2
Si-PPM-5	0.11	13	93.5	22	94.5	3.9	85
Si-PPM-4	0.19					1.4	86.9
Si-PPM-2	0.2	11	91.2	19	93.1	1.2	82.2

See Experimental part for details.

^a The observed rate is given as max. turnover frequency [min⁻¹].

mononuclear one for the more active catalyst was postulated and confirmed by ESCA and IR measurements.

No explanation can be given for the significantly lower selectivity of the immobilized neutral catalysts. The fact that the selectivity is not influenced by the local catalyst concentration (see experiments with BPPM and bis-PPM ligands) indicates that additional factors like e.g. interactions with the support surface may also be important.

It is interesting to note that with only very few exceptions, all immobilized enantioselective Rh-diphosphine catalysts that have been reported in the literature so far were neutral [1] and were much less active than their homogeneous analogs. This may be due to improper preparation or choice of the supports, or, as indicated by our experiments, in some cases also to catalyst deactivation caused by the formation of inactive dimers.

3.2. Hydrogenation of MEI with Ir-catalysts

We have recently developed a new class of Ir-catalyst for the enantioselective hydrogenation of imines (Fig. 3) [9]. These catalysts are highly active but have a strong tendency to deactivate. NMR-experiments indicated that deactivation may be due to the formation of hydride-bridged Ir-dimers as they have been observed in the hydrogenation of alkenes [13]. We were therefore interested to see whether deactivation can be avoided by preventing the active sites to interact. The results in Table 2. show that this is indeed possible. While the homogeneous Ir-BPPM catalyst is deactivated after 26% conversion, the immobilized catalysts are much more active and productive. The fact that their activity increases with decreasing catalyst loading is a clear indica-

Table 2

Influence of catalyst loading on the hydrogenation of MEI with IR catalysts

Ligand	Loading mol lig/g support	rate _{obsvd} ^a	ee
BPPM		0 ^b	45.2
Si-PPM-1	0.016	5.1	55.2
Si-PPM-2	0.058	2.4	55.5
Si-PPM-4	0.19	0.45	4.8

See experimental part for experimental details.

^a The observed rate is given a turnover frequency [min^{-1}] at 50% conversion.

^b Catalyst was deactivated after 26% conversion.

tion for a site isolation effect. No explanation can be given for the significantly better selectivity of the immobilized catalysts.

To our knowledge there is only one other example for an immobilized enantioselective Ir-catalyst described in the literature [14]. Similarly as we observed with our catalysts, heterogenization of functionalized chiral diamine-Ir-complexes through copolymerization resulted in catalysts that were significantly more active and selective in the transfer-hydrogenation of ketones.

3.3. Discussion of site isolation

General aspects

If k is the rate of a monomeric catalyst for a given reaction and this catalyst forms inactive dimers with an equilibrium constant K , the observed reaction rate will depend on k , K and the catalyst concentration. The hydrogenations with free BPPM were run with a catalyst concentration of about $6 \cdot 10^{-4}$ mol/l. With bis-ligands the catalyst concentration is estimated to be much higher: 0.27 mol/l for PPM-C12-PPM and 0.79 mol/l for PPM-C6-PPM (based on the assumption that two catalyst-molecules are within a sphere with a

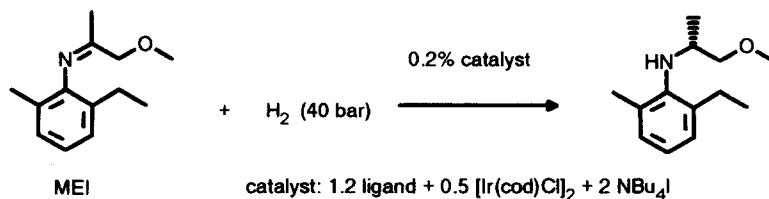


Fig. 3. Hydrogenation of MEI with Ir-catalyst.

