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Supporting Information

Combinatorial Strategies to find New Catalysts for Asymmetric Hydrogenation Based on the Versatile Coordination Chemistry of METAMORPhos Ligands

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1.0 General

$[Rh(nbd)_2]BF_4$ was purchased from Alfa, substrate **A** was purchased from Merck. All other substrates and ligands were synthesized according to literature procedures.[1,2,3]

Unless stated otherwise, reactions were carried out under an inert atmosphere of nitrogen or argon using standard Schlenk techniques. THF was distilled from sodium benzophenone ketyl; methanol was distilled from CaH_2; and toluene was distilled from sodium, all under nitrogen atmosphere. Every solution addition or transfer was performed via syringes or in a glovebox unless otherwise stated. All solvents were dried and distilled using standard procedures.[4]

The water content of dichloromethane was tested with a Karl-Fisher titrator (the value was always below 4 ppm).

Nuclear Magnetic Resonance experiments were performed on a Varian Inova spectrometer (^1H: 500 MHz, $^{31}P\{1H\}$: 202.3 MHz) or a Bruker AV 400 (^1H: 400 MHz, $^{31}P\{1H\}$: 162 MHz) at room temperature. Chemical shifts are reported in ppm and are referenced to the solvent signal (5.32 ppm in ^1H for CD_2Cl_2) or 85% H_3PO_4 ($^{31}P\{^1H\}$) as an external standard.

High resolution ESI (electrospray ionization) mass spectra were obtained on a time-of-flight JEOL AccuTOF LC-plus mass spectrometer (JMS-T100LP) equipped with an ESI source.

2.0 Asymmetric hydrogenation

All hydrogenation reactions were done at 20 bars for 18h at 21 °C.

2.1 Initial automated ligand screening

Stock solutions of the ligands (8.8 mM), catalyst precursor $[Rh(nbd)_2]BF_4$ (8 mM), and substrate (0.2 M) in dry dichloromethane were prepared manually under nitrogen. The rest of the procedure were carried out in a Chemspeed Accelerator robot equipped with high pressure blocks. 0.3 mL of each 2 ligands stock solution were combined. The resulting solution was stirred (vortex stirring) for 5 min. 0.3 mL of the Rh precursor solution was subsequently added. The resulting solution was stirred (vortex stirring) for 5 min. 0.3 mL of the substrate solution was subsequently added. This procedure resulted in catalyst and substrate concentrations of 0.05 and 0.002 M respectively, in the reaction mixture (substrate to Rh ratio is 25, ligand to Rh ratio is 1.1 for each ligand). The hydrogenation was carried out under vortex stirring (20 bars, 18 h).

2.2 Focussed ligand optimization

Stock solutions of the ligands (4.4 mM), catalyst precursor $[Rh(nbd)_2]BF_4$ (4 mM), and substrate (0.4 M) in dry dichloromethane, as well as the reaction mixtures were prepared in a glovebox. 0.2 mL of each two ligands stock solution were combined. The resulting solution was shaken until it became homogeneous. 0.2 mL of the Rh precursor solution was subsequently added. The resulting solution was shaken until homogeneous. 0.2 mL of the substrate solution was subsequently added. This procedure resulted in catalyst and substrate concentrations of 0.1 M and 1 mM respectively in the reaction mixture (substrate to Rh ratio is 100, ligand to Rh ratio is 1.1 for each ligand). The hydrogenation was carried out under vortex stirring (20 bars, 18 h) in the Chemspeed Accelerator robot equipped with high pressure blocks.

2.3 Ligand ratio study

Stock solutions of the ligands (1.375 mM), catalyst precursor $[Rh(nbd)_2]BF_4$ (5 mM), and substrate (1 M) in dry dichloromethane, as well as the reaction mixtures were prepared in a glovebox. The reaction mixtures were prepared in a glovebox as well. Various volume (see table below) of each ligands stock solution were combined 2 by 2 (total volume of 0.4 mL). The resulting solution was magnetically stirred for 1 min. 0.05 mL of the Rh precursor solution was subsequently added. The resulting solution was magnetically stirred for 1 min. 0.05 mL of the substrate solution was subsequently added. This procedure resulted in catalyst and substrate concentrations of 0.1M and 0.5 mM respectively, in the reaction

mixture (substrate to Rh ratio is 200, total ligand to Rh ratio is 2.2). The hydrogenation was carried out under magnetic stirring (20 bars, 18h) in an high pressure autoclave.

