Secondary Phosphine Oxides in Rhodium(III) Catalyzed Transfer Hydrogenation of Ketones

*Pascal M. Castro, Henrik Gulyás, Jordi Benet-Buchholz Zoraida Freixa, and Piet W. N. M. van Leeuwen,**

General procedures

All manipulations were performed under inert atmosphere using standard Schlenk and glovebox techniques. All solvents were dried with an SPS of IT-Inc except isopropanol which was either dried over activated molecular sieves or distilled from Mg/I_2. Water content was checked to be below 20 ppm by titration on a Karl Fisher titration unit Metrohm 831 KF. All reagents were purchased from commercial sources and used as received. Cyclohexanone and acetophenone (Acros) were dried over CaH_2 or used as received. (R)- and (S)- dinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphepin, 4-oxide (**2**) were synthesized from (R)- and (S)- [1,1'-Binaphthalene]-2,2'-diol (binol) respectively and PCl_3 according to a literature procedure.[1]
NMR spectra were recorded by using Teflon capped or J. Young NMR tube with a Bruker Avance 400 Ultrashield NMR spectrometer or a Bruker Avance 500 Ultrashield NMR spectrometer for the variable temperature experiments. Electrospray ionization mass spectra (ESI-MS) spectra were recorded with a Waters LCT Premier spectrometer in dry MeOH or MeCN. Gas chromatography analyses were carried out on an Agilent Technologies 6890N/G1530N spectrometer equipped with a FID detector and a Supelco Beta Dex 120 fused silica capillary chiral column (30m × 0.25mm diameter × 0.25μm film thickness).

Synthesis of R*-4,5-dihydro-3H-dinaphtho[2,1-c:1',2'-e]phosphepine-4-oxide (3)*

2,2'-di(lithiomethyl)-1,1'-binaphthyl · 2 N,N,N',N'-tetramethylethylenediamine (10.48 g, 19.9 mmol), prepared from optically pure (*R*)-binol according to the literature procedures,[2] was treated with hexane (70 mL). Diethylphosphoramidous dichloride (3.3 mL, 22.5 mmol), in a small amount of hexane (~3 mL), was slowly added to the suspension with a Hamilton syringe at 0 °C external temperature (ice bath). The residual reagent from the Hamilton syringe was rinsed into the reaction mixture with hexane (5 mL + 3 mL). The reaction mixture was refluxed for 4 hours. The hexane was removed in vacuum. The obtained yellow solid was extracted with toluene (3 × 50mL). The toluene was removed from the combined extracts in vacuum, and the crude 4-diethylamino-4,5-dihydro-3H-dinaphtho(2,1-c; 1',2'-e)phosphepine was dissolved in THF (50 mL). Aqueous HCl solution (50 mL, 6N, 300 mmol) was added at 0 °C external temperature. The ice bath was removed, and the reaction mixture was stirred at room temperature overnight. All the volatiles were removed in vacuum. The obtained yellow solid was extracted with a mixture of toluene (50 mL) and THF (60 mL). The

[1] T. C. H. Lam, W-L. Mak, W-L. Wong, H-L. Kwong, H. H. Y. Sung, S. M. F. Lo, I. D. Williams, W-H. Leung, *Organometallics* **2004**, *23*, 1247.
[2] H. Klein, R. Jackstell, K.-D. Wiese, C. Borgmann, M. Beller, *Angew. Chem. Int. Ed.*, **2001**, *40*, 3408-3411.

insoluble residue, a yellowish waxy material, was washed again with toluene (50 mL). The extracts were combined, and solvents were removed in vacuum. The crude product was purified by column chromatography (1. silica, CH_2Cl_2, CH_2Cl_2:EtOH (v/v 9/1); 2. silica, CH_2Cl_2:EtOH (v/v 9/1)). The product is a white foamy solid. Overall yield: 3.00 grams (46%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 2.94-3.14 (m, 2H, CH*H*, C'H*H*); 3.26-3.47 (m, 2H, C*H*H, C'*H*H); 7.26 (dd, J_{PH} = 461 Hz, J_{HH} = 7.9 Hz, P(O)H), 7.19-7.33 (m, 4H, binaphthyl); 7.45-7.56 (pseudo q, 3H, binaphthyl); 7.66 (d, J_{HH} = 8.2 Hz, 1H, binaphthyl); 7.92-8.03 (m, 4H, binaphthyl). ^{13}C{^{1}H}-NMR (400 MHz, $CDCl_3$): δ = 33.95 (d, J_{PC} = 63 Hz, CH_2); 34.60 (d, J_{PC} = 62 Hz, CH_2); 125.84 (d, J_{PC} = 1.5 Hz, binaphthyl CH); 126.05 (d, J_{PC} = 1.5 Hz, binaphthyl CH); 126.54 (s, binaphthyl CH); 126.70 (s, 2C overlapped, binaphthyl CH); 126.96 (d, J_{PC} = 1.5 Hz, binaphthyl CH); 127.45 (d, J_{PC} = 4.4 Hz, binaphthyl CH); 127.90 (d, J_{PC} = 8.1 Hz, binaphthyl); 128.19 (d, J_{PC} = 3.7 Hz, binaphthyl CH); 128.31 (d, J_{PC} = 1.5 Hz, binaphthyl CH); 128.43 (d, J_{PC} = 1.5 Hz, binaphthyl CH); 128.66 (d, J_{PC} = 11.0 Hz, binaphthyl); 129.08 (d, J_{PC} = 2.9 Hz, binaphthyl CH); 129.4 (d, J_{PC} = 1.5 Hz, binaphthyl CH); 131.94 (d, J_{PC} = 1.5 Hz, binaphthyl); 132.37 (d, J_{PC} = 2.2 Hz, binaphthyl); 133.0 (d, J_{PC} ~ 2 Hz, binaphthyl) overlapped with 130.01 (d, J_{PC} ~ 3 Hz, binaphthyl); 133.58 (d, J_{PC} = 3.7 Hz, binaphthyl); 134.17 (d, J_{PC} = 4.4 Hz, binaphthyl). ^{31}P{^{1}H}-NMR (162 MHz, $CDCl_3$): δ = 45.84 (s). ^{31}P-NMR (162 MHz, $CDCl_3$): δ = 45.84 (dm, $^1J_{PH}$ = 461 Hz). HRMS (TOF ES^-) calculated for $C_{22}H_{16}OP$ ($M\text{-}H^+$): 327.0939. Found: 327.0942.

