Electronic Supplementary Material (ESI) for Faraday Discussions.

Multi-Nuclear, High-pressure, *Operando* FlowNMR Spectroscopic Study of Rh/PPh_3 - Catalysed Hydroformylation of 1-Hexene

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Supplementary information

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Experimental

Materials and methods:

Unless stated otherwise, all manipulations were carried out under an inert atmosphere of argon using standard Schlenk line techniques. 1-hexene was purchased from Acros Organics, stirred over potassium overnight followed by a fractional distillation under argon over the same metal. Triphenylphosphine, $[Rh(acac)(CO)_2]$ and 1,3,5-trimethoxybenzene were purchased in the highest purity available and used without further purification. Toluene was freshly distilled from sodium under argon before every use. Carbon monoxide (99.99 %) and hydrogen (99.95 %) gases were supplied by BOC.

The hydroformylation of 1-hexene was carried out in a Büchi Miniclave pressure reactor made of glass and stainless-steel lid connected to the flow NMR apparatus via 1/16" Swagelok connections. A micro-annular gear pump (mzr-6355from HNP Mikrosysteme GmbH) was used to circulate the reaction mixture through the 1/16" polyetheretherketone (PEEK, Upchurch Scientific) tubing with 0.76 mm i.d. connected to an InsightMR flow tube (Bruker) placed in the probe of the spectrometer. The inner volume the flow system was approximately 6.4 mL.

NMR spectra were recorded on a Bruker 500 MHz Advance II$^+$ Ultrashield equipped with a nitrogen-cooled BBO Prodigy CryoProbe. ^{1}H NMR chemical shifts are referenced against TMS (99.5 % purity in $CDCl_3$) and ^{31}P NMR shifts are referenced to 85% H_3PO_4. The reaction monitoring software used was InsightMR, and data processing was performed with TopSpin 4.0.6 and DynamicCenter 2.5.6.

Procedure for Rh-hydroformylation of 1-hexene studied by operando FlowNMR

Caution: carbon monoxide is a colourless, odourless and highly toxic gas – experiments should only be conducted in the presence of a calibrated CO sensor.

The FlowNMR apparatus was flushed with laboratory grade toluene and then purged with argon for at least 10 minutes to remove traces of air and moisture. Triphenylphoshine (see table below), dicarbonyl(acetylacetonato)rhodium(I) (12.90 mg, 0.05 mmol) and 1,3,5-trimethoxybenzene (33.64 mg, 2 mmol) were added to the pressure glass vessel together with a teflon-coated stir bar followed by sealing of the autoclave with all tubing attached (see Figure S1). The system was leak-checked, vacuum-argon cycled three times at room temperature and then kept under argon. The inlet of the flow tube was then moved into a separate Schlenk flask that contained dry toluene under argon, and the outlet to the waste bottle. Dry toluene was then pumped through the flow tube for 5 minutes to leave the transfer lines, pump and flow tube filled with dry solvent (6.4 mL). Thereafter, both flow tube ends were reconnected to the reactor which was topped up with dry toluene (15 mL) and 1-hexene (84.16 mg, 1.25 mL, 10 mmol) against a flow of argon. The NMR tube and tip were then inserted into the spectrometer, stirring started and the reaction mixture was pumped through the system at 4 mL/min once all solids had fully dissolved. The reactor, heat exchanger and NMR probe were heated to 50 °C, and once the temperature had stabilised throughout the system the NMR spectrometer lock was turned off, shimmed on ^{1}H peaks and tuned to proton and phosphorus. Spectra of the reagents were recorded both statically and at 4 mL/min. Acquisition parameters for interleaved ^{1}H, selectively excited ^{1}H and ^{31}P{^{1}H} NMR measurements were entered (details below) and the sequence commenced to start the FlowNMR reaction monitoring. After acquisition of at least one sequence of measurements the autoclave was firstly pressurised with 6 bar H_2 followed by other 6 bar of CO to start the reaction. At the end of the reaction additional calibration spectra with and without flow were recorded before all heating was switched off, the flow stopped and the reactor carefully vented into the fumehood. An aliquot of the reaction mixture was taken by syringe and analysed by GC-FID/MS to confirm ^{1}H NMR spectral assignments.

Table S1. Amounts of PP_3 charged within the autoclave reactor for each flow run reaction with different number of ligand equivalents.

	PPh_3 loadings
[PPh_3]/[Rh] = 0	-
[PPh_3]/[Rh] = 1	13.12 mg, 0.05 mmol
[PPh_3]/[Rh] = 3	39.35 mg, 0.15 mmol
[PPh_3]/[Rh] = 6	78.69 mg, 0.3 mmol
[PPh_3]/[Rh] = 10	131.15 mg, 0.5 mmol
[PPh_3]/[Rh] = 20	262.30 mg, 1 mmol

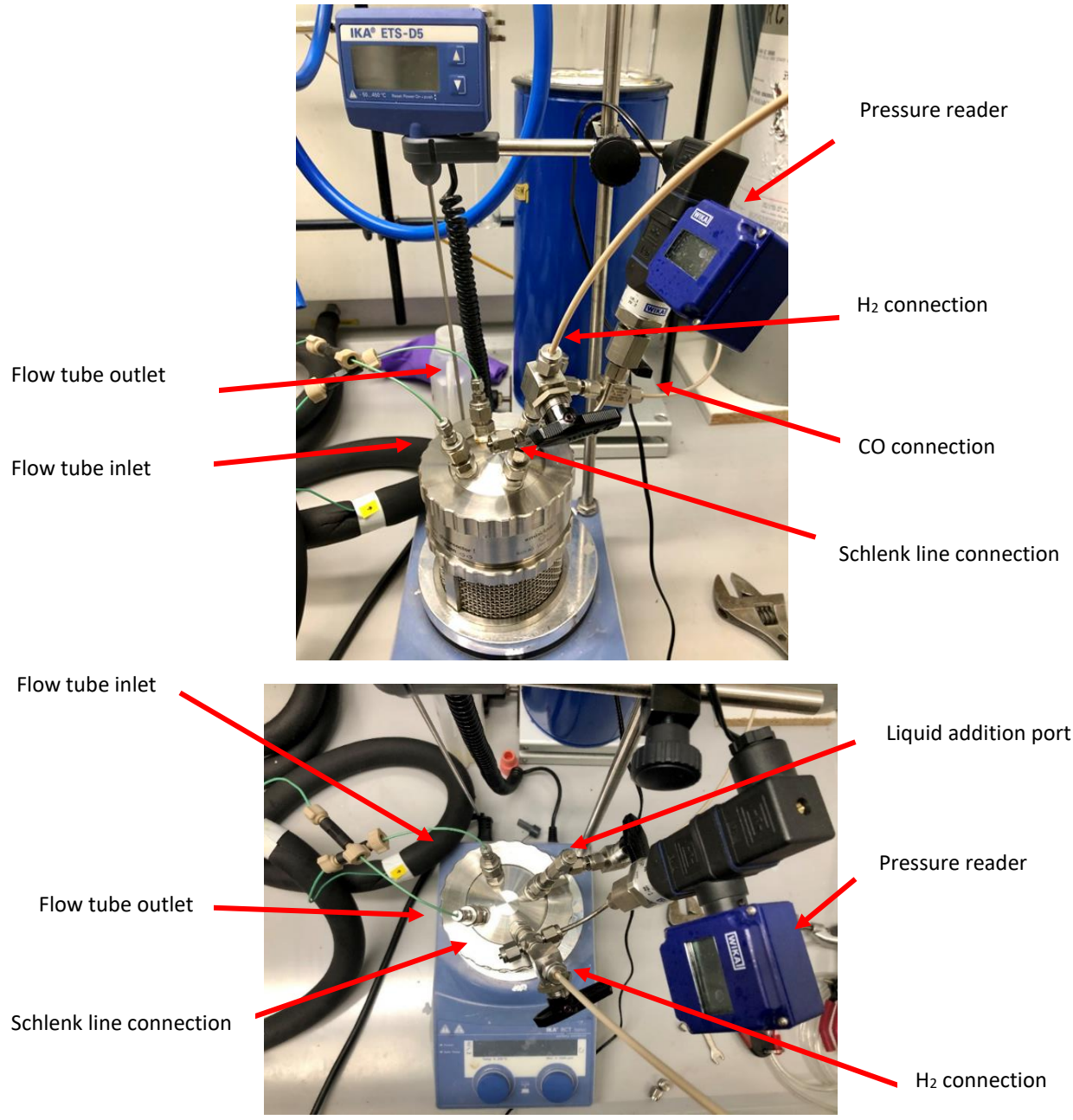

Figure S1. Autoclave used for the Rh-catalysed hydroformylation of 1-hexene. CO, H_2 and both flow tube parts are shown connected to the reactor lid.

