

**Enantioselective hydrogenation of prochiral substrates in catalytic  
membrane reactors**

**Pierluigi Barbaro,\*<sup>a</sup> Claudio Bianchini,<sup>a</sup> Francesca Liguori,<sup>a</sup> Claudio Pirovano<sup>b</sup> and  
Haruo Sawa<sup>c</sup>**

<sup>a</sup> *Istituto di Chimica dei Composti Organo Metallici - Consiglio Nazionale delle Ricerche (ICCOM-CNR), Via Madonna del Piano 10, 50019 Sesto Fiorentino; Firenze, Italy. Fax: +39 055 5225203; Tel: +39 055 5225287; E-mail: pierluigi.barbaro@iccom.cnr.it*

<sup>b</sup> *Istituto di Scienze e Tecnologie Molecolari (ISTM-CNR), Via C. Golgi 19, 20133 Milano, Italy. Fax: +39 02 50314405; Tel: +39 02 50314428*

<sup>c</sup> *Nippon Kodoshi Corporation, 648 Hirookakami, Haruno, Kochi, 781-0395, Japan.*

## General information

All reaction and manipulations were performed under nitrogen atmosphere by using standard Schlenk techniques, unless otherwise stated. All solvents were distilled under nitrogen prior to use, *n*-Pentane from LiAlH<sub>4</sub>, dichloromethane and methanol from CaH<sub>2</sub>, Et<sub>2</sub>O from Na. All other chemicals were reagent grade and used as received for commercial suppliers without further purification. [Rh(NBD)Cl]<sub>2</sub>, [((-)-BINAP)Rh(NBD)]PF<sub>6</sub>, [((-)-DIOP)Rh(NBD)]PF<sub>6</sub> and [((-)-TMBTP)Rh(NBD)]PF<sub>6</sub> were prepared as previously reported.<sup>1,2</sup>

<sup>31</sup>P {<sup>1</sup>H} and <sup>1</sup>H NMR spectra were recorded on a Bruker Avance DRX-400 spectrometer operating at 161.98 and 400.13 MHz, respectively. Chemical shift are relative to external 85% H<sub>3</sub>PO<sub>4</sub> (<sup>31</sup>P) with downfield values reported as positive and to tetramethylsilane (<sup>1</sup>H) as external reference.

ESEM (Environmental Scanning Electron Microscopy) measurements were performed on a FEI Quanta200 microscope operating at 25 KeV accelerating voltage in the low-vacuum mode (1.0 torr) and equipped with an EDAX Energy Dispersive X-ray Spectrometer (EDS).

The rhodium content in the catalytic membranes was determined both by Inductively Coupled Plasma Atomic Emission Spectroscopy (ICP-AES) using a Intrepid Iris (Thermo Elemental) instrument and by EDS using a FEI Quanta200 ESEM.

The amount of rhodium and tungsten leached in solution after catalysis was determined by Grafite Furnace Atomic Absorption Spectroscopy (GF-AAS) a GBC 908AA instrument.

GC analyses were performed on a Shimadzu GC 2010 gas chromatograph equipped with flame ionization detector and a 30 m (0.25 mm i.d., 0.25 μm film thickness) SPB-1 Supelco fused silica capillary column; GC-MS analyses were performed on a Shimadzu QP5000 apparatus equipped with the same capillary column..

Enantiomeric excess (e.e.) were determined by GC analyses using a Shimadzu GC-17A chromatograph equipped with a flame ionization detector and a 50 m (0.25 mm i.d., 0.40 mm o.d.) Lipodex-E (Macherey-Nagel) column.