Table 2. Ligand ratio study (data of **Figure 3**).

substrate	ligand 1	ligand 2	ligand ratio		
	(S)-Lan3	(R)-Lneu1	an/neu	ee (%)	conversion (%)
A	0 µL	400 µL	0/100	16	3
	40 µL	360 µL	10/90	-67	35
	80 µL	320 µL	20/80	-75	71
	120 µL	280 µL	30/70	-76	87
	160 µL	240 µL	40/60	-78	96
	200 µL	200 µL	50/50	-75	92
	240 µL	160 µL	60/40	-75	89
	280 µL	120 µL	70/30	-74	82
	320 µL	80 µL	80/20	-67	63
	360 µL	40 µL	90/10	-52	39
	400 µL	0 µL	100/0	8	19
	(S)-Lan3	(R)-Lneu3	an/neu	ee (%)	conversion (%)
B	0 µL	400 µL	0/100	-17	100
	40 µL	360 µL	10/90	13	100
	80 µL	320 µL	20/80	42	100
	120 µL	280 µL	30/70	73	100
	160 µL	240 µL	40/60	93	100
	200 µL	200 µL	50/50	94	100
	240 µL	160 µL	60/40	94	100
	280 µL	120 µL	70/30	93	100
	360 µL	40 µL	90/10	77	100
	400 µL	0 µL	100/0	77	100
	(R)-Lan4	(R)-Lneu1	an/neu	ee (%)	conversion (%)
C	0 µL	400 µL	0/100	46	6
	40 µL	360 µL	10/90	88	49
	80 µL	320 µL	20/80	90	78
	120 µL	280 µL	30/70	90	92
	160 µL	240 µL	40/60	91	95
	200 µL	200 µL	50/50	92	99
	240 µL	160 µL	60/40	91	97
	280 µL	120 µL	70/30	93	100
	320 µL	80 µL	80/20	92	95
	360 µL	40 µL	90/10	92	91
	400 µL	0 µL	100/0	90	77
	(R)-Lan2	(R)-Lneu3	an/neu	ee (%)	conversion (%)
F	0 µL	400 µL	0/100	-70	99
	40 µL	360 µL	10/90	-72	100
	80 µL	320 µL	20/80	-80	100
	120 µL	280 µL	30/70	-85	100
	160 µL	240 µL	40/60	-88	100
	200 µL	200 µL	50/50	-87	100
	240 µL	160 µL	60/40	-88	100
	280 µL	120 µL	70/30	-88	100
	320 µL	80 µL	80/20	-87	95
	360 µL	40 µL	90/10	-87	97
	400 µL	0 µL	100/0	-80	43
	(R)-Lan4	(R)-Lneu3	an/neu	ee (%)	conversion (%)
H	0 µL	400 µL	0/100	34	97
	40 µL	360 µL	10/90	38	98
	80 µL	320 µL	20/80	44	99
	120 µL	280 µL	30/70	57	100
	160 µL	240 µL	40/60	75	99
	200 µL	200 µL	50/50	89	93
	240 µL	160 µL	60/40	90	91
	280 µL	120 µL	70/30	89	91
	320 µL	80 µL	80/20	90	74
	360 µL	40 µL	90/10	88	57
	400 µL	0 µL	100/0	68	16

3.0 GC and HPLC methods

The sign of the enantiomeric excesses is arbitrary and does not reflect the optical rotation.
All conversions were determined by Gas Chromatography on an Interscience Focus GC Ultra (FID detector) with a Chiralsil DEX-CB column (25m x 0.32mm). Enantiomeric excesses were determined by the same GC for the substrates **A** to **F** and by HPLC for substrates **G** and **H**.
For **A**, conversions and *ee* were determined after derivatization of the products and the unreacted substrate to their methyl esters. Typical procedure: after hydrogenation, the reaction mixture was diluted twice with methanol. Trimethylsilyldiazomethane was subsequently added dropwise under vigorous magnetic stirring until the solution remains pale yellow. Acetic acid was subsequently added dropwise under vigorous magnetic stirring until the solution remains transparent.