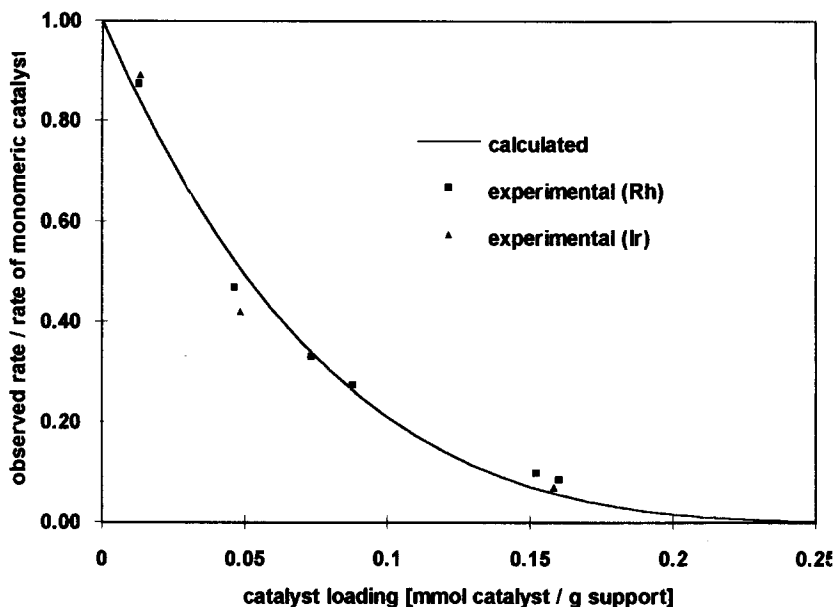


Fig. 4. Observed rates of hydrogenations of MAC with neutral Rh and of MEI with Ir as a function of catalyst loading. The calculations are based on $n=4$; specific surface area of the support = $324 \text{ m}^2/\text{g}$. The catalyst site area (1.74 nm^2) and the rate of the monomeric Rh-catalyst (14.4 min^{-1} (max. TOF)) was obtained from a least squares fit of our Rh-results. The same catalyst site area was used to fit the rate of the monomeric Ir-catalyst (5.7 min^{-1} (TOF at 50% conversion)).

diameter of a stretched bis-PPM ligand). Accordingly, the formation of dimers and deactivation will be highly favored with the bis-ligands. In contrast to free catalysts, immobilized catalysts have a fraction of catalytic sites which are sufficiently close to each other to interact and another fraction of sites that are completely isolated. It can be assumed that the first fraction will behave like catalysts with bis-ligands, that is, the probability for the formation of inactive dimers will be very high, while the second fraction will remain active. If the catalytic sites can be bound to the support surface with random distribution, the ratio between these two fractions can be controlled by the catalyst loading. Therefore, with such immobilized catalysts, the observed reaction rate will mainly depend on the catalyst loading.

Fit of our results with a mathematical model

A mathematical model that describes the observed reaction rate as a function of catalyst loading has been proposed [6]. It is based on the assumption that the catalyst-molecules are bound in a random distribution on a rigid surface and that if two catalyst-molecules are within reaction dis-

tance they become inactive. The equation of this model can be adapted for experiments, where the number of catalyst molecules is kept constant and only the catalyst loading is varied. The equation then is:

$$\text{rate}_{\text{obsvd}} = k(1 - \rho)^n$$

where

k = rate constant of monomeric catalyst

ρ = (moles loaded) (6.023×10^{23} * (area of each complex) / (total surface area of support))

$n = 4$ or 6 for squares sites or circular sites

$(1 - \rho)^n$: fraction of catalyst molecules that cannot form dimers

Although our experiments are only semiquantitative, we tried to fit the observed rates for neutral Rh and for Ir. From a non-linear least square fit with the Rh-results, we obtained the area of the catalytic site (1.74 nm^2) and the rate of the monomeric Rh-catalyst (14.3 min^{-1} (max. TOF)). As was observed with titanocenes [6], this site area is significantly smaller than expected. In the case of titanocenes this was accounted for by recognizing that the dimerization reaction may require a very specific relative orientation and that

the normal surface area measurements may not truly reflect the solution reaction area. In our reactions, the formation of dimers may not be irreversible and the dimers not completely inactive. This may also be reflected in this apparent site area. The same catalytic site area was used to fit the rate of the monomeric Ir-catalyst (5.7 min^{-1} (TOF at 50% conversion)). As is shown in Fig. 4 the experimental data are in good agreement with the calculated curve. This is a further support for the occurrence of site isolation effects.