*Caution: All manipulations involving hydrogen are potentially hazardous. Safety precautions must be taken; work under a well-vented fume-cupboard is recommended.*

**Synthesis of [((-)-Monophos)<sub>2</sub>Rh(NBD)]PF<sub>6</sub>**

Solid [Rh(nbd)Cl]<sub>2</sub> (0.100 g, 0.216 mmol), was added to a solution of (-)-Monophos (0.374 g, 1.04 mmol) in acetone (65 mL). AgPF<sub>6</sub> (0.136 g, 0.540 mmol) was added and the resulting suspension was stirred for 15 min. After AgCl was filtered off, acetone was partially evaporated under a stream of nitrogen and the addition of diethyl ether caused the precipitation of orange microcrystals. The compound was washed with diethyl ether, collected on a sintered glass frit, dried in a stream of nitrogen and stored under nitrogen atmosphere. Yield 50.2 %. <sup>31</sup>P{<sup>1</sup>H} NMR (161.98 MHz, CD<sub>2</sub>Cl<sub>2</sub>): δ= 138.19 (d, <sup>1</sup>J<sub>PRh</sub>=249 Hz). <sup>1</sup>H NMR (400.13 MHz, CD<sub>2</sub>Cl<sub>2</sub>): δ= 8.14-7.99 (m, 8H, Ph), 7.62-7.48 (m, 4H, Ph), 7.38-7.28 (m, 10H, Ph), 7.10-7.08 (m, 2H, Ph), 6.01 (bm, 2H), 5.23 (bm, 2H), 4.04 (bm, 2H), 2.74 (t, 12H, <sup>3</sup>J<sub>HP</sub>=<sup>5</sup>J<sub>HP</sub>=5.49 Hz), 1.76 (bm, 2H).

**Immobilization of preformed molecular Rh-complexes onto hybrid PVA / inorganic membranes: Preparation of the catalytic membranes**

The following is the general procedure used for the immobilization of the preformed molecular Rh catalyst onto the hybrid PVA / inorganic membranes described in Ref. 3 (see Table S1).

A sample of hybrid inorganic / PVA membrane was clamped between two Teflon<sup>®</sup> windows and was plugged at the bottom end of an all-Teflon<sup>®</sup> mechanical stirrer. The assembly was introduced into a 100 mL stainless steel PARR 4565 reactor whose inner walls were covered with Teflon<sup>®</sup> and equipped with a bottom drain valve and a pressure controller. The reactor was charged with methanol (10 mL) and degassed with 3 cycles vacuum / nitrogen. A nitrogen-degassed solution of preformed rhodium complex in methanol (6·10<sup>-3</sup> M, 5 mL) was then transferred via a Teflon<sup>®</sup> capillary into the autoclave under a stream of nitrogen. The solution in the autoclave was stirred mechanically via the Teflon<sup>®</sup> - membrane assembly at room temperature under nitrogen atmosphere for 24 h. After that time, the solution was removed from the autoclave under a stream of nitrogen, and the membrane assembly was carefully washed with consecutive addition / removal of degassed MeOH portions (3 x 30 mL) via a Teflon<sup>®</sup> capillary. The catalytic membrane thus obtained is ready-to-use for the subsequent hydrogenation reaction without remove it from the reactor nor opening the same.

For the purpose of evaluate the metal loading in the catalytic membrane, the reactor was flushed with a stream of nitrogen for 2 hours. The membrane was removed form the reactor, dried under high vacuum overnight and analyzed by ICP-AES and by EDS. A typical EDS spectrum is reported in Figure S1.

### **Analysis of Rh content in the catalytic membranes and reaction solutions**

The catalytic membranes were treated with nitric acid 65% (1,5mL) sulphuric acid 95% (2 mL), 0.4 g of Selenium in K<sub>2</sub>SO<sub>4</sub> (Thompson & Capper LTD 0.1% Se in K<sub>2</sub>SO<sub>4</sub>) in a microwave-heated digestion bomb (Milestone, MLS 200). After the acid-treatment, the solution was diluted to 25 mL with H<sub>2</sub>O Mq . The solution was analyzed by ICP-AES for Rh and W contents.

The rhodium content in the methanolic catalysis solutions was determined by GF-AAS. The solutions were analyzed directly with a GBC 908AA instrument after 1:100 dilution in methanol.