Procedure for obtention of acyl complexes

Caution: carbon monoxide is a colourless, odourless and highly toxic gas – experiments should only be conducted in the presence of a calibrated CO sensor.

$[RhH(CO)(PPh_3)_3]$ (18,37 mg, 0.02 mmol) and triphenylphosphine (15.73 mg ,0.06 mmol) were added to a pressure NMR tube, and this was introduced in an NMR chamber to vacuum-argon the tube three times. Toluene (0.8 mL) and 1-hexene (33.66 mg, 0.05 mL, 0.4 mmol) were added against a flow of argon. The NMR tube was sealed and connected to the system (see below), that was vacuum-argon cycled three times and kept under argon. The ^{13}CO cylinder was smoothly opened and the leaving pressure controlled by pressure gauge.

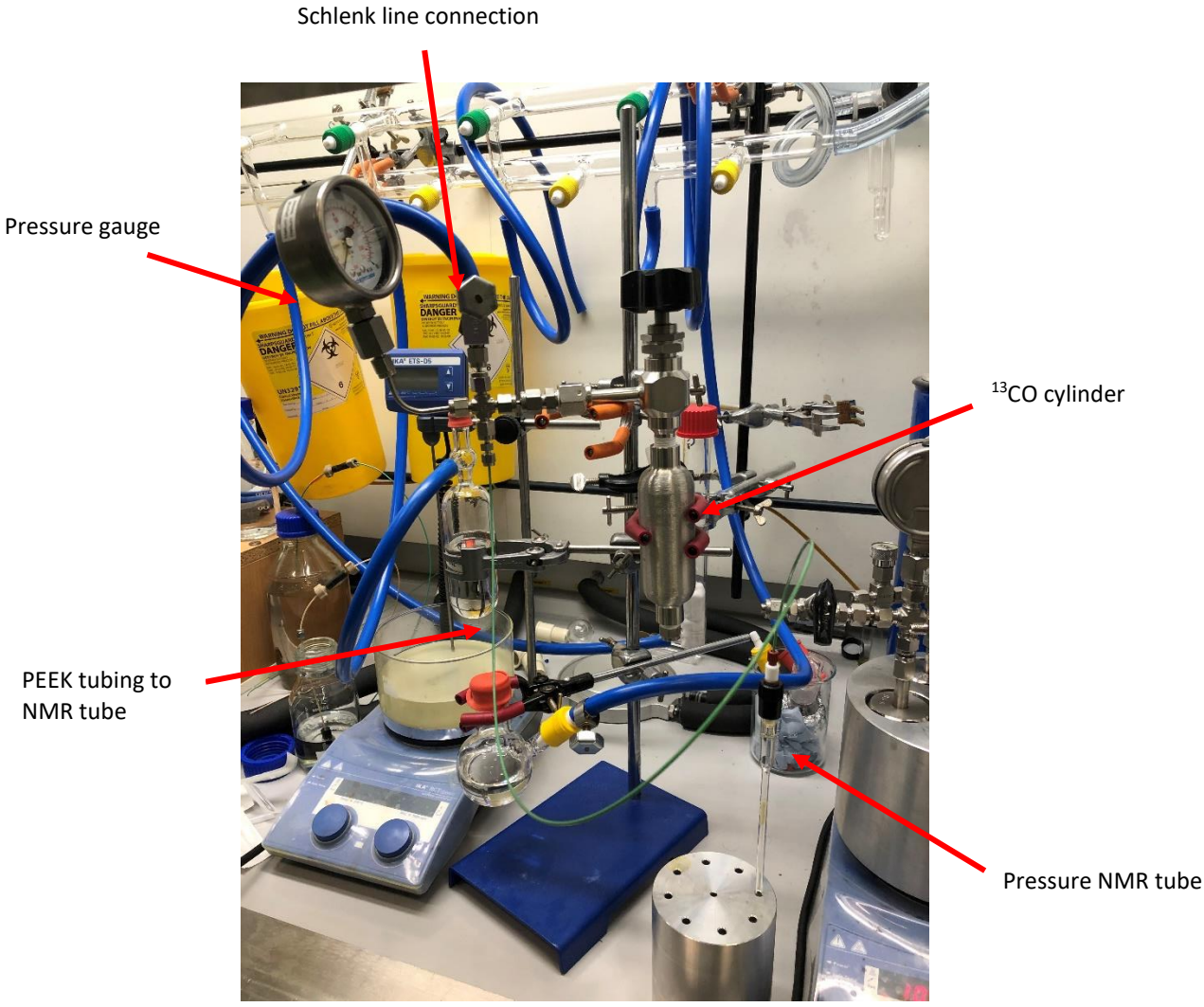

Figure S2. System used to obtain Rh acyl complexes under pressure of ^{13}CO in an NMR tube.

Analysis

FlowNMR acquisition parameters:

^{1}H, selectively excited ^{1}H, and $^{31}P\{^{1}H\}$ NMR experiments were interleaved in each cycle and continuously executed every 5 minutes until the end of the reaction.

^{1}H NMR (zg30):

- NS = 16 s
- D1 = 1 s
- RG = 9
- O1P = 4.7 ppm
- SW = 40 ppm
- Expt = 42 s

Selective excitation ^{1}H NMR (seldpfgse_calc.ptg):

- NS = 32 s
- D1 = 1 s
- RG = 203
- O1P = -5 ppm
- SW = 20 ppm
- CNST 21 = -8 ppm
- CNST 55 = 5 ppm
- Expt = 1 min 37 s

$^{31}P\{^{1}H\}$ NMR (zgpg):

- NS = 160 s
- D1 = 0.5 s
- RG = 203
- O1P = 50 ppm
- SW = 400 ppm
- Expt = 2 min 27 s

Static calibration spectra were recorded with the same parameters but with longer D_1 that were changed for every experiment as follows:

- ^{1}H NMR spectra ➔ D_1 = 60 s
- Selective excitation ^{1}H NMR spectra ➔ D_1 = 10 s
- $^{31}P\{^{1}H\}$ NMR spectra ➔ D_1 = 90 s

GC analyses:

GC-FID/MS analyses were carried out on a Shimadzu GCMS-QP2020 ultra NCI with a non-polar BPX5 column (30 m x 0.25 mm x 0.25 μm) using pentane as solvent to prepare samples and electron ionization for MS mode. Split ratio was 10:1, column pressure 320.5 kPa, column flow = 3.14 mL/min, injector temperature 250 °C, FID temperature 250 ° C with argon. The initial oven temperature was 50 °C, then hold for 3 minutes, ramp at 3 °C /min to 120 °C, ramp at 20 °C /min to 250 °C, then hold for 3 minutes.