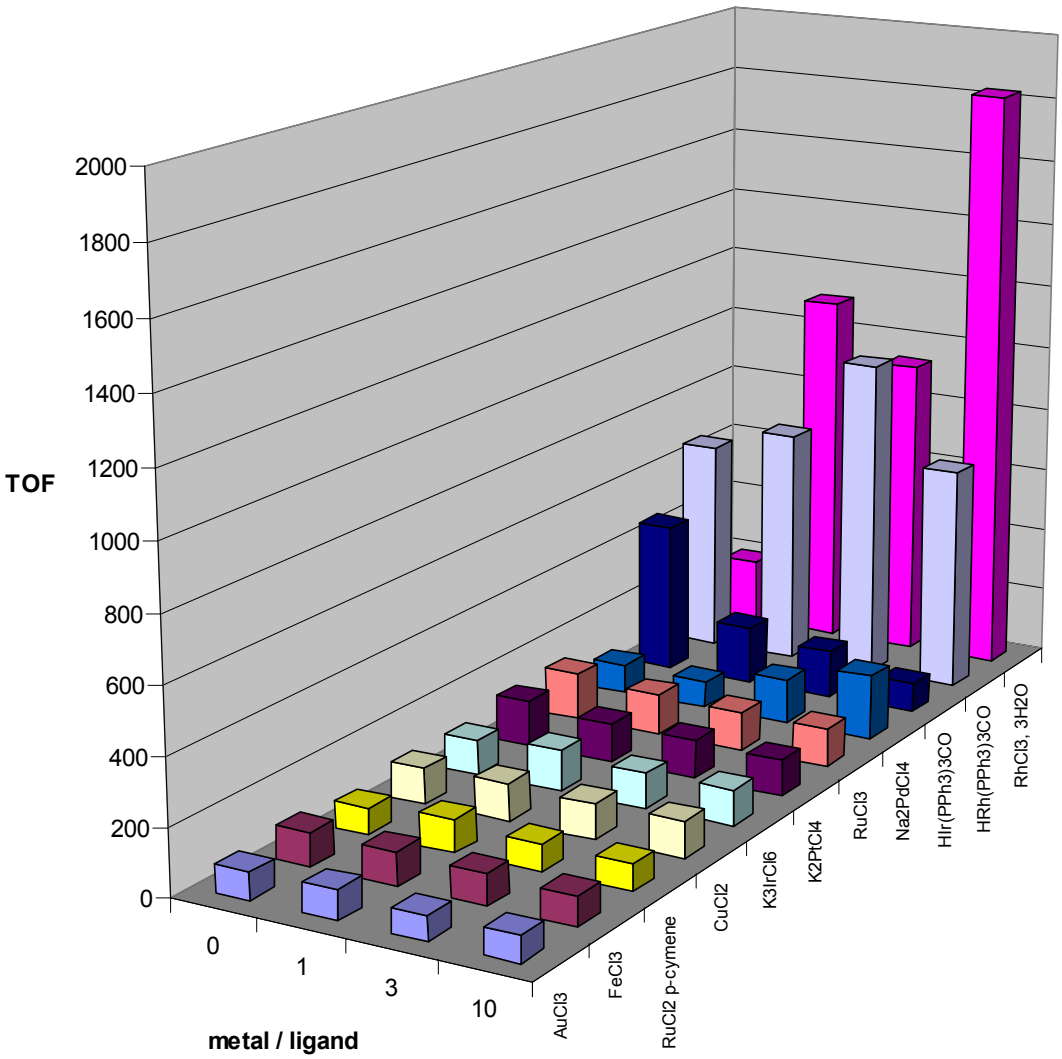
Transfer hydrogenation experiments

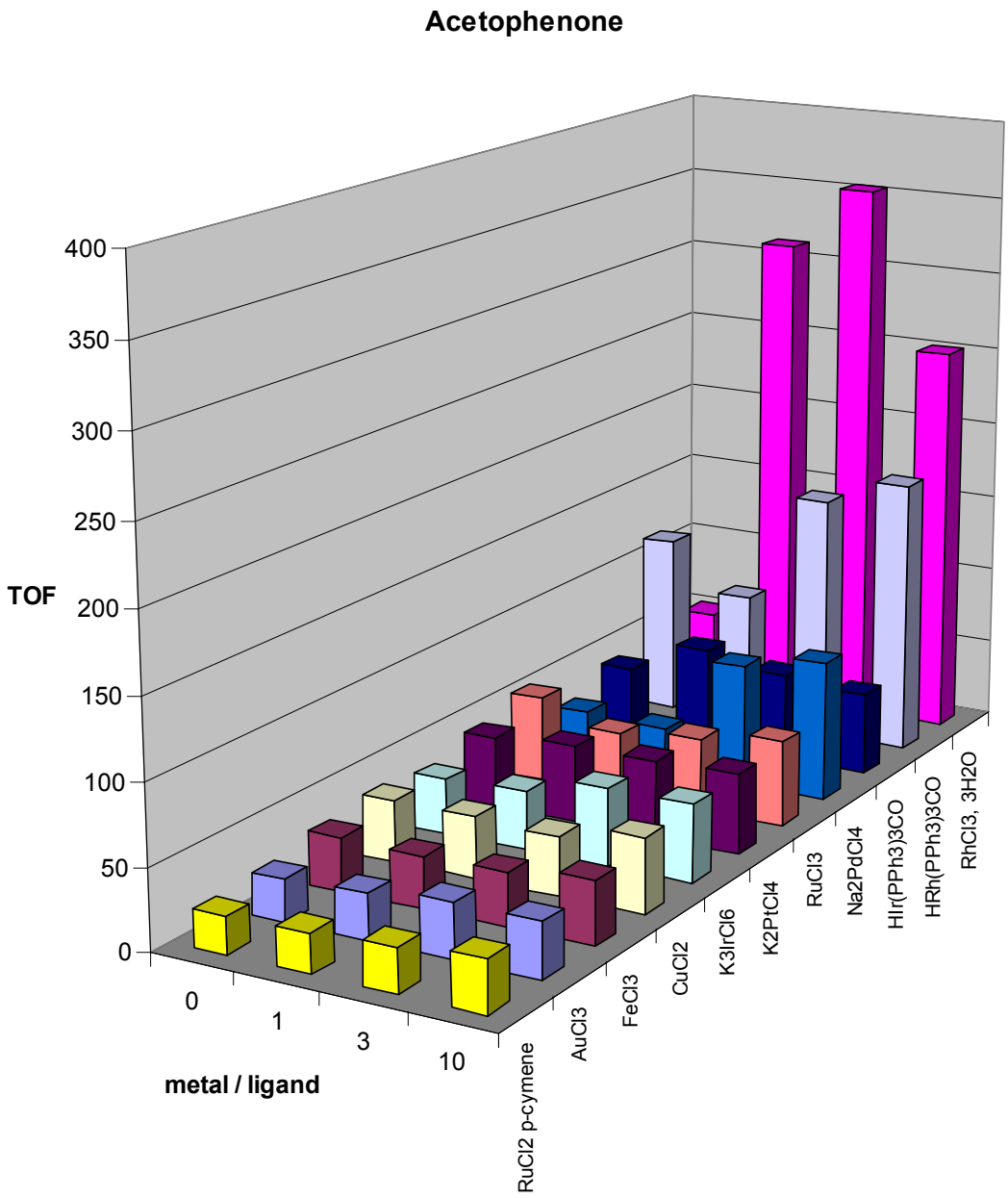
Reactions were performed in a parallel manner on a Radleys Discovery Technologies Carousel 12 reaction station.
In a typical transfer hydrogenation experiment, the corresponding metal salt and the desired amount of ligand were reacted in dry isopropanol at 80°C during one hour under an inert atmosphere to form the catalyst precursor. After this incubation period, if necessary the temperature was adjusted to the targeted value and the desired quantities of substrate (acetophenone or cyclohexanone) and base (potassium *tert*-butoxide) were added. Aliquots were taken after controlled periods of time, filtered through a silica pad and analyzed by gas-chromatography to determine conversions.

Metal screening with ligand **1**

Conditions: [metal] = 0.5 mmol/L, [metal] : [tBuOK] : [substrate] = 1:100:2000, 1 hour incubation at 80ºC and 1 hour reaction time at 80ºC. Ligand to metal ratios of 0, 1, 3 or 10 were used for this screening.
$AuCl_3$, $FeCl_3$, [(*p*-cymene)$RuCl_2$]$_2$, $CuCl_2$, K_2IrCl_6, K_2PtCl_4, $RuCl_3$, Na_2PdCl_4, $HIr(PPh_3)_3CO$, $HRh(PPh_3)_3CO$ and $RhCl_3 \cdot 3H_2O$ were used as the metal precursors.