### **Homogeneous hydrogenation reactions using preformed molecular Rh complexes**

All experiments were carried out using the procedure previously described.<sup>2</sup>

### **Heterogeneous hydrogenation reactions using catalytic membranes**

The following is the general procedure adopted to carry out the hydrogenation reactions using the catalytic membranes prepared as above described.

A hydrogen-degassed  $1.7 \cdot 10^{-2}$  M methanol solution of the substrate was transferred via a Teflon<sup>®</sup> capillary under a stream of hydrogen into the reactor containing the catalytic membrane. The autoclave was flushed with hydrogen for 10 minutes and then charged with the desired hydrogen pressure. The solution in the autoclave was stirred mechanically via the Teflon<sup>®</sup> catalytic membrane assembly (140 RPM) at room temperature for the desired time. After that time, the autoclave was depressurized and the reaction solution was removed from the bottom drain valve under a stream of hydrogen. A sample of this solution (0.5  $\mu$ L) was analyzed by gas chromatography to determine both conversion and enantiomeric excess (*ee*) using the appropriate column and conditions. The remaining solution aliquot was used for the determination of the amount of metal leached into solution via GF-AAS analysis. Recycling

experiments were performed as follows: the same volume as above of a hydrogen-degassed  $1.7 \cdot 10^{-2}$  M methanol solution of the substrate was transferred via a Teflon<sup>®</sup> capillary, under a stream of hydrogen, into the autoclave containing the catalytic membrane after its use in the previous hydrogenation reaction. The autoclave was charged with the desired hydrogen pressure and the solution was stirred mechanically (140 RPM) at room temperature for the desired time. After that time, the autoclave was depressurized and the reaction solution was removed from the bottom drain valve under a stream of hydrogen. A sample of this solution (0.5  $\mu$ L) was analyzed by gas chromatography to determine both the conversion and the enantiomeric excess (*ee*). The remaining solution aliquot was used for the determination of the amount of metal leached into solution via GF-AAS analysis.

The same recycling procedure was used in the subsequent hydrogenation cycles. Selected results are reported in Table S2.

### **Catalyst leaching test**

At the end of each hydrogenation cycle using the catalytic membranes, the reaction solution was sampled from the reactor under a stream of hydrogen with the aid of a gas-tight syringe, immediately analyzed by GC for conversion determination, and transferred under hydrogen into an identical reactor with no catalyst in it. The reactor was pressurized with 10 bar of hydrogen and stirred at room temperature for 2h. After that time, the autoclave was depressurized and the reaction solution was analyzed by gas chromatography.

### **Heterogeneous hydrogenation reactions using catalytic membranes in a fixed-frame reactor**

A 250 mL Büchi Inertclave<sup>®</sup> equipped with a bottom drain valve, a mechanical stirrer and PFA inlet valves was used for this purpose. A 14 cm<sup>2</sup> sample of preformed hybrid PVA membrane was clamped in an Teflon ring holder, and the catalytic membrane prepared as described above by a one-pot procedure. A hydrogen-degassed  $1.7 \cdot 10^{-2}$  M methanol solution of the substrate was then transferred via a Teflon<sup>®</sup> capillary under a stream of hydrogen into the reactor containing the catalytic membrane. The autoclave was flushed with hydrogen for 10 minutes and then charged with the desired hydrogen pressure. The solution in the autoclave was stirred mechanically at room temperature for the desired time. The flow of the