3.1 GC methods

Table 3. GC methods

substrate	methods					retention times (min)		
	initial temperature (˚C)	ramp (˚C/min)	temperature (˚C)	ramp (˚C/min)	final temperature (˚C)	substrate	first enantiomer	second enantiomer
A	90	0.2	100	40	220	52.4	46.2	47.3
B	90	isothermal 15min	90	40	220	13.1	11.6	12.4
C	160	0.1	163	40	220	29.3	13.7	14.3
D	160	1	182	40	220	21.2	14.4	15.5
E	150	0.5	168	40	220	39.9	33.7	35
F	100	0.5	130	40	220	60	22.2	24.6
G	155	0.2	162	40	220	25.7	22.1	22.3
H	170	0.5	195	40	220	38.5	41.2	

3.2 HPLC methods

Table 4. HPLC methods

substrate	HPLC method			retention times (min)		
	temperature (˚C)	eluent	flow	substrate	first enantiomer	second enantiomer
G	30	10% isopropanol in heptane	0.9 mL/min	16.4	13.5	15.0
H	30	12% isopropanol in heptane	0.9 mL/min	39.2	24.7	30.6

4.0 Complex preparation and characterization

General procedure for the rhodium(nbd) complexes

Ligand $HNEt_3$**Lan**, **Lneu** or a 1:1 mixture of ligands (0.035 mmol in total, 2eq.) was dissolved in 0.7 mL of CD_2Cl_2, homogenized and subsequently added to $[Rh(nbd)_2]BF_4$ (0.0175 mmol, 1 eq.). The reaction was complete within 5 min.

$[Rh((R)\text{-}Lneu3)_2(nbd)]BF_4$

$^{31}P\{^1H\}$ NMR (162 MHz, CD_2Cl_2) δ (ppm): 154.53 (d, $J_{P\text{-}Rh}$ = 186.3 Hz)
HR-MS (ESI+): *m*/*z* calcd. for $C_{59}H_{56}N_2O_8P_2Rh$ ([Rh(**(R)-Lneu3**)$_2$(nbd)]BF_4 minus BF_4^-): 1085.26; obsd.: 1085.35
m/*z* calcd. for $C_{52}H_{48}N_2O_8P_2Rh$ ([Rh(**(R)-Lneu3**)$_2$(nbd)]BF_4 minus nbd, minus BF_4^-): 993.19; obsd.: 993.21

$HNEt_3$[Rh((R)-Lan4)$_2$(nbd)]

$^{31}P\{^1H\}$ NMR (162 MHz, CD_2Cl_2) δ 128.82 (d, $J_{P\text{-}Rh}$ = 251.5 Hz).

HR-MS (ESI+): *m*/*z* calcd. for $C_{55}H_{65}F_6N_3O_8P_2RhS_2$ ($HNEt_3$[Rh(**(R)-Lan4**)$_2$(nbd)] plus H^+): 1238.26; obsd.: 1238.30

m/*z* calcd. for $C_{61}H_{80}F_6N_4O_8P_2RhS_2$ ($HNEt_3$[Rh(**(R)-Lan4**)$_2$(nbd)] plus $HNEt_3^+$): 1339.38; obsd.: 1339.42

m/*z* calcd. for $C_{54}H_{72}F_6N_4O_8P_2RhS_2$ ($HNEt_3$[Rh(**(R)-Lan4**)$_2$(nbd)] minus nbd, plus $HNEt_3^+$): 1247.32; obsd.: 1247.36

$HNEt_3$[Rh((S)-Lan3)$_2$(nbd)]

$^{31}P\{^1H\}$ NMR (162 MHz, CD_2Cl_2) δ 122.41 (d, $J_{P\text{-}Rh}$ = 261.0 Hz).