Analyte retention times were: 1-hexene (1.55 min), 2-hexene (1.60 min), 3-hexene (1.60 min), toluene (2.94 min), 2-methylhexanal (4.56 min), *n*-heptanal (5.53 min), 1,3,5-trimethoxybenzene (20.94 min), triphenylphosphine (26.33 min). A sample chromatogram is shown in Figure S2. The same methods as for FID separation were used in GC-MS(EI) mode: 1-hexene (m/z = 56 $[M]^+$, 100 %), 2-hexene (m/z = 55 $[M]^+$, 100 %), 3-hexene (m/z = 56 $[M]^+$, 100 %), 2-methylhexanal (m/z = 58 $[M]^+$, 100 %), *n*-heptanal (m/z = 70 $[M]^+$, 100 %), 1,3,5-trimethoxybenzene (m/z = 168 $[M]^+$, 100 %), triphenylphosphine (m/z = 262 $[M]^+$, 100 %). Mass fragmentation spectra are shown in Figures S3-S9.

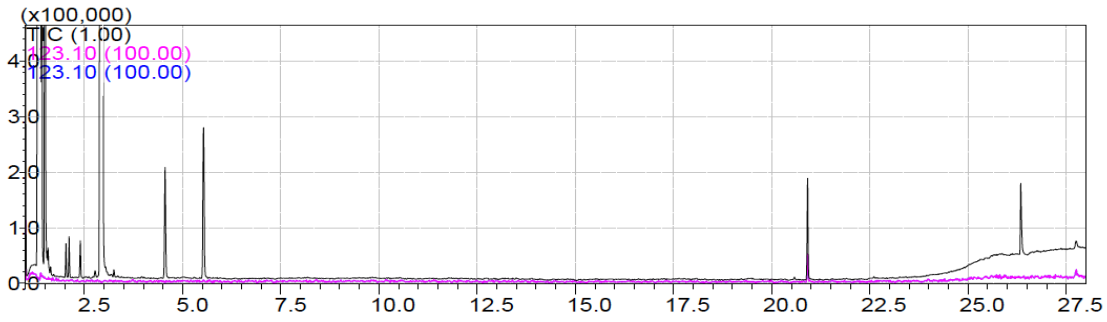

Figure S3. Chromatogram obtained from the hydroformylation reaction mixture of 1-hexene.