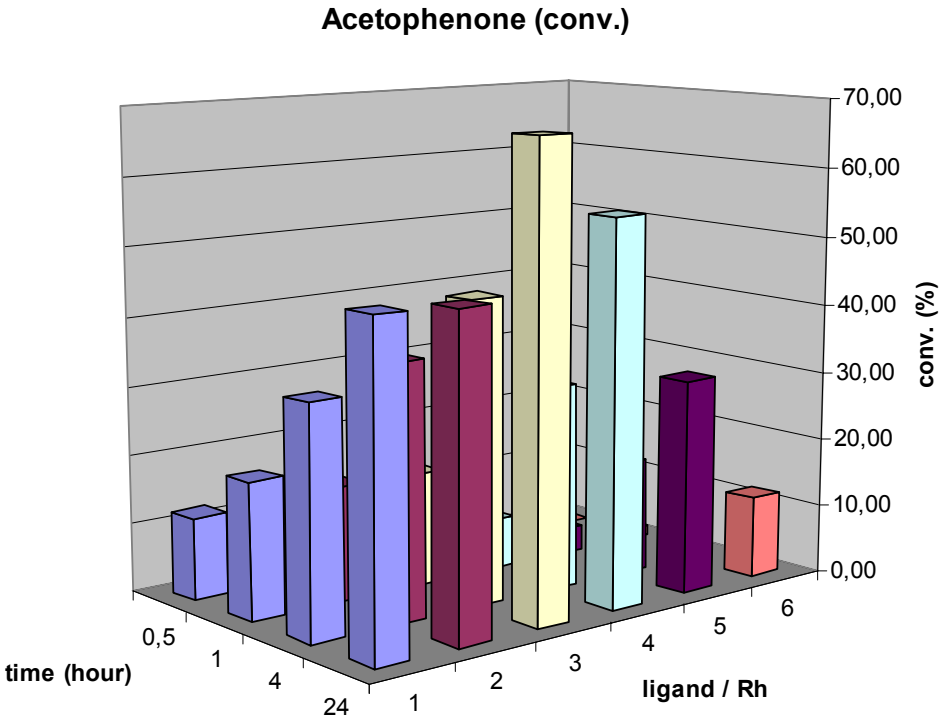
Cyclohexanone

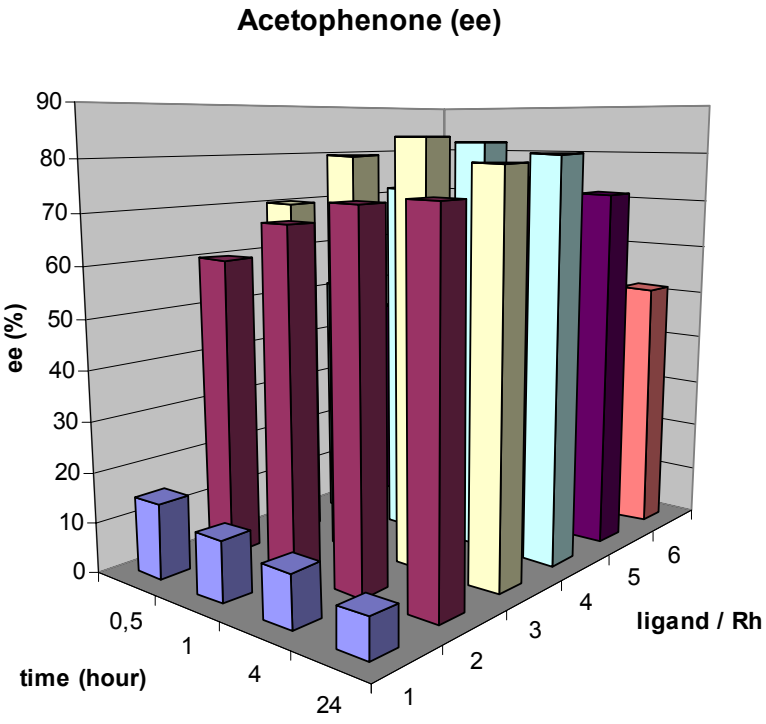




***High-throughput screening of acetophenone hydrogenation with ligand* 2**

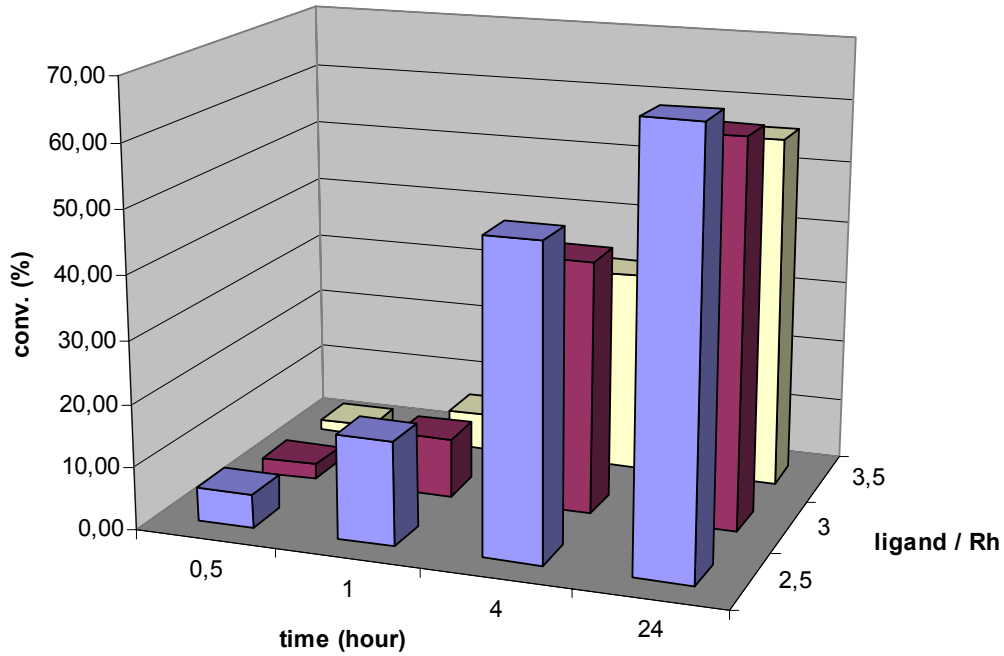
I) Ligand/metal ratio optimization.
Conditions: Ligand to metal ratios from 1 to 6 were used for this screening. [Rh] = 6.7 mmol/L, [Rh] : [tBuOK] : [acetophenone] = 1:20:200, 1 hour incubation at 80ºC and 24 hour reaction time at 40ºC with aliquots withdrawn after desired time and analyzed by GC.



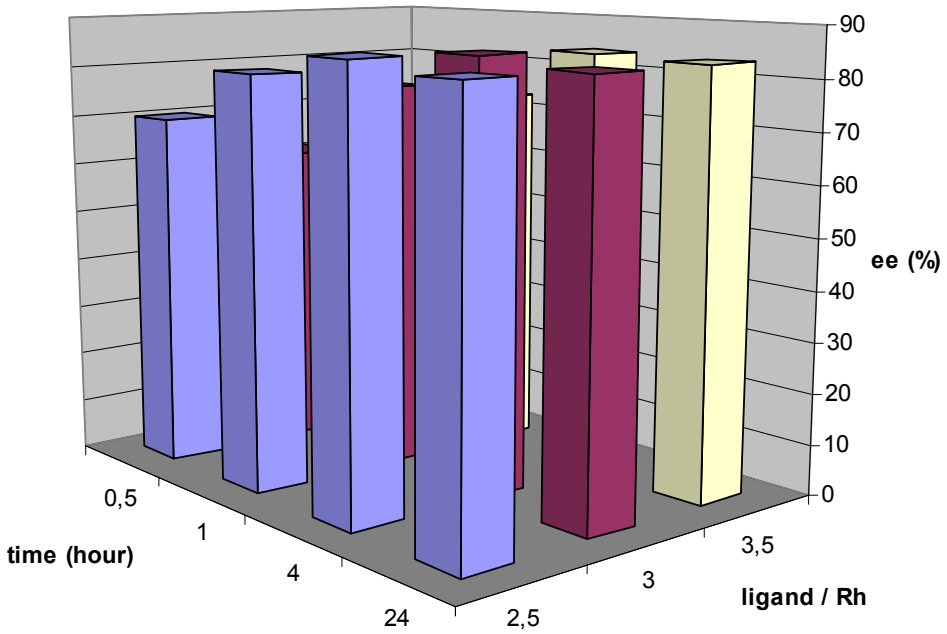


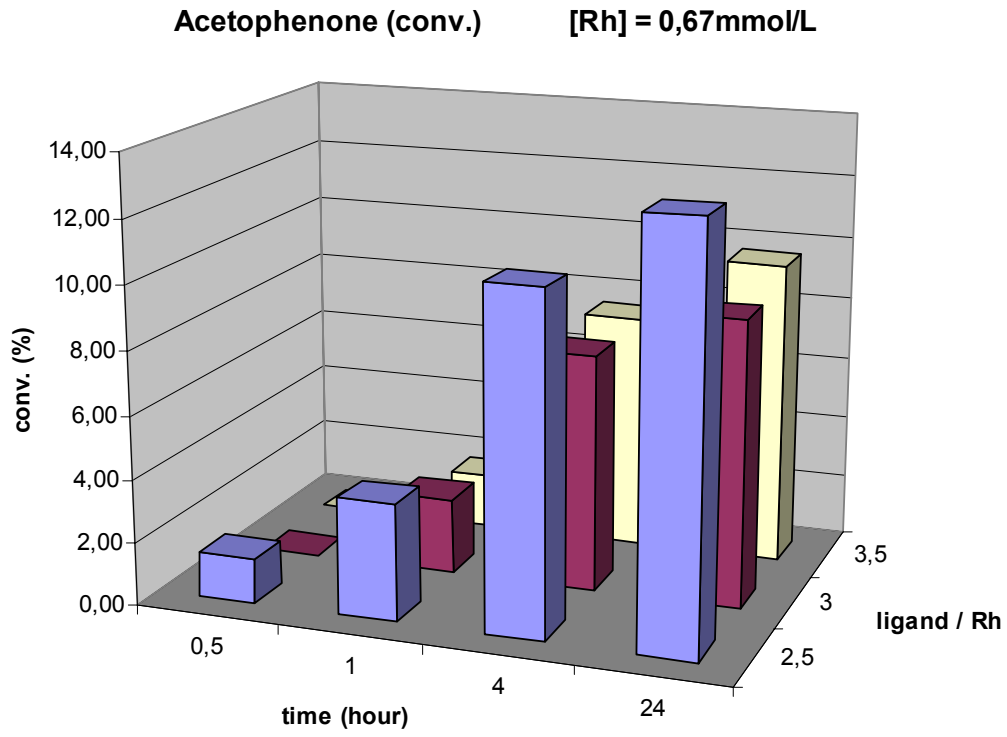
II) Ligand to metal ratio and catalyst concentration.
Conditions: Ligand to metal ratios close to the optimum value of 3 ([**2**]/[Rh] of 2.5, 3 and 3.5) and influence of catalyst concentration ([Rh] = 6.7 mmol/L and 0.67 mmol/L) were analyzed. [Rh] : [tBuOK] : [acetophenone] = 1:20:200, 1 hour incubation at 80ºC and 24 hour reaction time at 40ºC.