3.4. Practical aspects

The fact that catalyst loading can have a strong influence on catalyst performance has important implications on the preparation and the usefulness of immobilized catalysts. In all cases, catalysts that are not affected by high local concentrations are preferred. With catalysts which deactivate through interactions between themselves site isolation has to be achieved. To do so, large amounts of support are required: Our immobilized catalyst with the lowest loading has a weight of 63 kg per mole and, according to the above model has about 85% of isolated sites. Due to the low specific weight of the highly porous silicagel supports these 63 kg correspond to a catalyst volume of about 180 l/mol. In a hydrogenation with a substrate/catalyst ratio of 1000 and a substrate with a molecular weight of 200 g the volumes of the catalyst and of the substrate will be about the same. It is obvious that the handling of such large amounts of supports for the catalyst-preparation and in catalytic processes will be circumstantial and expensive. Therefore, the practical use of such catalysts will be restricted.

Acknowledgements

The author thanks Hans-Peter Jalett, Andrea Schwendemann and Heidi Landert for the experimental work and is also grateful to Hans-Ulrich Blaser and Martin Studer for the valuable discussions and for the critical reading of the manuscript.

References

- [1] R. Selke, K. Häuptke and H.W. Krause, *J. Mol. Catal.*, 56 (1989) 315, and refs. therein.
- [2] B. Pugin, F. Spindler and M. Müller, EP 496699-A1 (25. Jan. 1991) and EP 496700-A1 (25. Jan. 1991); B. Pugin and M. Müller, in M. Guisnet al. (Ed.), *Heterogeneous Catalysis and Fine Chemicals III*, Stud. Surf. Sci. and Cat., 78 (1993) 107.
- [3] W. Dumont, J.-C. Poulain, T.P. Dang and H.B. Kagan, *J. Am. Chem. Soc.*, 95 (1973) 8295.
- [4] C.U. Pittman, in P. Hodge and D.C. Sherrington (Eds.), *Polymer Supported Reactions in Organic Synthesis*, Wiley, Chichester, 1980, p. 249–291; F.R. Hartley, in F.R. Hartley (Ed.), *The Chemistry of the Metal–Carbon Bond*, Vol. 4, John Wiley & Sons Ltd., Chichester, 1987, p. 1163–1225; D.C. Sherrington, *Pure & Appl. Chem.*, 60 (1988) 401; M. Capka, *Collect. Czech. Chem. Commun.*, 55 (1990) 2803.
- [5] R.H. Grubbs, C. Gibbons, L.C. Kroll, W.D. Bonds and C.H. Brubaker, *J. Am. Chem. Soc.*, 95 (1973) 2374; W.D. Bonds, C.H. Brubaker, E.S. Chandrasekaran, C. Gibbons, R.H. Grubbs and L.C. Kroll, *J. Am. Chem. Soc.*, 97 (1975) 2128; E.S. Chandrasekaran, R.H. Grubbs and C.H. Brubaker, *J. Organomet. Chem.* 120 (1976) 49.
- [6] R. Grubbs, C.P. Lau, R. Cukier, and C. Brubaker, *J. Am. Chem. Soc.*, 99(13) (1977) 4517.
- [7] B.L. Booth, G.C. Ofune, C. Stacey and P.J.T. Tait, *J. Organometal. Chem.*, 315 (1986) 143.
- [8] M. Capka and Alena Reissova, *Collect. Czech. Chem. Commun.*, 54 (1989) 1760.
- [9] F. Spindler, B. Pugin and H.U. Blaser, *Angew. Chem. Int. Ed. Engl.*, 29 (1990) 558.
- [10] J. Vilim and J. Hetflejš, *Collect. Czech. Chem. Commun.*, 43 (1978) 122.
- [11] M. Czakova and M. Capka, *J. Mol. Catal.*, 11 (1981) 313.
- [12] I.Z. Michalska, M. Capka and J. Stoch, *J. Mol. Catal.*, 11 (1981) 323.
- [13] R. Crabtree, *Acc. Chem. Res.*, 12 (1979) 331; D. Chadosh, R. Crabtree, H. Felkin S. Morehouse and G. Morris, *Inorg. Chem.*, 21 (1982) 1307; H.H. Wang and L.H. Pignolet, *Inorg. Chem.*, 19 (1980) 1470.
- [14] J. Kaschig, EP251994 A1 (16.5.1986). G. Zassinovich, G. Mestroni and S. Gladioli, *Chem. Rev.*, 92 (1992) 1051.