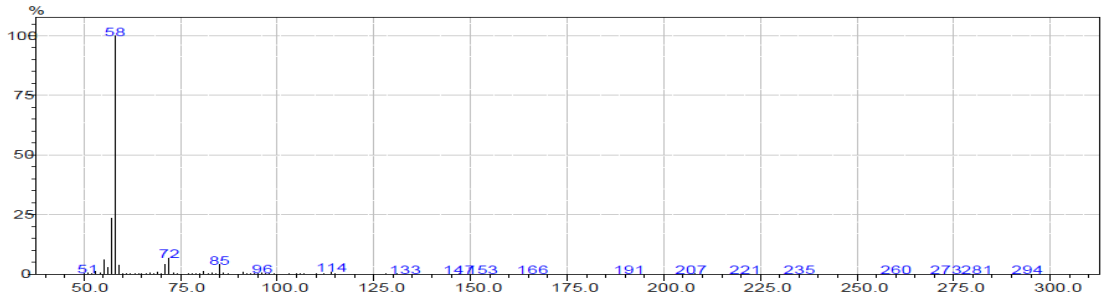

Figure S4. Mass spectrum fragmentation of 2-methylhexanal

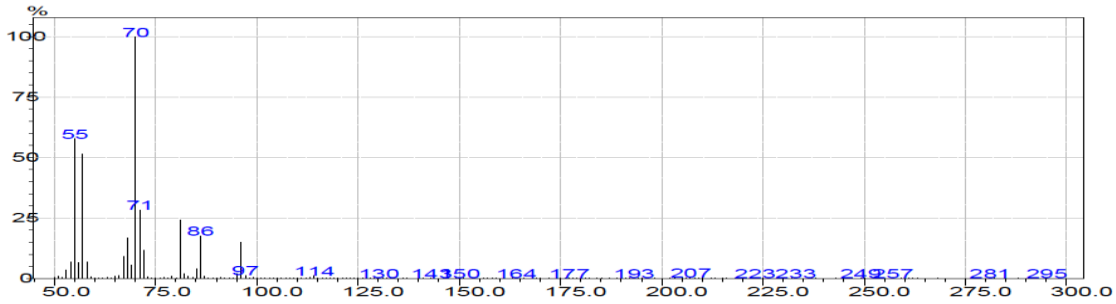

Figure S5. Mass spectrum fragmentation of n-heptanal

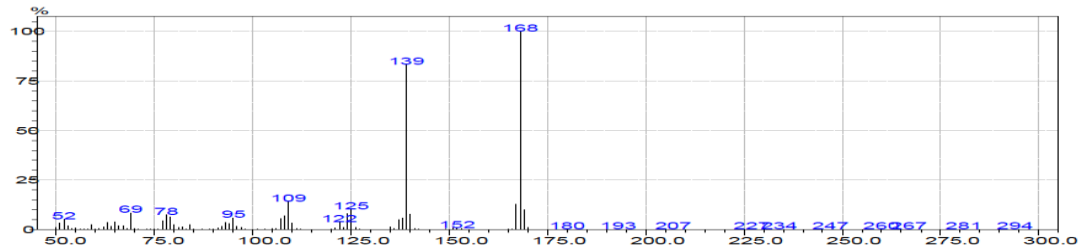

Figure S6. Mass spectrum fragmentation of 1,3,5-trimethoxybenzene

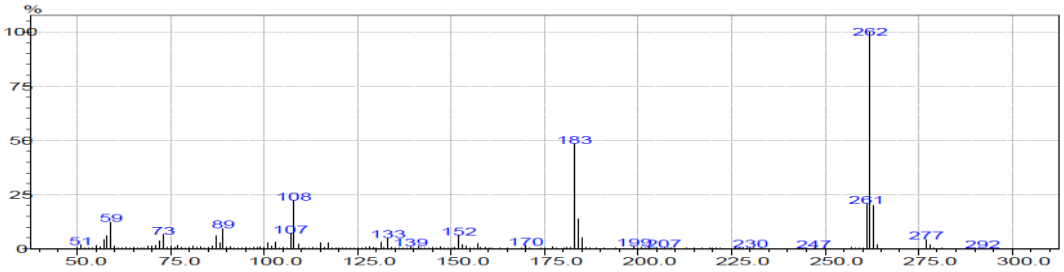

Figure S7. Mass spectrum fragmentation of triphenylphosphine

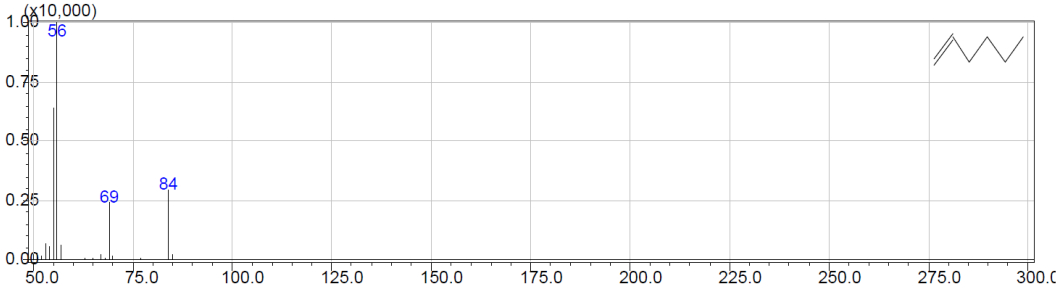

Figure S8. Mass spectrum fragmentation of 1-hexene

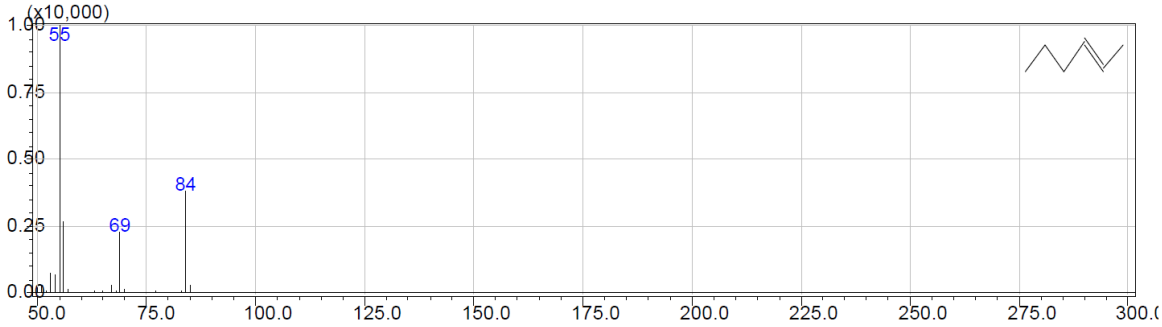

Figure S9. Mass spectrum fragmentation of 2-hexene

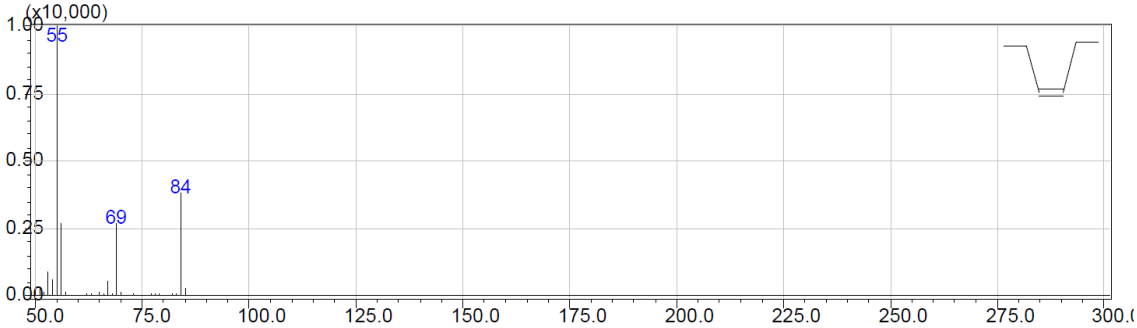

Figure S10. Mass spectrum fragmentation of 3-hexene

Quantitative NMR acquisition

Correction factors

Flow effects resulting from different degrees of pre-magnetisation may be corrected for by comparing integral values from flow spectra with static reference measurements.[1] A correction factor is then calculated for each peak comparing the integral at static and flow conditions and used for quantifying the data (Figure S11 and Table S2).

$$\mathrm{CF} = \frac{I_{\mathrm{static}}}{I_{\mathrm{flow}}}$$

$$I_{\mathrm{corrected}} = \mathrm{CF} \times I$$

$$C_{\mathrm{compound}} = \frac{I_{\mathrm{compound\ corrected}}}{I_{\mathrm{internal\ standard\ corrected}}} \times \frac{\mathrm{N}_{\mathrm{internal\ standard}}}{\mathrm{N}_{\mathrm{compound}}} \times \mathrm{C}_{\mathrm{internal\ standard}}$$

Figure S11. Formulae used to calculate the concentrations of each compound during the reaction. I=peak integral, CF= correction factor, C= concentration and N=number of nuclei contributing to the peak.

Table S2. Correction factors obtained from ^{1}H NMR spectra of the mixture of compounds present during hydroformylation of 1-hexene at 50 °C under 12 bar of syngas. Substrate and internal standard (1,3,5- trimethoxybenzene) could be calculated at the beginning and end of flow run whereas hydrogen and products were only calculated when the acquisition was stopped.

	1-hexene (start)	1-hexene (end)	TMB aromatic (start)	TMB aromatic (end)	TMB methyl (start)	TMB methyl (end)	1-heptanal (end)	2-methylhexanal (end)	Hydrogen (end)
CF	4.54	4.29	2.56	2.71	1.76	1.69	5.09	4.70	1.13

Selectively excited ^{1}H spectra were recorded at a much higher RG settings. Thus, to allow these experiments to be quantitative relative to other signals detected without selective excitation, a relative integral value (RIV) has to be calculated to account for the difference in receiver gains (Figure S12).[1]

$$RIV = \frac{I_{\text{hydride}}\ x\ RG_{normal}\ x\ RGCF}{RG\ hydride}$$

$$[Hydride] = RIV x\ \frac{C_{internal\ \text{standard}}}{\frac{I_{internal\ standard}}{N_{internal\ standard}}}$$

Figure S12. Formulas used to calculate the concentrations of hydride species. I=peak integral, CF= correction factor, C= concentration and N=number of nuclei causing the peak.

T_1 longitudinal relaxation time

A fully quantitative NMR experiment requires a detection time of at least 5 times T_1 relaxation time. The latter can vary with temperature, solvent, reaction mixture and concentration. We thus measured T_1 for each ^{1}H and ^{31}P {^{1}H} NMR signal under our hydroformylation conditions. The D_1 for static experiment was then chosen to be 5 times higher than the longest T_1 found for each type of nuclei.

Table S3. T_1 values obtained for a mixture of compounds in protonated toluene under 6 bar of H_2 and 50 °C.

Longitudinal relaxation time T_1 on ^{1}H spectra (s)							
n-heptanal (1)	**PPh3=O (2)**	**PPh3 (3)**	**TMB aromatic (4)**	**1-hexene terminal alkene (5)**	**1-hexene internal alkene (6)**	**Hydrogen (7)**	**TMB methyl (8)**
8.65	4.08	4.98	5.59	8.01	7.18	1.22	3.06