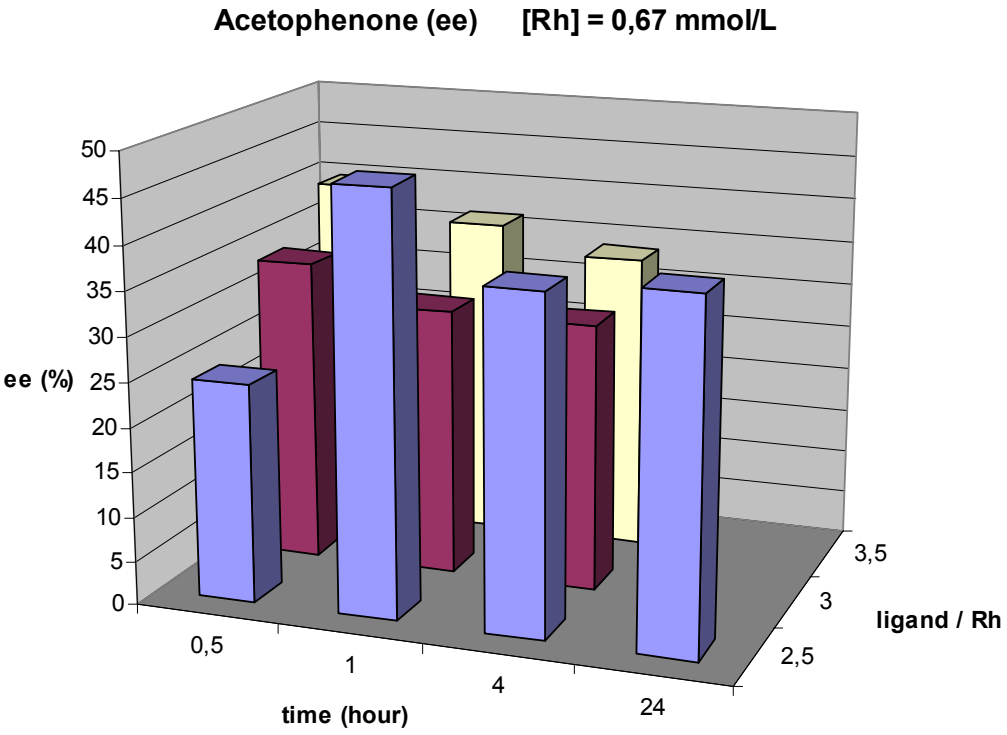
Acetophenone (conv.) [Rh] = 6,7mmol/L



Acetophenone (ee) [Rh] = 6,7 mmol/L

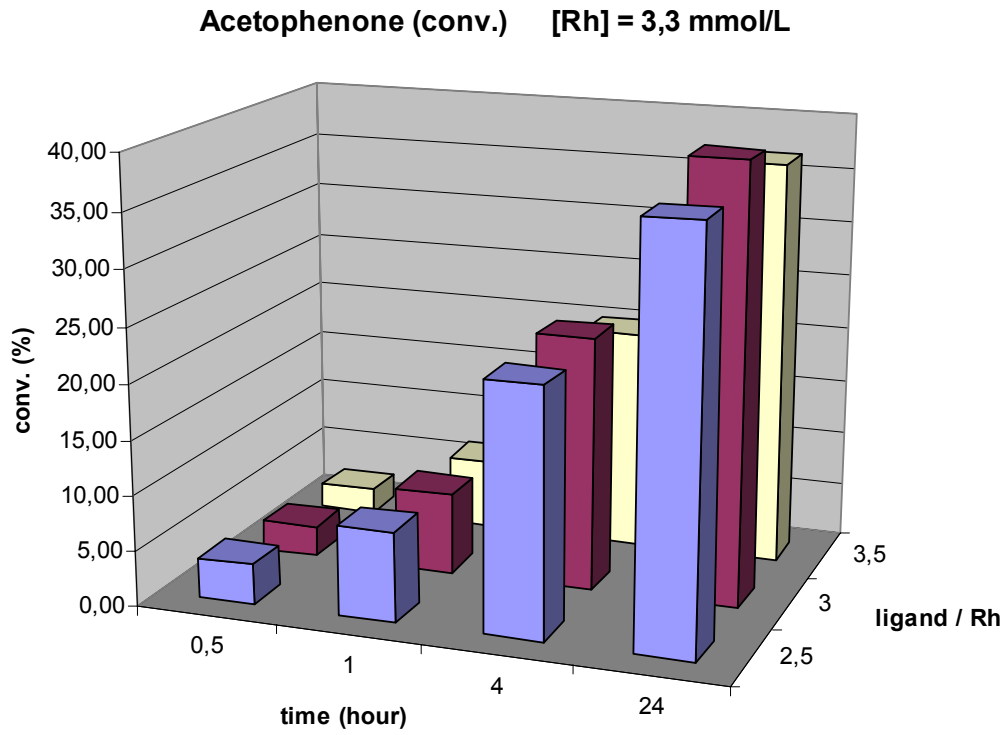


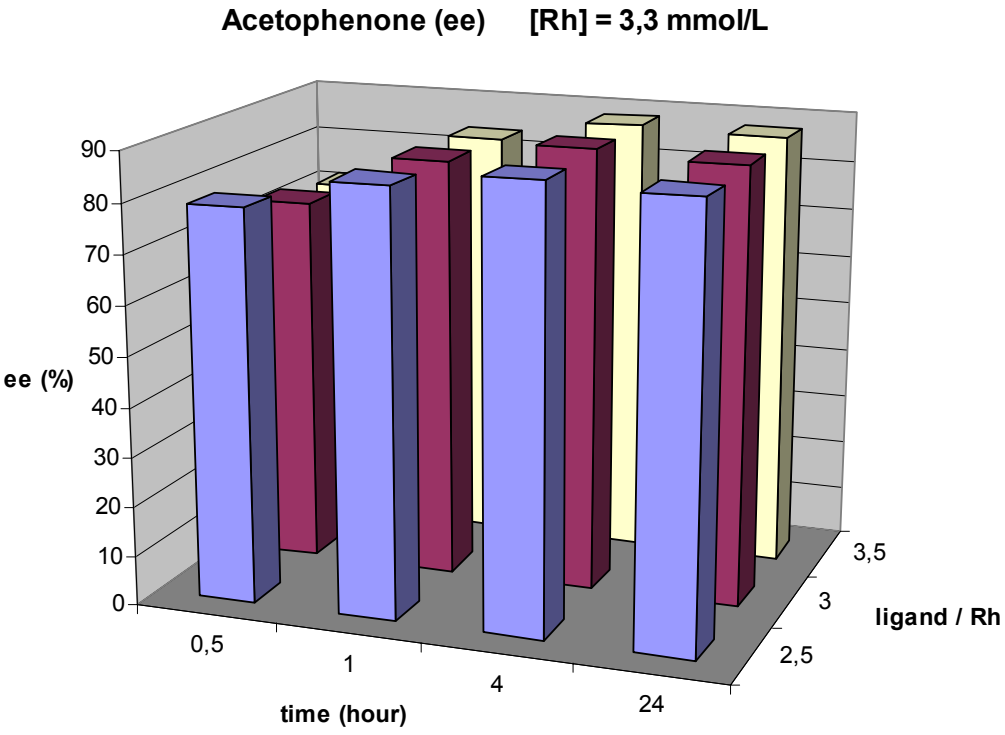




III) Ligand to metal ratio and substrate to metal ratio.
Ligand to metal ratios close to the optimum value of 3 ([**2**]/[Rh] of 2.5, 3 and 3.5) at higher substrate to metal ratio were investigated ([acetophenone]/[Rh] = 1000). Conditions: [Rh] = 3.3 mmol/L, [Rh] : [tBuOK] : [acetophenone] = 1:20:1000, 1 hour

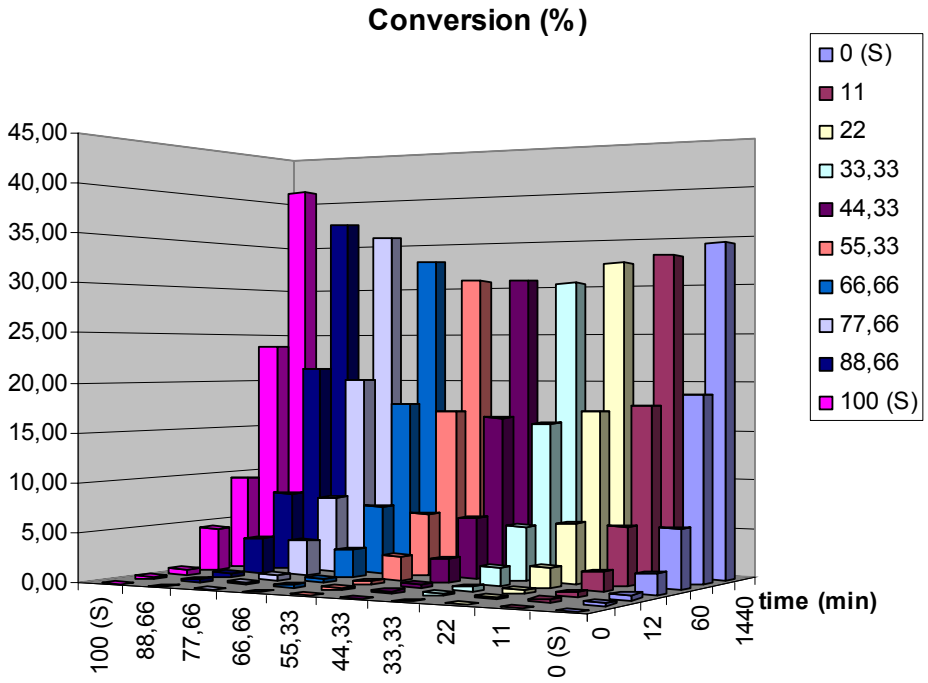
incubation at 80ºC and 24 hour reaction time at 40ºC with aliquots withdrawn after desired time and analyzed by GC.