HR-MS (ESI+): *m*/*z* calcd. for $C_{65}H_{72}F_6N_4O_8P_2RhS_2$ $HNEt_3$[Rh(**(S)-Lan3**)$_2$(nbd)] plus $HNEt_3^+$): 1379.32; obsd.: 1379.36

m/*z* calcd. for $C_{58}H_{64}F_6N_4O_8P_2RhS_2$ $HNEt_3$[Rh(**(S)-Lan3**)$_2$(nbd)] minus nbd plus $HNEt_3^+$): 1287.26; obsd.: 1287.30

[Rh((R)-Lan4)((R)-Lneu3)(nbd)]

NB: $HNEt_3$[Rh((R)-Lan4)2(nbd)], [Rh(**(R)-Lneu3**)$_2$(nbd)]BF_4 and unidentified species are also formed.

$^{31}P\{^1H\}$ NMR (162 MHz, CD_2Cl_2) δ 140.41 (dd, $J_{P\text{-}Rh}$ = 256.1, $J_{P\text{-}P}$ = 61.5 Hz), 129.77 (dd, $J_{P\text{-}Rh}$ = 233.5, $J_{P\text{-}P}$ = 61.5 Hz).

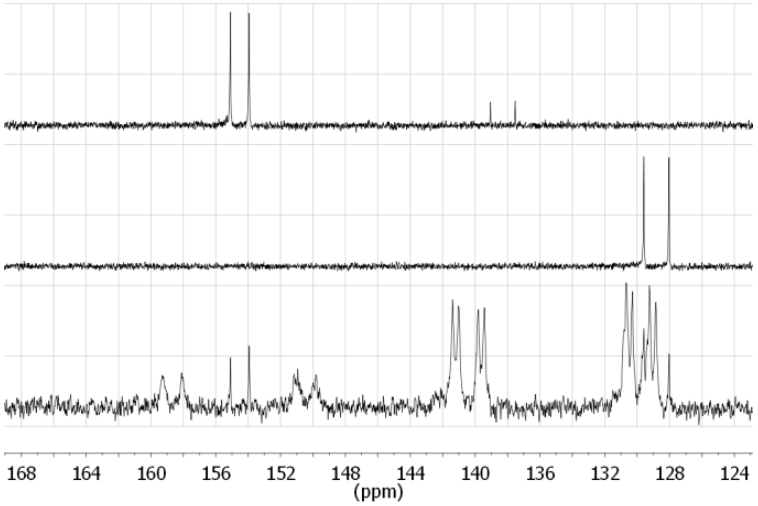

Figure 4. Top: $^{31}P\{^1H\}$ NMR spectrum of [Rh(**(R)-Lneu3**)$_2$(nbd)]$^+$; middle: $^{31}P\{^1H\}$ NMR spectrum of [Rh(**(R)-Lan4**)$_2$(nbd)]$^-$; bottom: $^{31}P\{^1H\}$ NMR spectrum of [Rh(**(R)-Lan4**)(**(R)-Lneu3**)(nbd)].

Complexation of **$HNEt_3$(S)-Lan3** and **(R)-Lneu3** to [Rh(nbd)$_2$]BF_4 **"[Rh((S)-Lan3)$_x$((R)-Lneu3)$_y$(nbd)$_z$]"**

NB: $HNEt_3$[Rh(**(S)-Lan3**)$_2$(nbd)] is contain some free ligand (quartet at 163 ppm).