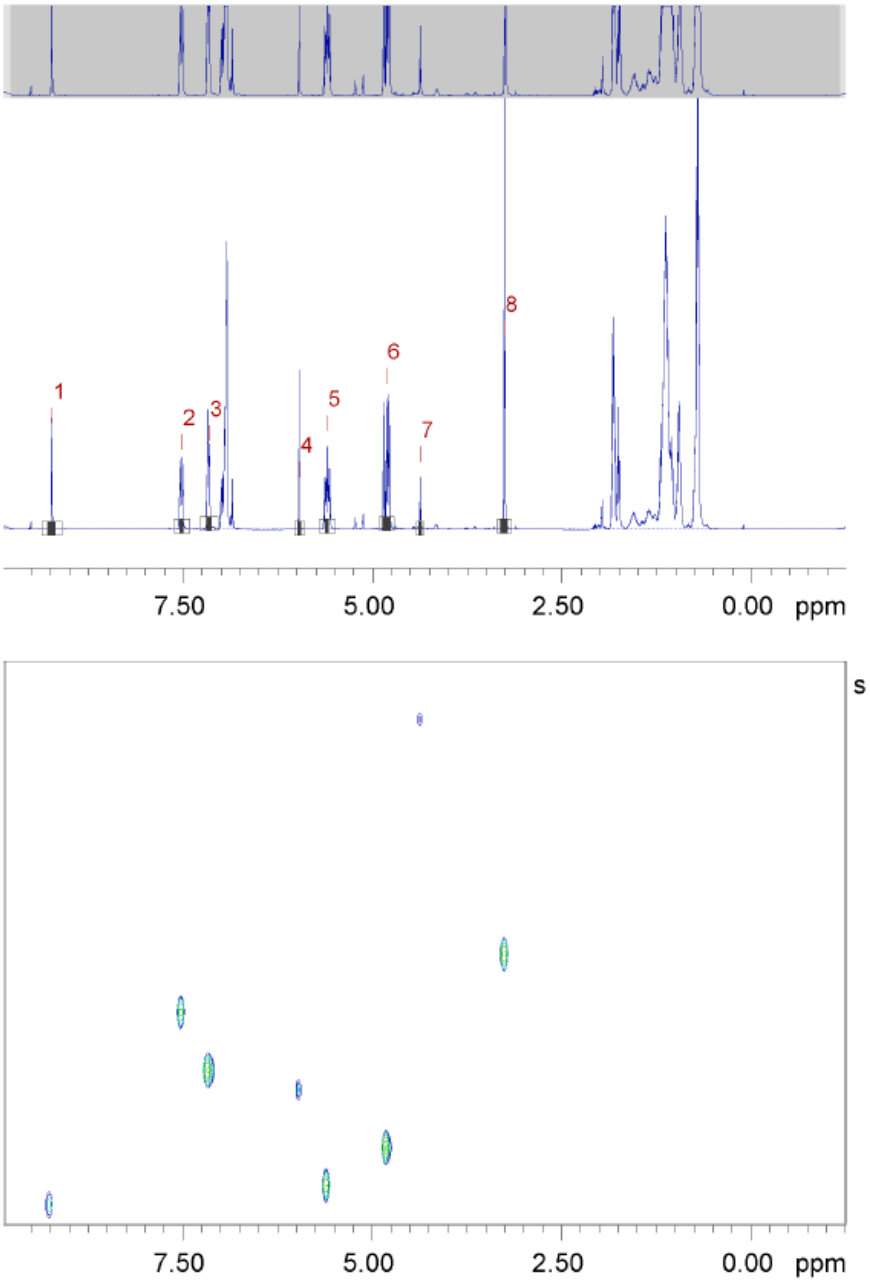

Figure S13. T_1 function found by ^1H NMR for a mixture of compounds in protonated toluene under 6 bar of H_2 and 50 °C.

Table S4. T_1 values obtained by $^{31}P\{^1H\}$ NMR for a mixture of compounds in protonated toluene under 6 bar of H_2 and 50 °C.

Longitudinal relaxation time T_1 on $^{31}P\{^1H\}$ (s)	
PPh_3=O (1)	**PPh_3 (2)**
3.83	17.1

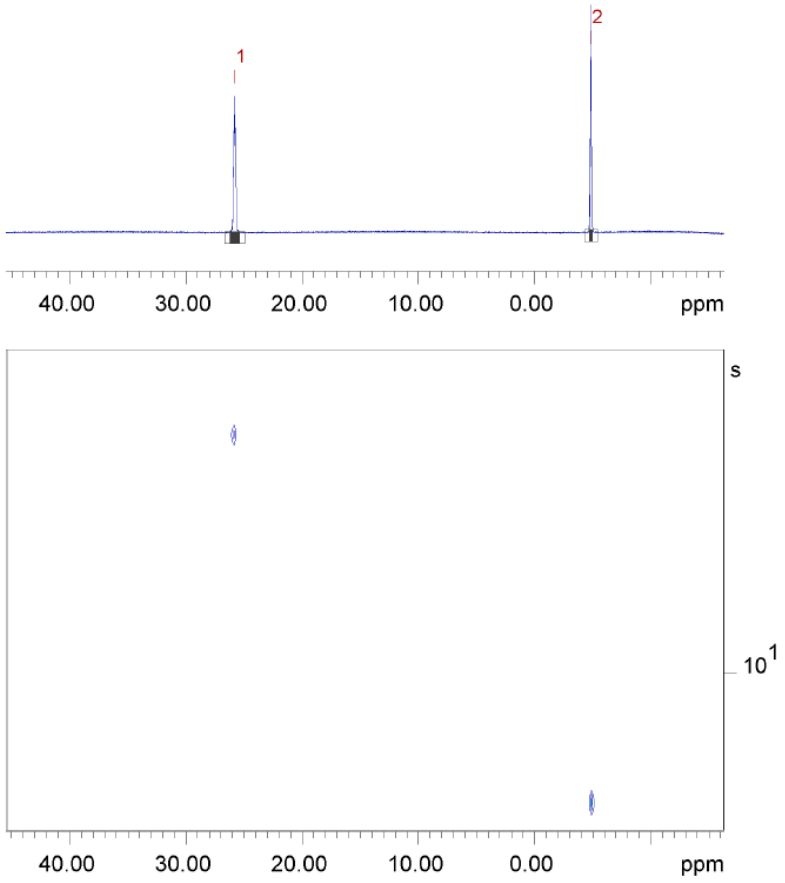

Figure S14. T_1 function found by $^{31}P\{^1H\}$ NMR for a mixture of compounds in protonated toluene under 6 bar of H_2 and 50 °C.

Catalysis

Reaction selectivity

Chemoselectivity towards hydroformylation is calculated as: % = ([n-heptanal] +[2-methylhexanal])/ ([h-heptanal] + [2-methylhexanal] + [2- and 3-hexene]) * 100.

Linear-to-branched product ratio is calculated as: L:B = ([n-heptanal] / [2-methylhexanal]).

Conversion is calculated as: % = 100 – ([1-hexene]/[1-hexene]$_0$ * 100).

Reaction kinetics

Reaction rate constants were calculated from the compound concentration profiles in the first 100 min of the reaction. Linear regressions in suitable regimes were used that did not necessarily span the same time intervals.

Table S5. Calculated reaction rate constant for each compound present in the reaction mixture of the hydroformylation reaction for six experiments loaded with same [Rh] = 2.5 mM, [1-hexene] = 500 mM and [TMB] = 100 mM and different [PPh_3]. The rate constants were calculated in the first 100 min of the reaction.

	[PPh_3]/[Rh]=0	**[PPh_3]/[Rh]=1**	**[PPh_3]/[Rh]=3**	**[PPh_3]/[Rh]=6**	**[PPh_3]/[Rh]=10**	**[PPh_3]/[Rh]=20**
Consumption of 1-hexene (k_{obs}=mM/min)	0.69	0.82	2.43	1.95	1.30	1.23
Formation of n-heptanal (k_{obs}=mM/min)	0.22	0.46	1.62	1.75	1.19	1.08
Formation of 2-methylhexanal (k_{obs}=mM/min)	0.09	0.2	0.51	0.58	0.39	0.33
Formation of 2- and 3-hexene (k_{obs}=mM/min)	0.53	0.37	-	-	-	-

NMR experiments

^{31}P and ^{1}H DOSY NMR experiments were carried out to calculate the diffusion of various rhodium complexes. By comparison, this allowed us to derive whether these species were monomeric or dimeric.