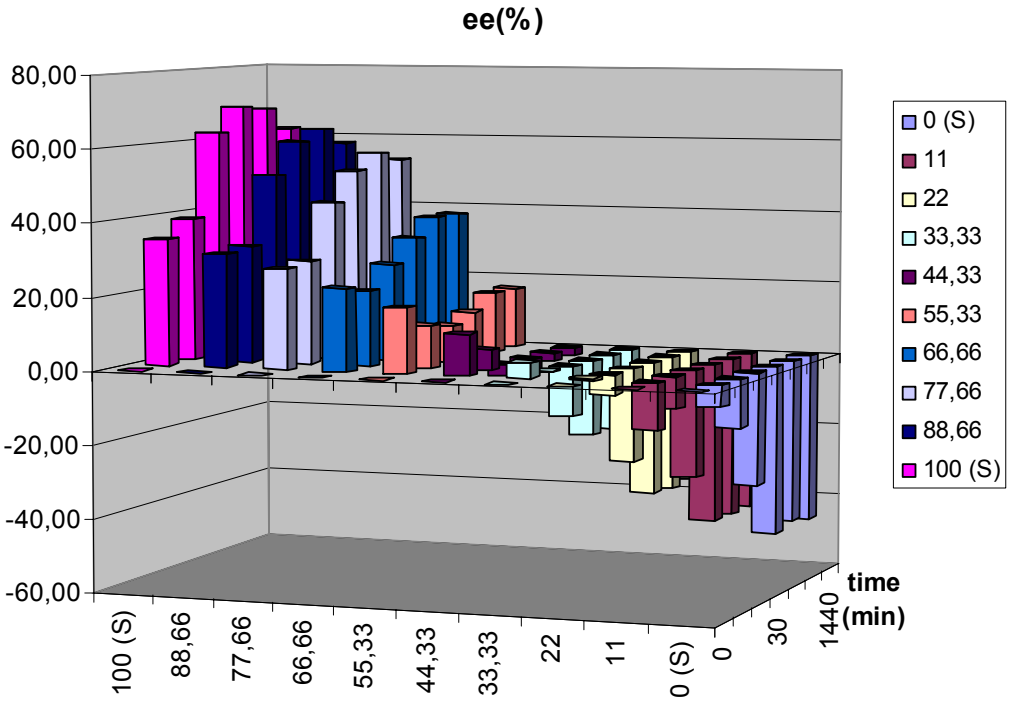


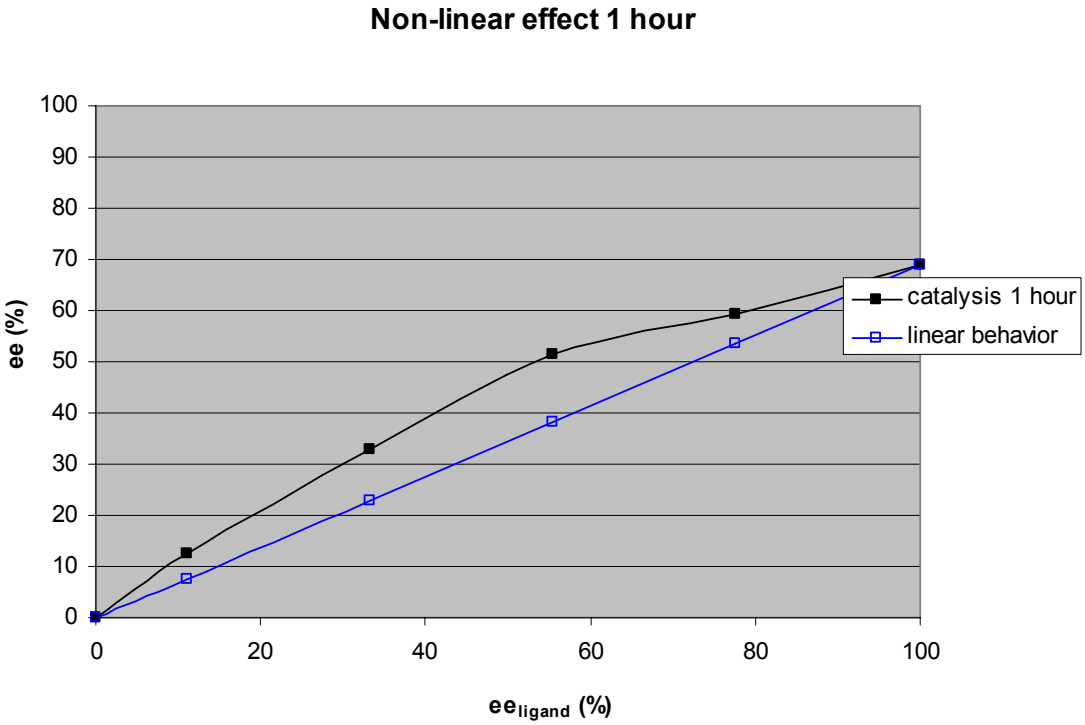


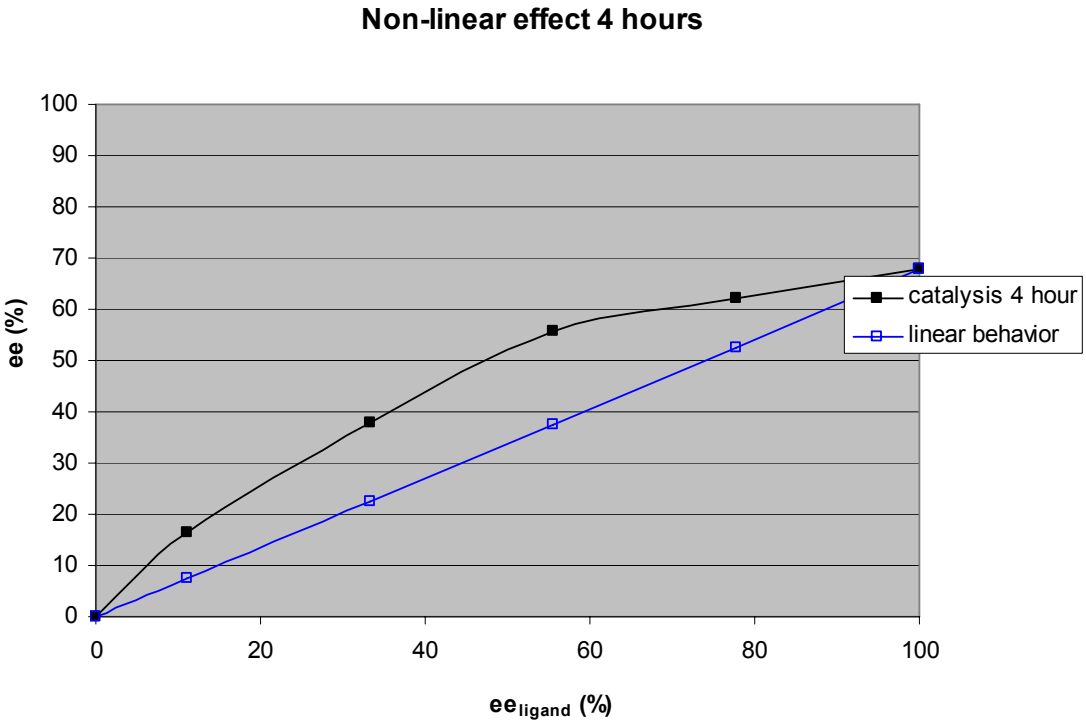
Non-linear effect

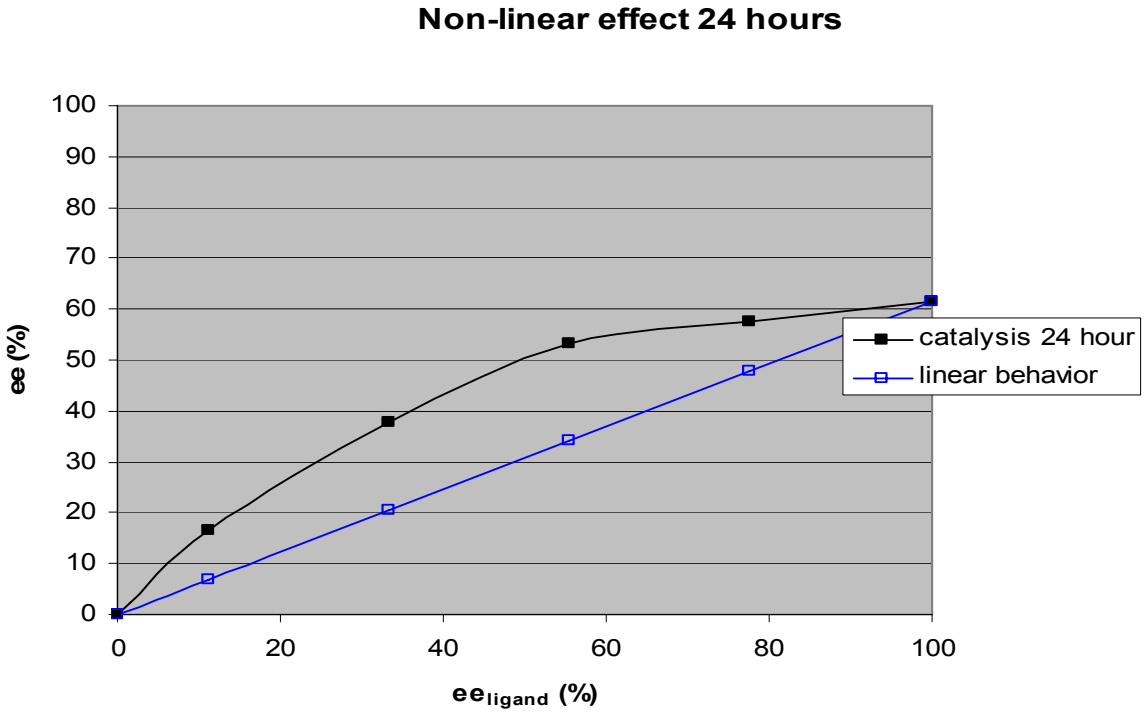
A test for a non-linear effect was undertaken with ligand **2** of varying enantiopurities. To this end, stock solutions of pure (S)-**2** and (R)-**2** in isopropanol were prepared and mixed in the desired ratio to obtain **2** from racemic to 100% enantiopure. The experiment was carried out in a Radleys Discovery Technologies Carousel 12 reaction station: [Rh] = 6.7 mmol/L, [Rh] : [tBuOK] : [acetophenone] = 1:20:1000, 1 hour incubation at 80ºC and 24 hour reaction time at 40ºC with aliquots withdrawn after desired time and analyzed by GC. The experiment was repeated twice, and in both cases it leaded to conversions and ee values inferior to the ones obtained before in isolated experiments. This phenomenon was attributed to the use of ligand stock solutions which might cause partial ligand decomposition.