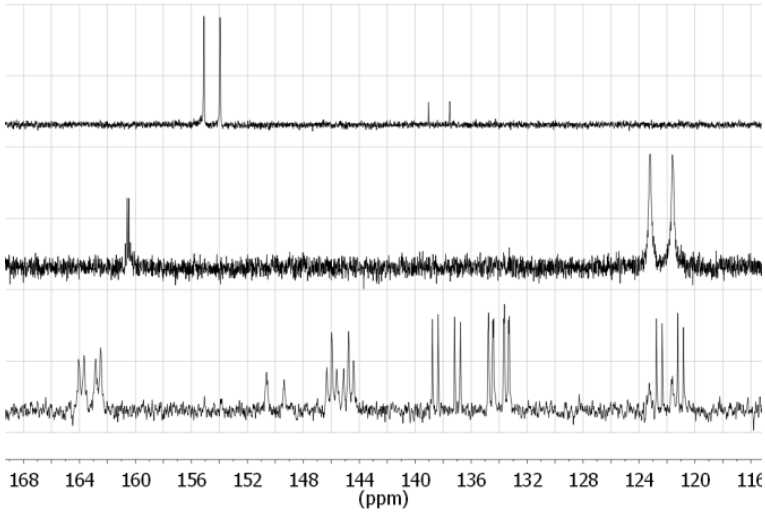

Figure 5. Top: $^{31}P\{^1H\}$ NMR spectrum of [Rh(**(R)-Lneu3**)$_2$(nbd)]$^+$; middle: $^{31}P\{^1H\}$ NMR spectrum of [Rh(**(S)-Lan3**)$_2$(nbd)]$^-$; bottom: $^{31}P\{^1H\}$ NMR spectrum of [Rh(**(S)-Lan3**)$_x$(**(R)-Lneu3**)$_y$(nbd)$_z$]

General procedure for the in-situ complex characterization

Ligand **Lan**, **Lneu** or a mixture of ligands (0.0125 mmol in total, 2eq.) was dissolved in 0.5 mL of CD_2Cl_2 and mixed with $[Rh(nbd)_2]BF_4$ (0.0125 mmol, 1 eq.). The solution was subsequently transferred to a high pressure NMR tube, submitted to 5 bars of H_2 gas and gently shaken to dissolve the H_2.

$[Rh(\mathbf{(R)\text{-}Lneu3})_2]BF_4$

^{31}P NMR (162 MHz, CD_2Cl_2) δ 150.93 (d, $J_{P\text{-}Rh}$ = 305.6 Hz).

HR-MS (ESI+): *m/z* calcd. for $C_{52}H_{48}N_2O_8P_2Rh$ ($[Rh(\mathbf{(R)\text{-}Lneu3})_2]BF_4$ minus BF_4^-)*:* 993.19; obsd.: 993.20

$(HNEt_3)_2[Rh_2((R)\text{-}Lan4)_4]$

^{31}P NMR (162 MHz, CD_2Cl_2) δ 135.65 (dd, $J_{P\text{-}Rh}$ = 289.0, $J_{P\text{-}P}$ = 33.4 Hz, chelate ligands), 115.07 (d, $J_{P\text{-}Rh}$ = 344.0 Hz, bridging ligands).

HR-MS (ESI+): *m/z* calcd. for $C_{96}H_{113}F_{12}N_6O_{16}P_4Rh_2S_4$ ($(HNEt_3)_2[Rh_2(\mathbf{(R)\text{-}Lan4})_4]$ plus H^+): 2292.40; obsd.: 2292.44

m/z calcd. for $C_{90}H_{98}F_{12}N_5O_{16}P_4Rh_2S_4$ ($(HNEt_3)_2[Rh_2(\mathbf{(R)\text{-}Lan4})_4]$ minus NEt_3 plus H^+): 2191.28; obsd.: 2191.31

$HNEt_3[Rh(\mathbf{(S)\text{-}Lan3})_2]$

^{31}P NMR (162 MHz, CD_2Cl_2) δ 137.79 (d, $J_{P\text{-}Rh}$ = 303.5 Hz).

HR-MS (ESI+): *m/z* calcd. for $C_{58}H_{64}F_6N_4O_8P_2RhS_2$ ($HNEt_3[Rh(\mathbf{(S)\text{-}Lan3})_2]$ plus $HNEt_3^+$): 1287.26; obsd.: 1287.29

m/z calcd. for $C_{52}H_{49}F_6N_3O_8P_2RhS_2$ ($HNEt_3[Rh(\mathbf{(S)\text{-}Lan3})_2]$ plus H^+): 1186.14; obsd.: 1186.16

[Rh((R)-Lneu3)((R)-Lan4)]

^{31}P NMR (162 MHz, CD_2Cl_2) δ 149.83 (dd, $J_{P\text{-}Rh}$ = 332.3, $J_{P\text{-}P}$ = 45.5 Hz), 134.36 (dd, $J_{P\text{-}Rh}$ = 285.9, $J_{P\text{-}P}$ = 45.5 Hz). See spectra in the main text (Figure 1).