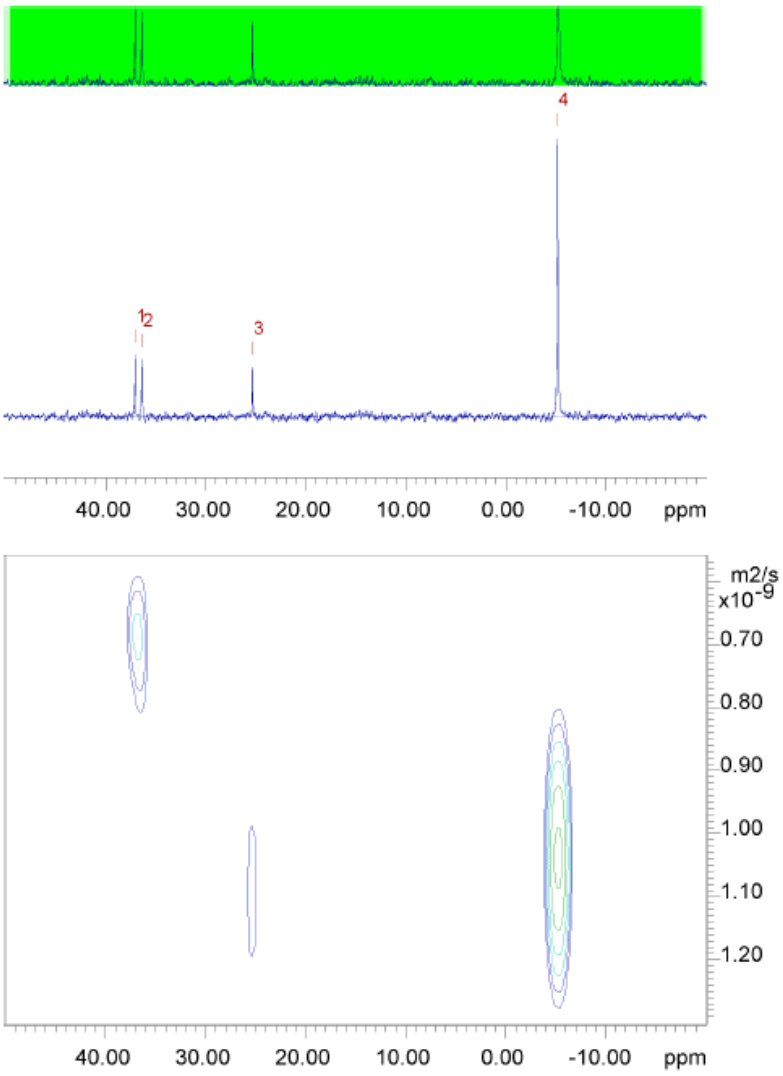

*Figure S15. ^{31}P DOSY diffusion curve of $[RhH(CO)_2(PPh_3)_2]$ (**A**/**B**).*

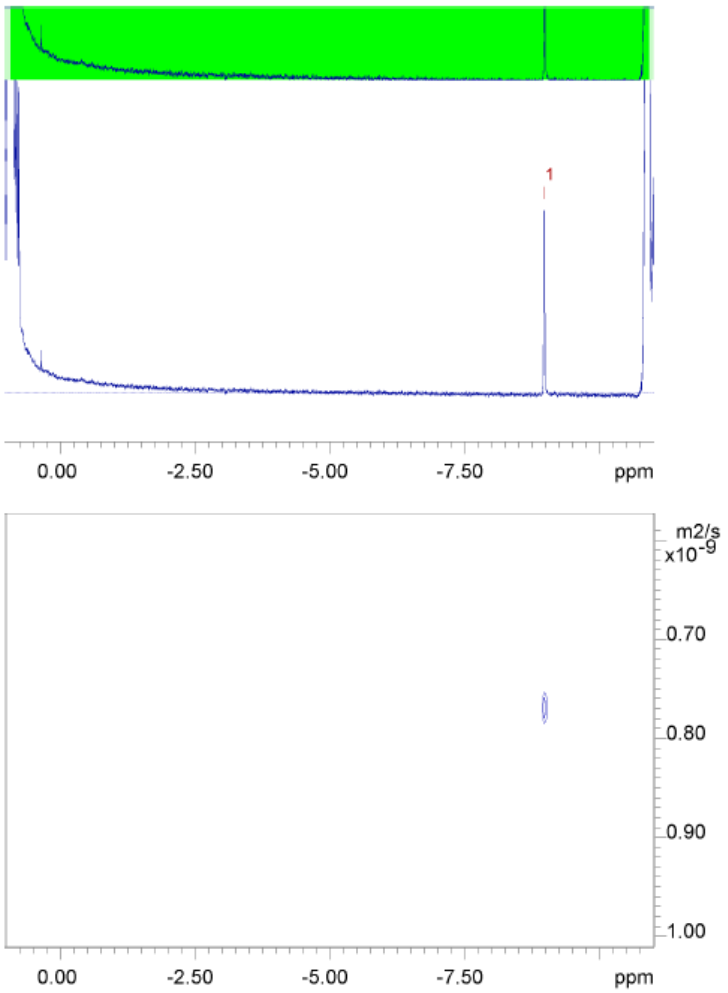

*Figure S16. ^{1}H DOSY diffusion curve of $[RhH(CO)_2(PPh_3)_2]$ (**A**/**B**).*

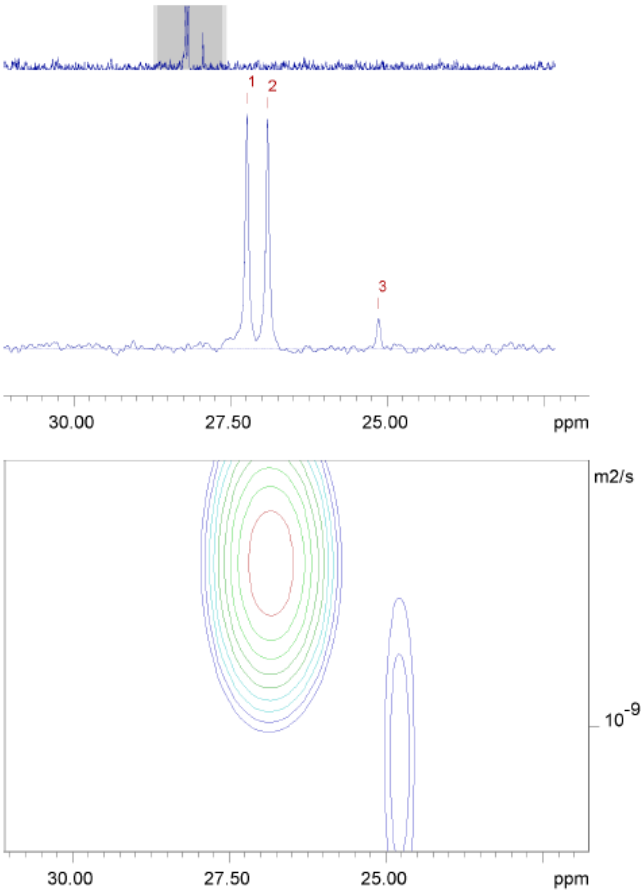

*Figure S17. ^{31}P DOSY diffusion curve of acyl rhodium complex **Q**.*

In addition, ^{1}H-^{31}P HMBC measurements were carried out to verify the correlation of some hydride and phosphorus peaks.

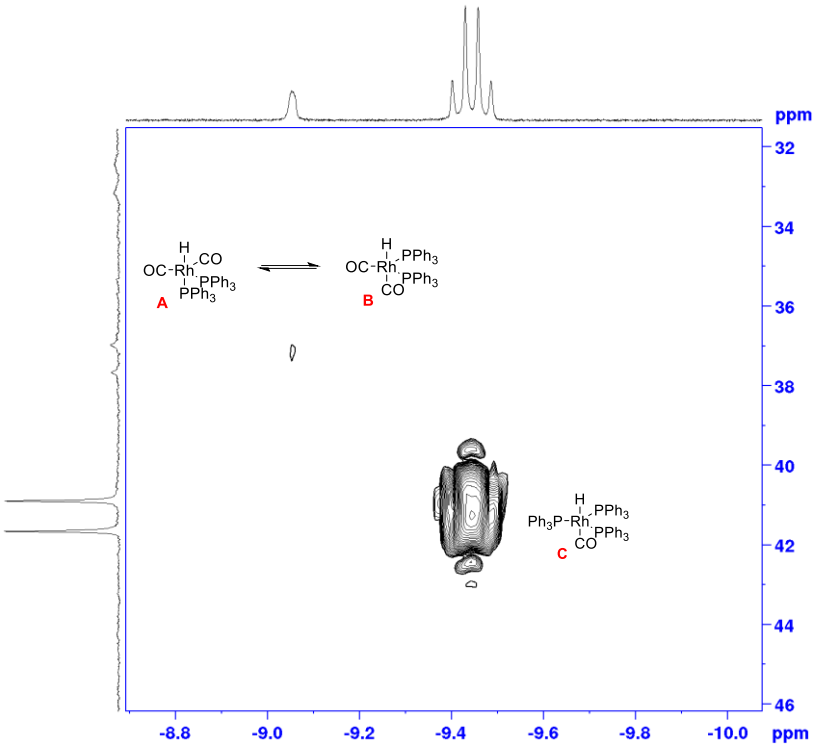

Figure S18. $^{1}H - ^{31}P$ HMBC spectrum of $[RhH(CO)_2(PPh_3)_2]$ and $[RhH(CO)(PPh_3)_3]$.