ee(%)
80,00
60,00
40,00
20,00
0,00
-20,00
-40,00
-60,00
0 (S)
11
22
33,33
44,33
55,33
66,66
77,66
88,66
100 (S)
100 (S)
88,66
77,66
66,66
55,33
44,33
33,33
22
11
0 (S)
0
30
1440
time
(min)


Non-linear effect 1 hour
100
90
80
70
60
50
40
30
20
10
0
ee (%)
0
20
40
60
80
100
ee ligand (%)
catalysis 1 hour
linear behavior

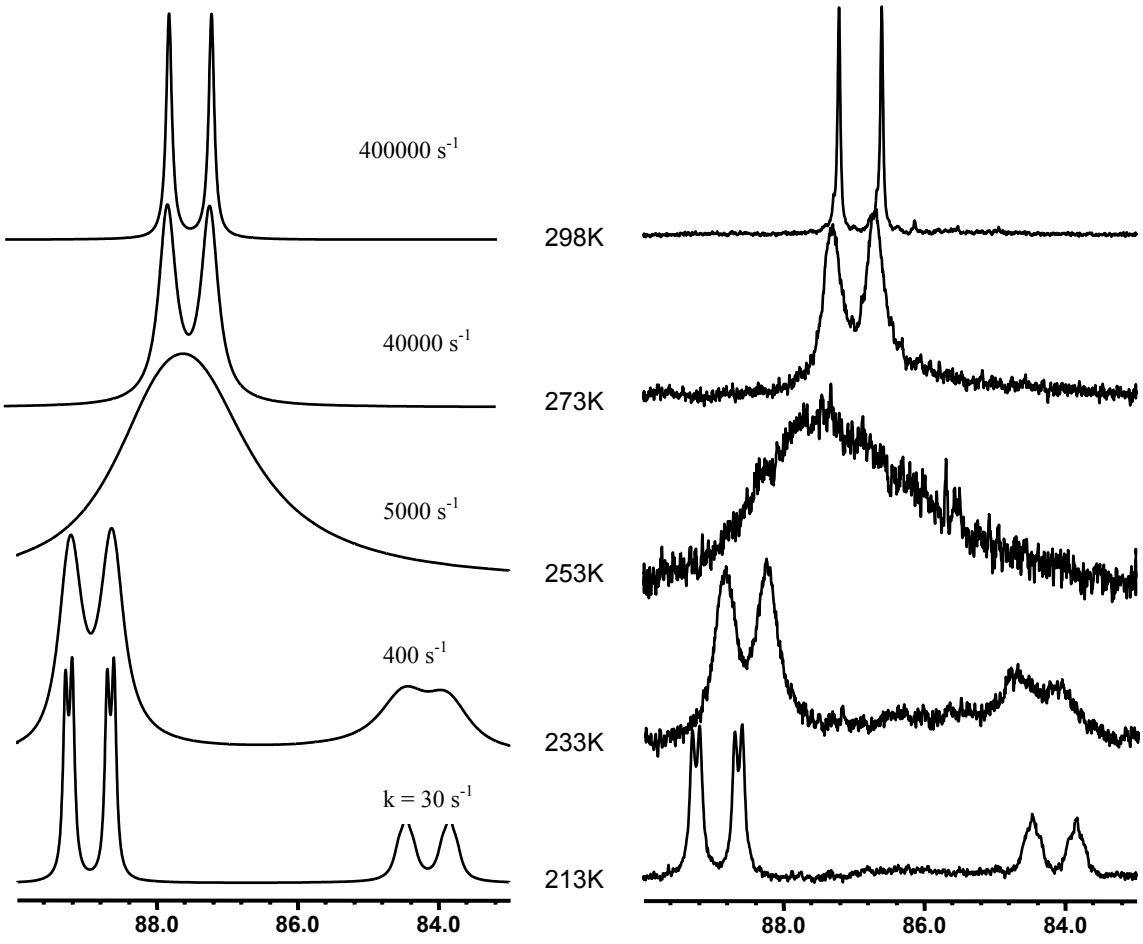




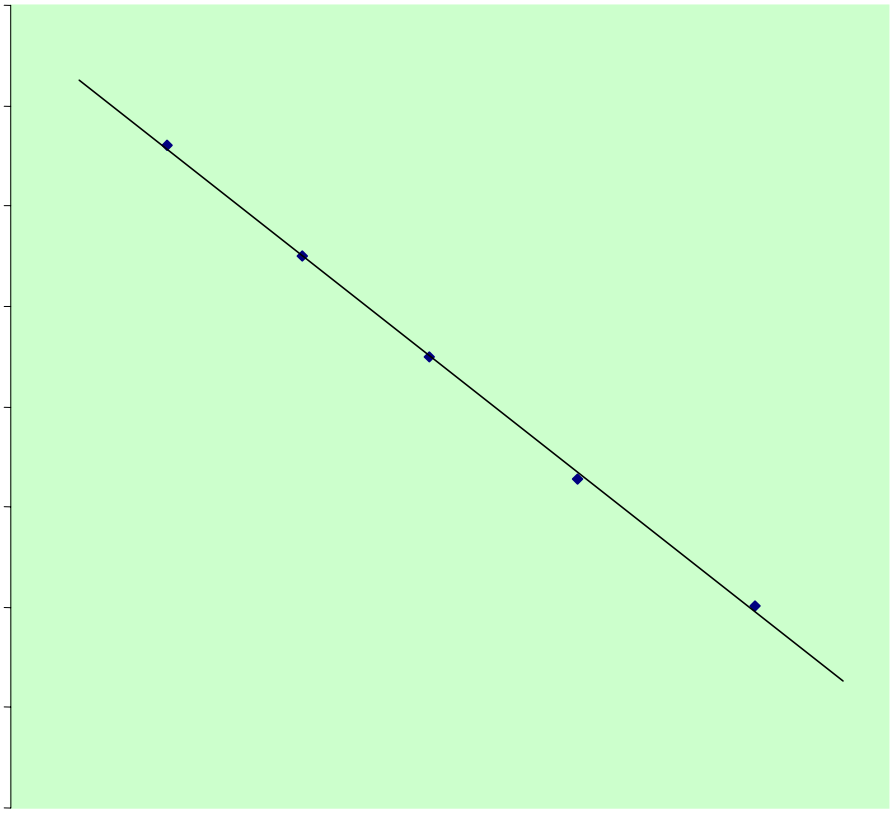
Variable temperature NMR experiments

$^{31}P\{^{1}H\}$ NMR spectra of complex **4** were recorded at different temperatures (from 213K to 298K) in dry $CDCl_3$ with a Young type NMR tube. Spectral simulations were

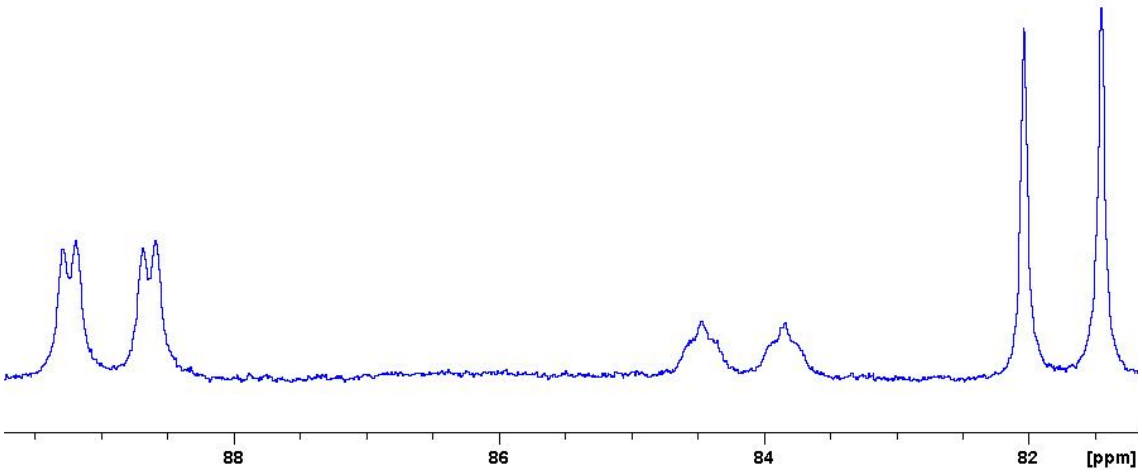
performed using gNMR 5.0. Activation parameters were obtained from a standard Eyring analysis according to the equation: $\ln k/T = (\ln k_b/h_p + \Delta S^{\neq}/R) - (\Delta H^{\neq}/R) \cdot 1/T$.