HR-MS (ESI+): *m/z* calcd. for $C_{53}H_{60}F_3N_3O_8P_2RhS$ ($[Rh(\mathbf{(R)\text{-}Lneu3})(\mathbf{(R)\text{-}Lan4})]$ plus $HNEt_3^+$): 1120.26; obsd.: 1120.24

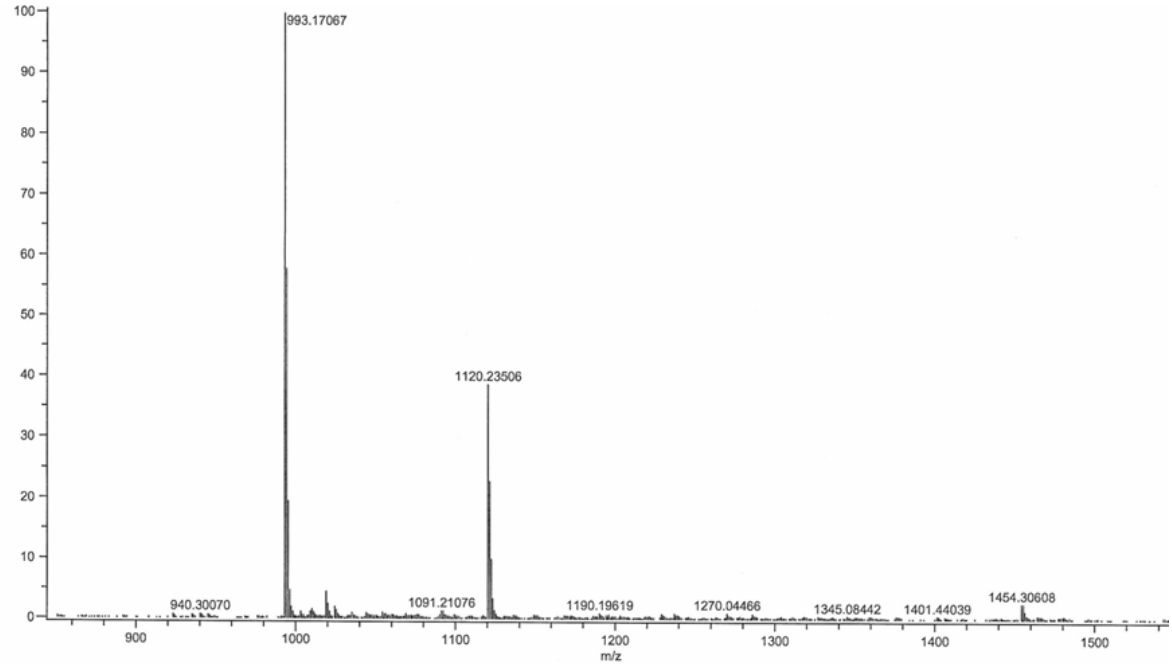

Figure 6. Mass spectrum of [Rh(**(R)-Lneu3**)(**(R)-Lan4**)]. Even if it is not observed in solution (by NMR), $[Rh(\mathbf{(R)\text{-}Lneu3})_2]BF_4$ minus BF_4^- is detected. Since it is a cationic complex, it will be detected even if it is present in trace amount.

NB: Even if it is not observed in solution (by NMR), ($[Rh_2(\mathbf{(R)\text{-}Lneu3})(\mathbf{(R)\text{-}Lan4})_3]$ plus $2H^+$) and its acetonitrile adduct is detected by mass (eluent used for MS measurements).