methanol reactants solution with respect to the membrane is tangent, in this case. After that time, the autoclave was depressurized and the reaction solution was removed from the bottom drain valve under a stream of hydrogen. A sample of this solution (0.5  $\mu\text{L}$ ) was analyzed by gas chromatography to determine both conversion and enantiomeric excess (*ee*) using the appropriate column and conditions. The remaining solution aliquot was used for the determination of the amount of metal leached into solution via GF-AAS analysis. Recycling experiments were performed as follows: the same volume as above of a hydrogen-degassed  $1.7 \cdot 10^{-2}$  M methanol solution of the substrate was transferred via a Teflon<sup>®</sup> capillary, under a stream of hydrogen, into the autoclave containing the catalytic membrane after its use in the previous hydrogenation reaction. The autoclave was charged with the desired hydrogen pressure and the solution was stirred mechanically (140 RPM) at room temperature for the desired time. After that time, the autoclave was depressurized and the reaction solution was removed from the bottom drain valve under a stream of hydrogen. A sample of this solution (0.5  $\mu\text{L}$ ) was analyzed by gas chromatography to determine both the conversion and the enantiomeric excess (*ee*). The remaining solution aliquot was used for the determination of the amount of metal leached into solution via GF-AAS analysis.

The same recycling procedure was used in the subsequent hydrogenation cycles.

### GC-analyses

SPB-1 Supelco\_30 m (0.25 mm i.d., 0.25  $\mu\text{m}$  film thickness) column

Temp. Inj.=250°C; Temp. det.=300°C; carrier Helium

Column temperature isotherm 100 °C

Linear velocity: 26 cm/sec

Rt = 6.92 min: N-Acetyl-alanine methyl ester

Rt = 7.13. min: = methyl 2-acetamidoacrylate

Lipodex-E 50 m (0.25 mm i.d., 0.40 mm o.d.) column

Temp. Inj.=280°C; Temp. Det.=310°C; carrier Helium

Column temperature isotherm 140°C

Linear velocity: 24 cm/sec

Rt = 10.69 min: N-Acetyl-L-alanine methyl ester

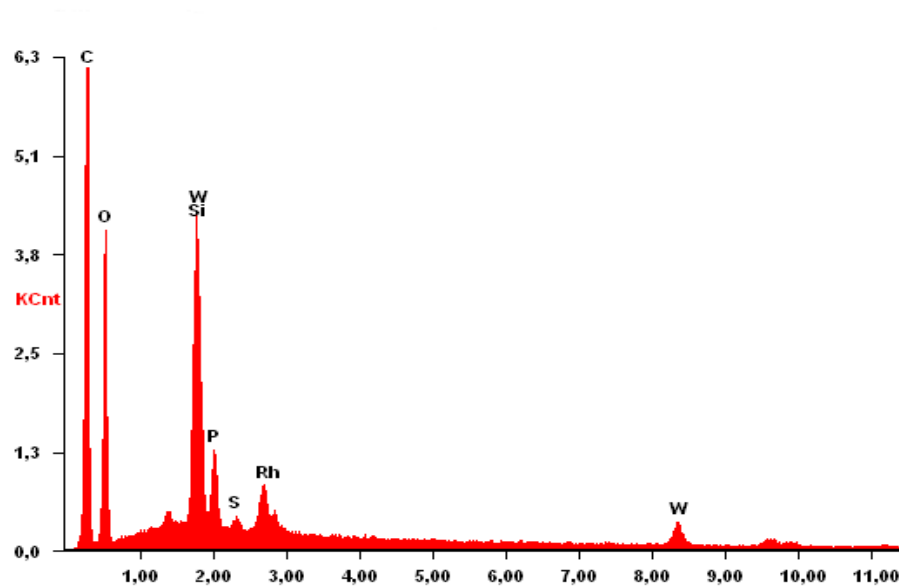
Rt = 11.48 min: N-Acetyl-D-alanine methyl ester



**Table S1.** Composition of selected hybrid membranes and rhodium loading.<sup>a</sup>

Identifier	PVA	WO <sub>3</sub>	SiO <sub>2</sub>	ZrO <sub>2</sub>	Na <sub>3</sub> PO <sub>4</sub>	OCS	PEG	PET	Rh (w/w) (%) <sup>b</sup>
NK-1	1	0.30	0.029	0	P	0.34	0	P	2.76
CSNKW-1	1	0.37	0.040	0	P	0.017	0	A	2.57
CSNKW-3	1	0.44	0.046	0	P	0.017	0.093	A	2.27
NKS-1	1	0	0.040	0	P	0.034	0	A	2.13
NKZ-1	1	0	0	0.38	P	0	0	A	0.00
NKW-3	1	0.36	0	0	P	0	0	P	1.47
NKW-6	1	0.36	0.040	0	P	0	0	A	2.81
NKW-9	1	0.30	0.058	0	P	0	0	P	1.55