Simulated (left) and experimental (right) variable temperature $^{31}P\{^{1}H\}$ NMR of complex **4** ($CDCl_3$, 161.98 MHz). Best-fit rate constants k are shown with the simulated spectra



Eyring plot for complex **4** deduced from the variable $^{31}P\{^{1}H\}$ NMR experiment.



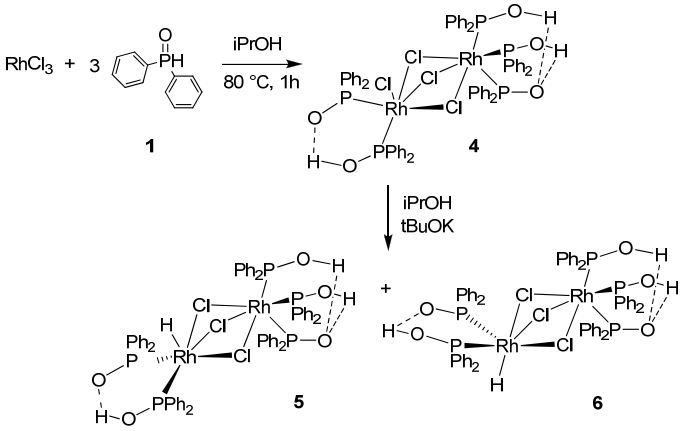
213K $^{31}P\{^{1}H\}$ NMR of complex **4** ($CDCl_3$, 161.98 MHz).

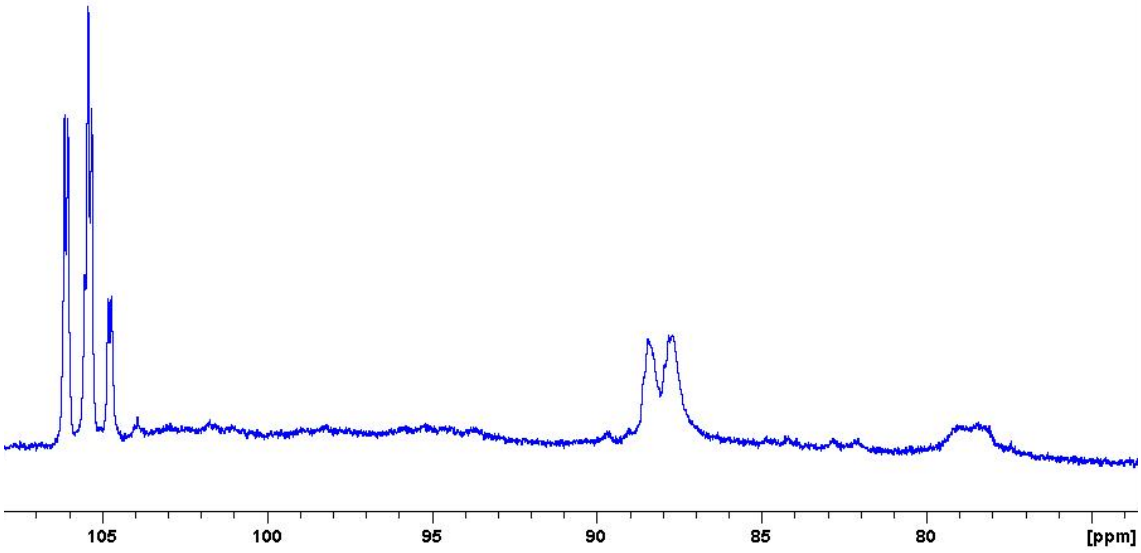
NMR spectra of complexes 5 and 6

Conditions: 20 mg of **4** (0.0147 mmol) were placed in a 25 mL Schlenk tube and dissolved in 5 mL of dry isopropanol, giving a turbid yellow solution. 5 equivalents of tBuOK (8.2 mg, 0.0735 mmol) were then added at room temperature and the system was stirred for ten minutes, giving a brown solution. The solvent was then removed under vacuum, yielding a beige powder which was dissolved in dry CD_2Cl_2 and transferred to a Young NMR tube under inert atmosphere. ^1H, $^1H\{^{31}P\}$, $^{31}P\{^1H\}$, ^{31}P, ^1H-^1H COSY and ^1H-^{31}P HMBC NMR experiments were recorded at 500 MHz (^1H) and 161.98 MHz (^{31}P).

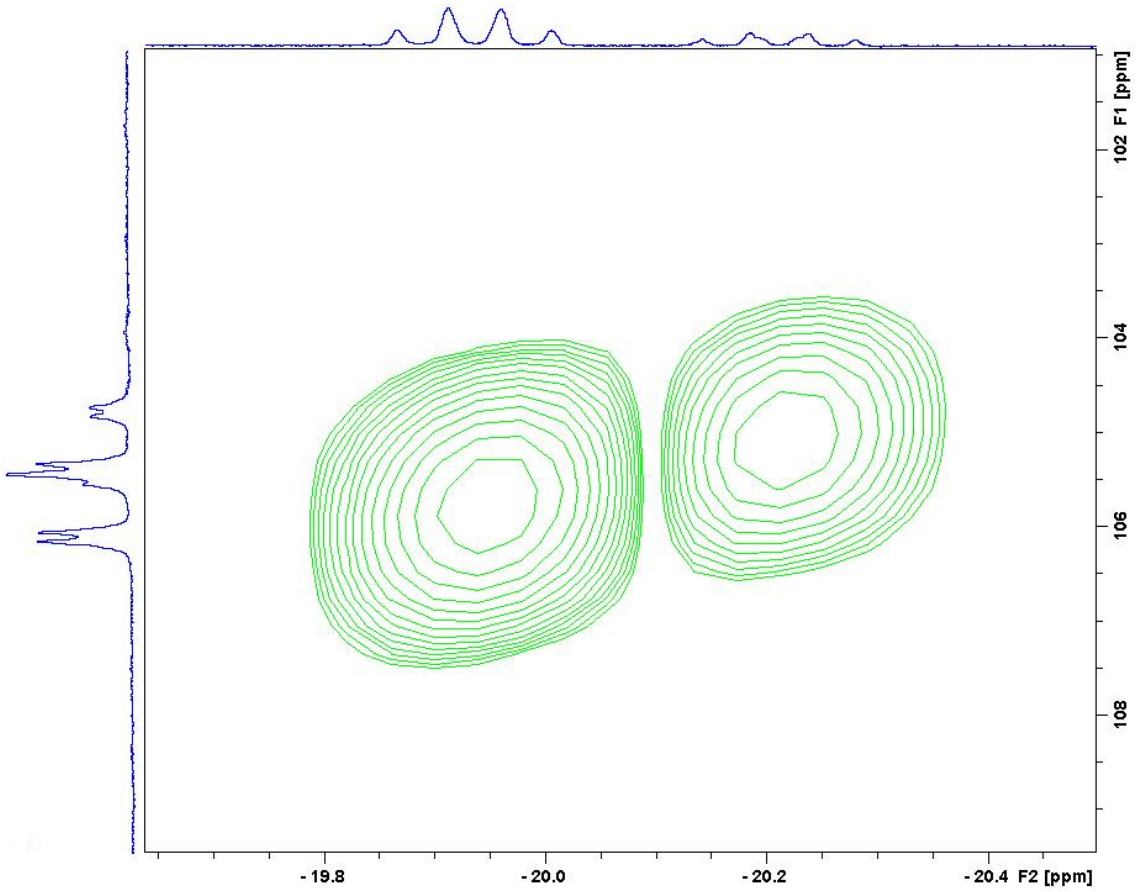
The ^1H NMR spectrum showed in the hydride region two quadruplets at -20 ppm. The lack of correlation between the two hydride signals in the ^1H-^1H COSY experiment, made us assume the presence of two similar but independent hydride complexes. In the $^1H\{^{31}P\}$ NMR spectrum, the hydride signals appeared as two doublets with a $J_{Rh\text{-}H}$ of 27 Hz. The higher multiplicity observed in the hydride signals on the coupled ^1H-NMR spectra should be attributed to the coupling of the hydride nucleus with two similar phosphorus atoms in relative cis positions ($J_{P\text{-}H}$ ~ 23Hz, as confirmed by the $^{31}P\{^1H\}$ NMR spectrum).
$^{31}P\{^1H\}$ NMR shows two doublets around 105 ppm, both displaying a $J_{Rh\text{-}P}$ of 146 Hz, and seemingly two other doublets at 78 ppm and 87 ppm with a $J_{Rh\text{-}P}$ close to 120 Hz. ^1H-^{31}P HMBC correlation shows that the two doublets around 100 ppm are respectively coupled with the two hydride signals at -20 ppm in the ^1H spectrum.

On account of the similarities between the observed $^{31}P\{^1H\}$ NMR spectrum and that of the parent compound **4**, we propose that a mixture of isomeric hydride species **5** and **6** are formed.