HR-MS (ESI+): *m/z* calcd. for $C_{89}H_{86}F_9N_4O_{16}P_4Rh_2S_3$ ($[Rh_2(\mathbf{(R)\text{-}Lneu3})(\mathbf{(R)\text{-}Lan4})_3]$ plus $2H^+$): 2064.21; obsd.: 2064.35

m/z calcd. for $C_{91}H_{89}F_9N_5O_{16}P_4Rh_2S_3$ ([Rh_2(**(R)-Lneu3**)(**(R)-Lan4**)$_3$] plus acetonitrile plus $2H^+$): 2105.24; obsd.: 2105.41

Note: A well-defined hydride is present at -21.8 ppm (J_{Rh-H} = 26.1 Hz). It should be noted that in the same conditions, when **Lan3**$^-$ is used alone, no hydride is observed; when only **Lneu** is utilized, a doublet at -9 ppm can be seen, but this species is not present in the hereocombination. Due to a very small abundance of this species (approximately 1% according to integrations), a full characterization was not possible.

^{1}H NMR hydride region (500 MHz, CD_2Cl_2) δ -21.83 (ddd, J_{Rh-H} = 25.9; J_{P-H} 13.1, 6.0 Hz).

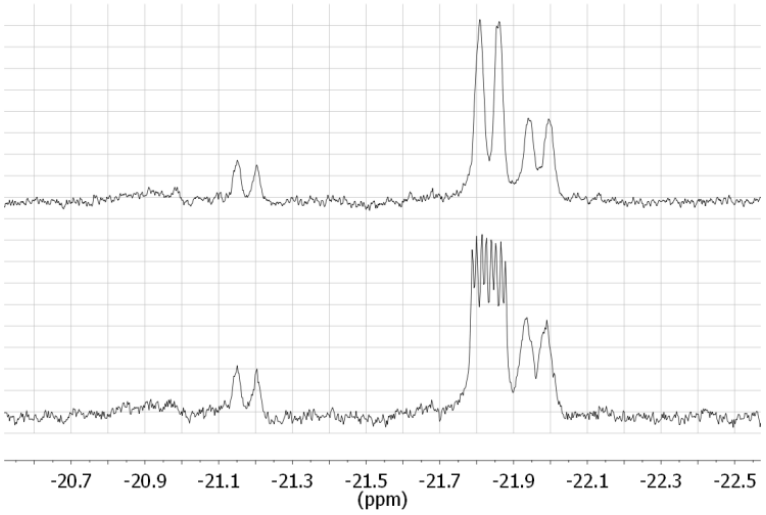

Figure 7. ^{1}H NMR spectrum of [Rh(**(R)-Lneu3**)(**(R)-Lan4**)]; top: ^{1}H {^{31}P} NMR spectrum; bottom: ^{1}H NMR spectrum without decoupling.