Rh-complexes characterization

Table S6. ^{1}H and $^{31}P\{^{1}H\}$ NMR data of the carbonyl ligands of various of $[HRh(L)_{2+x}(CO)_{2-x}]_{x=0,1}$ complexes.

Complex	**δ_H / ppm**	**δ_P/ ppm**	**$^{1}J_{RhP}$/ Hz**
$[RhH(CO)_2(PPh_3)_2]$ **(A/B)**	-9.2	37.3	139.2
$[RhH(CO)(PPh_3)_3]$ **(D)**	-9.4	41.5	154.1
$[Rh(CO(CH_2)_5CH_3)(CO)_2(PPh_3)_2]$ **(Q)**	-	27.7	71.8

Additional data

Flow NMR ^{1}H Spectra

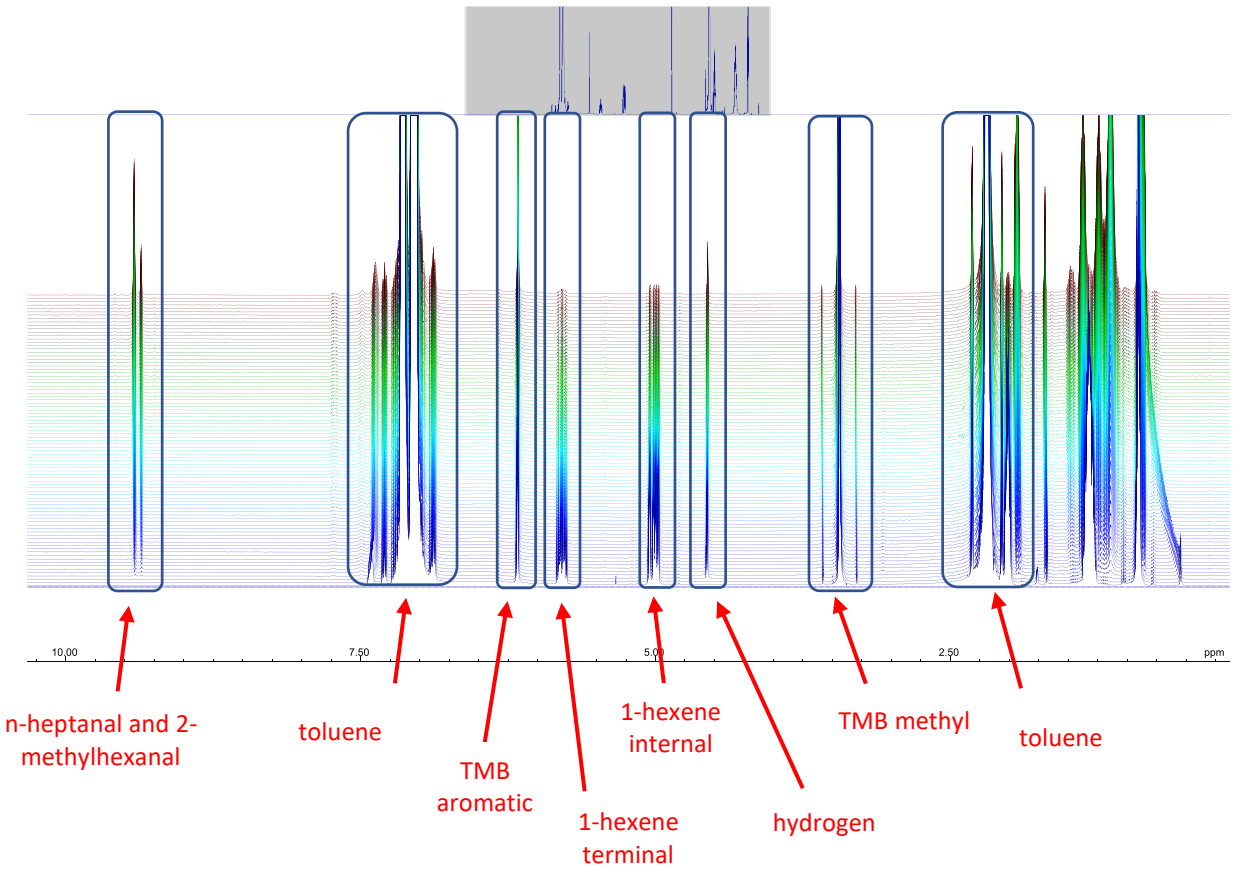

Figure S19. Flow ^{1}H NMR spectra of hydroformylation of 1-hexene under our reaction conditions.

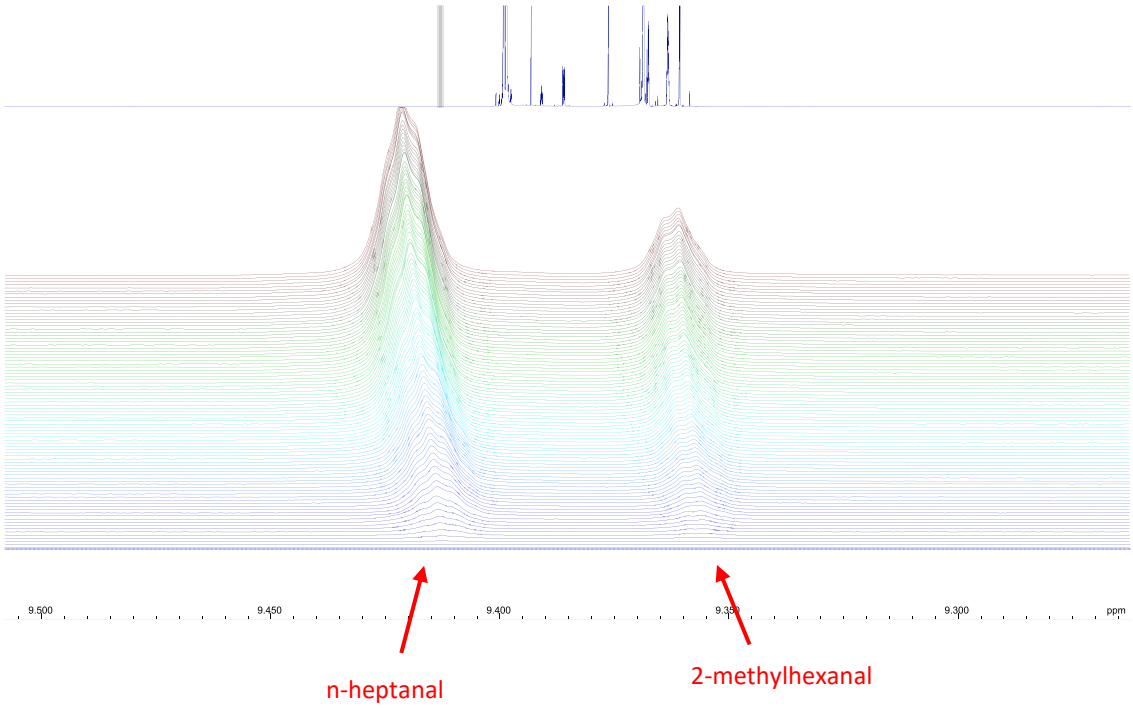

Figure S20. Flow ^{1}H NMR spectra showing hydroformylation product formation of n-heptanal and 2-methylhexanal.