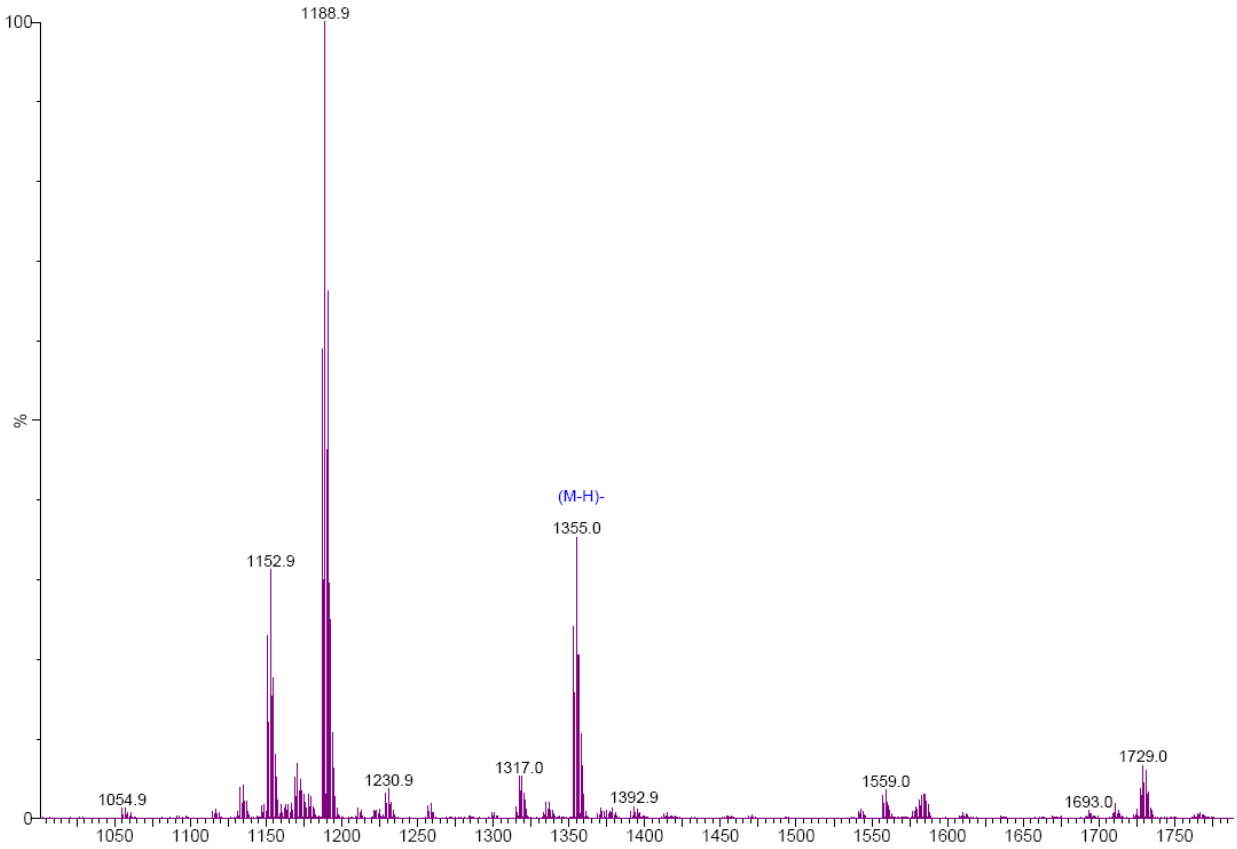


298K $^{31}P\{^{1}H\}$ NMR of the rhodium hydride species (CD_2Cl_2, 161.98 MHz).

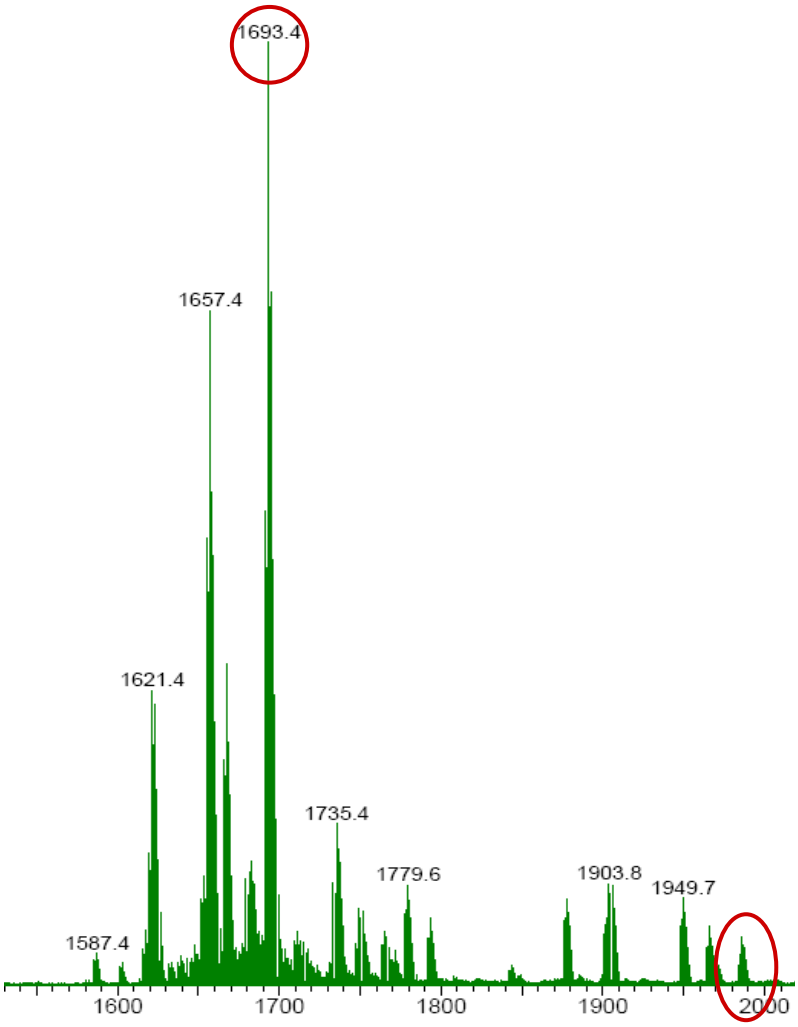


298K ^{1}H - ^{31}P HMBC correlation of the rhodium hydride species (CD_2Cl_2).

ESI-MS analysis



ESI-MS of **4** (m/z = 1355 Da, **4** - H) and [**(1)**$_4$$Rh_2Cl_5$ - 2H] (m/z = 1188.9 Da), in negative mode (solvent = MeOH).



ESI-MS of the **8** (m/z = 1985.1 Da, **8** - H) and **9** (m/z = 1693.4 Da, **9** - H) mixture in negative mode (solvent = MeOH).

***Single-crystal X-ray analysis of* 4**

Crystals of **4** were obtained by layering a solution of the rhodium complex in CH_2Cl_2 with Et_2O at 4 ºC. Although the measured crystal was stable under atmosphere conditions, it was prepared under inert conditions immersed in perfluoropolyether as protecting oil for manipulation.

Data Collection: Measurements were made on a Bruker-Nonius diffractometer equipped with an APPEX 2 4K CCD area detector, a FR591 rotating anode with $Mo_{K\alpha}$ radiation, Montel mirrors as monochromator and a Kryoflex low temperature device (T = -173 °C). Full-sphere data collection was used with ω and φ scans. Programs used: Data collection Apex2 V. 1.0-22 (Bruker-Nonius 2004), data reduction Saint + Version 6.22 (Bruker-Nonius 2001) and absorption correction SADABS V. 2.10 (2003). **Structure Solution and Refinement**: SHELXTL Version 6.10 (Sheldrick, 2000) was used.

Crystal data for 4 at 100 K: $C_{60}H_{53}Cl_4O_5P_2Rh_2$, 1356.49 $gmol^{-1}$, monoclinic, $P2_1/c$, a = 17.0585(15) Å, b = 17.1534(16) Å, c = 19.5448(17) Å, β = 90.797(2)°, V = 5718.5(9)

Å^3, Z = 4, ρ_{calcd} = 1.576 Mg/m^3, R_1 = 0.0379 (0.0775), wR2 = 0.0842 (0.1049), for 22866 reflections with I>2σ(I) (for 32712 reflections [R_{int}: 0.0463] with a total measured of 112410 reflections), goodness-of-fit on F^2 = 1.074, largest diff. peak (hole) = 1.842 (-1.977) e Å^{-3}. Taking in account the presence of an β angle close to 90º and the similarity between the *a* and *b* axes, cells with an orthorhombic and tetragonal metric and also twin refinement were considered without success.
Selected distances (Å): Rh1-P1: 2.3025(4); Rh1-P2: 2.3124(5); Rh1-P3: 2.2999(5); Rh1-Cl1: 2.4918(4); Rh1-Cl2: 2.4355(4); Rh1-Cl3: 2.4855(4); P1-O1: 1.5903(13); P2-O2: 1.5572(13); P3-O3: 1.5828(13); Rh2-P4: 2.2795(5); Rh2-P5: 2.2703(5); Rh2-Cl1: 2.5270(5); Rh2-Cl2: 2.4788(4); Rh2-Cl3: 2.3650(4); Rh2-Cl4: 2.3121(4); P4-O4: 1.5507(16); P5-O5: 1.5454(13).

CCDC ###### contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB21EZ, UK; (fax: (+44) 1223-336-033; or e-mail: deposit@ccdc.cam.ac.uk).