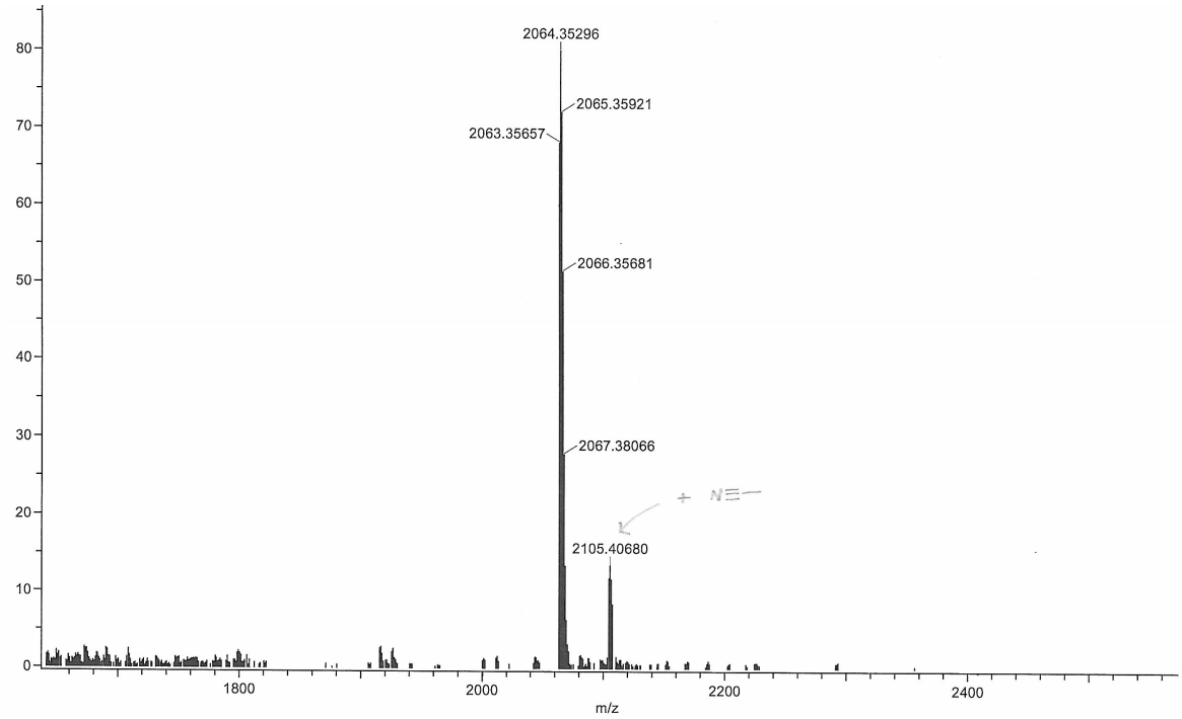

Figure 8. Mass spectrum of [Rh_2(**(R)-Lneu3**)(**(R)-Lan4**)$_3$] and its acetonitrile adduct.

Complexation of **HNEt$_3$(S)-Lan3** and **(R)-Lneu3** to [Rh(nbd)$_2$]BF_4 under H_2 pressure **[Rh$_x$((S)-Lan3)$_y$((R)-Lneu3)$_z$]**

HR-MS (ESI+): *m/z* calcd. for $C_{104}H_{96}F_6N_5O_{16}P_4Rh_2S_2$ ([Rh_2(**(R)-Lneu3**)$_2$(**(S)-Lan3**)$_2$] plus $HNEt_3^+$): 2179.33; obsd.: 2179.33

m/z calcd. for $C_{98}H_{81}F_6N_4O_{16}P_4Rh_2S_2$ ([Rh_2(**(R)-Lneu3**)$_2$(**(S)-Lan3**)$_2$] plus H^+): 2078.21; obsd.: 2078.19

m/z calcd. for $C_{55}H_{56}F_3N_3O_8P_2RhS$ ([Rh(**(R)-Lneu3**)(**(S)-Lan3**)] plus $HNEt_3^+$): 1140.23; obsd.: 1140.22

m/z calcd. for $C_{49}H_{41}F_3N_2O_8P_2RhS$ ([Rh(**(R)-Lneu3**)(**(S)-Lan3**)] plus H^+): 1039.11; obsd.: 1039.10

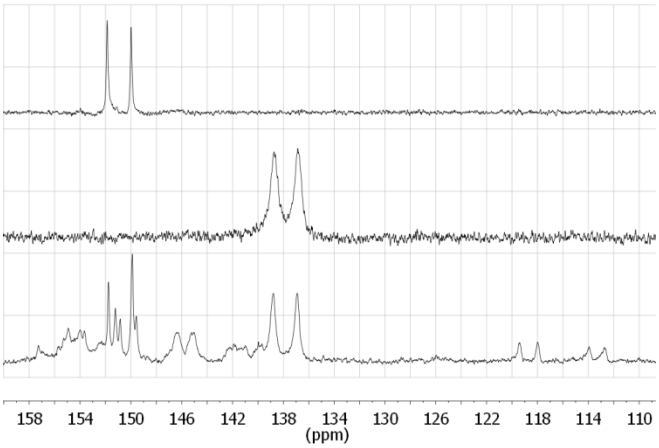

Figure 9. Top: ^{31}P {^{1}H} NMR of [Rh(**(R)-Lneu3**)$_2$]$^+$; middle: ^{31}P {^{1}H} NMR of [Rh(**(S)-Lan3**)$_2$]$^-$; bottom: ^{31}P {^{1}H} NMR of [Rh$_x$(**(S)-Lan3**)$_y$(**(R)-Lneu3**)$_z$].

5.0 References

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