<sup>a</sup> The additives content is denoted by the weight ratio to PVA normalized to 1. P = Present, A = Absent. OCS = polystyrenesulfonic acid. PEG = Polyethylene glycol. PET = PET paper for reinforcement. <sup>b</sup> After immobilization of  $[(-)\text{-Monophos}]_2\text{Rh(NBD)]PF}_6$ . Dry material. ICP-AES, average value over two samples.



**Figure S1.** Typical EDS spectrum of a catalytic membrane (20 KeV, 1 torr).



**Table S2.** Selected hydrogenation reactions of MAA using catalytic membranes.<sup>a</sup>

Membrane support type	Anchored Rhodium catalyst complex	Cycle no.	React. time (h)	Yield (%)	TOF (h <sup>-1</sup> )	ee (%)	Rh leach. (ppm) <sup>b</sup>
NK-1	[((-)-BINAP)Rh(NBD)]PF <sub>6</sub>	1	2	22,33	18,3	15,0	0,32
		2	2	19,85	16,2	12,8	0,28
		3	2	23,60	19,3	13,7	0,25
		4	17	77,93	7,5	10,6	0,36
		5	2	8,08	6,6	8,1	0,27
NK-1	[((-)-DIOP)Rh(NBD)]PF <sub>6</sub>	1	2	34,80	28,6	17,3	0,23
		2	2	20,12	16,5	17,3	0,31
		3	2	19,28	15,8	18,1	0,27
		4	17	53,90	5,2	14,7	0,77
		5	2	3,92	3,0	19,9	0,30
NK-1	[((-)-TMBTP)Rh(NBD)]PF <sub>6</sub>	1	2	26,39	21,6	98,5	0,73
		2	2	27,10	22,2	97,0	0,79
		3	2	23,72	19,4	97,0	0,80
		4	17	72,99	7,0	94,0	0,71
		5	2	7,70	6,3	96,0	0,66
CSNKW-1	[((-)-TMBTP)Rh(NBD)]PF <sub>6</sub>	1	2	91,81	75,3	98,3	1,74
		2	2	50,44	41,3	97,6	1,16
		3	2	32,48	26,6	98,8	1,29
		4	17	67,85	6,5	93,0	2,17
		5	2	25,08	24,2	93,0	0,53
CSNKW-1	[((-)-DIOP)Rh(NBD)]PF <sub>6</sub>	1	2	51,25	41,8	17,6	1,42
		2	2	36,29	29,6	16,4	1,33
		3	2	21,21	17,3	14,8	1,04
		4	17	52,76	5,1	11,0	1,29
		5	2	5,00	4,1	17,0	0,81
NKS-1	[((-)-Monophos) <sub>2</sub> Rh(NBD)]PF <sub>6</sub>	1	2	15,64	12,8	61,0	0,18
		2	2	15,56	12,9	60,3	0,85
		3	2	14,31	12,8	62,5	0,68
		4	17	45,85	5,2	67,1	0,74
		5	2	5,89	6,1	27,0	0,13
NKW-3	[((-)-Monophos) <sub>2</sub> Rh(NBD)]PF <sub>6</sub>	1	2	22,43	11,5	74,3	0,39
		2	2	19,17	9,9	77,7	0,72
		3	2	15,77	8,9	59,0	0,18
		4	17	71,99	5,7	71,8	0,72
		5	2	12,66	8,9	73,5	0,68

<sup>a</sup> Room temperature, methanol, 5 bar hydrogen. <sup>b</sup> GF-AAS (± 0.02).

## References

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