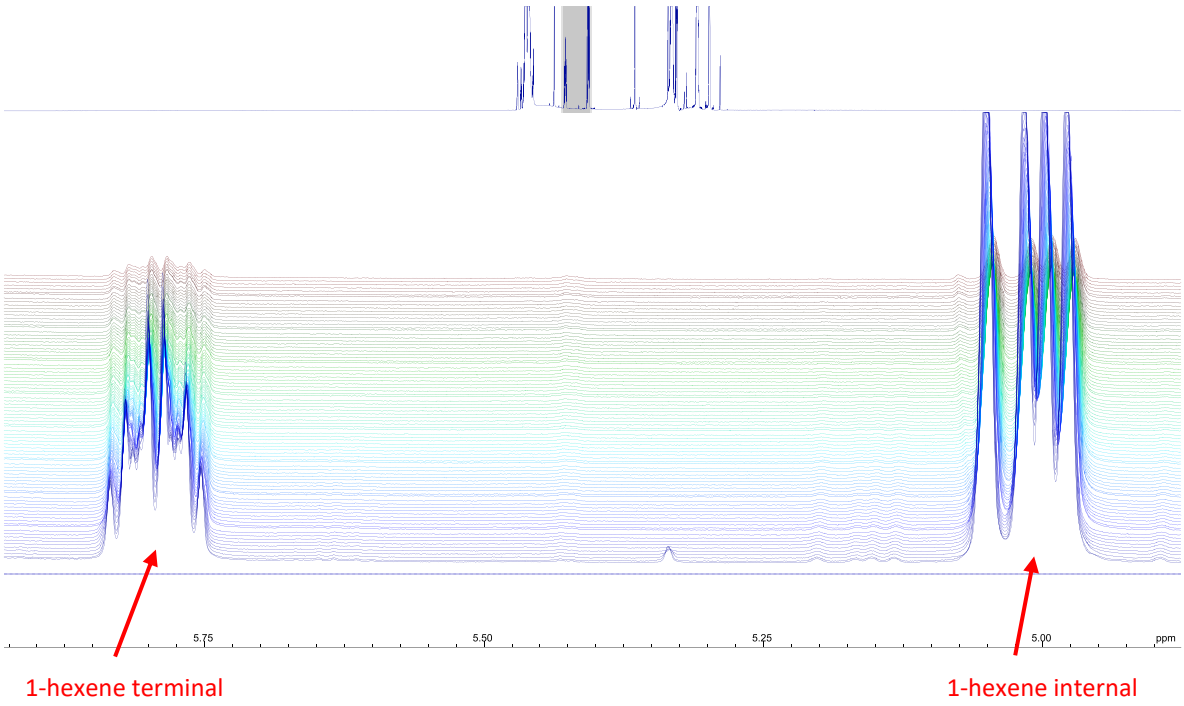

Figure S21. Flow ^{1}H NMR spectra showing hydroformylation substrate consumption of 1-hexene.

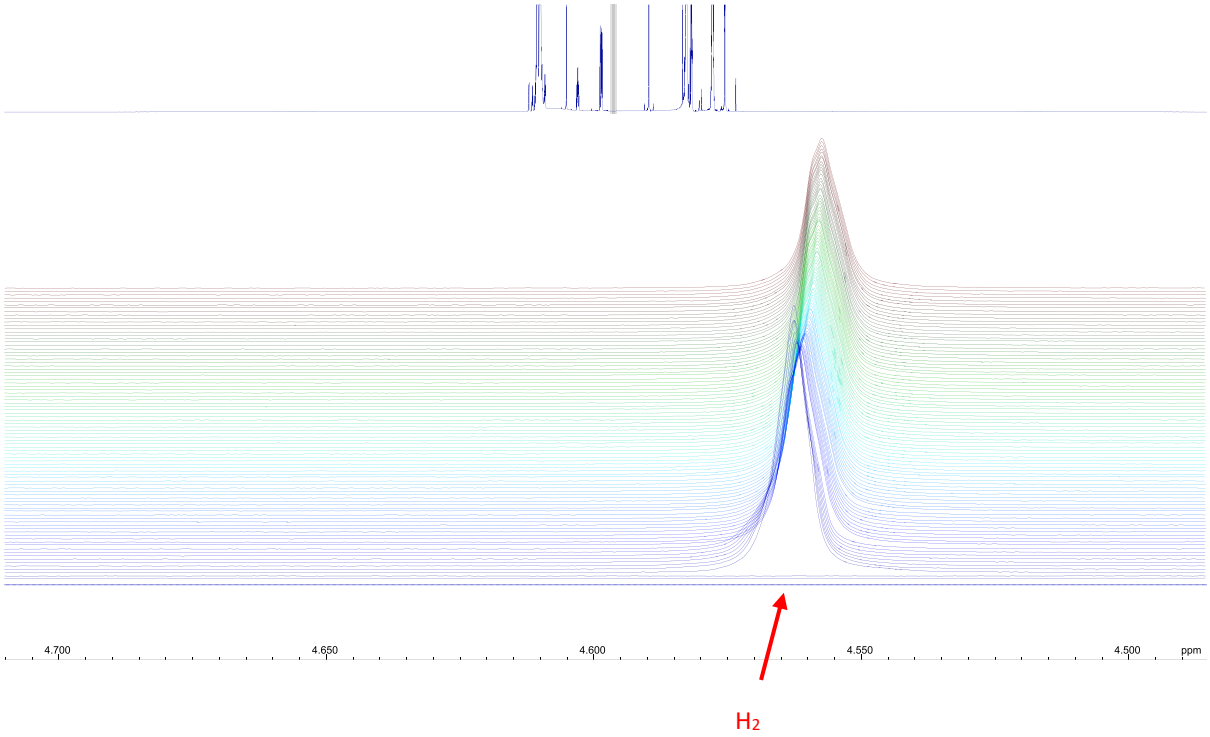

Figure S22. Flow ^{1}H NMR spectra showing dissolved hydrogen evolution during hydroformylation reaction.

Concentration profiles of hydroformylation reactions

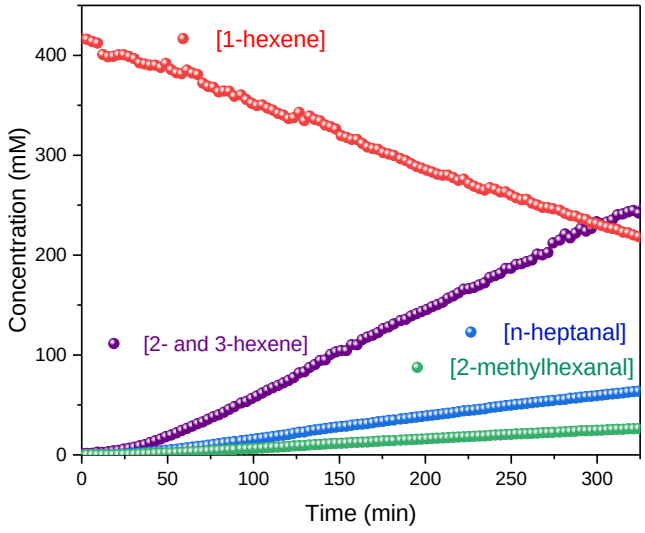

Figure S23. Concentration profiles of hydroformylation reactions at 50 °C under 12 bar of syngas (1:1 H_2/CO) using [$Rh(CO)_2(acac)$] = 2.5 mM, [1-hexene] = 500 mM, [TMB] = 100 mM and [PPh_3] = 0 mM. [PPh_3] /[$Rh(CO)_2(acac)$] used is 0.

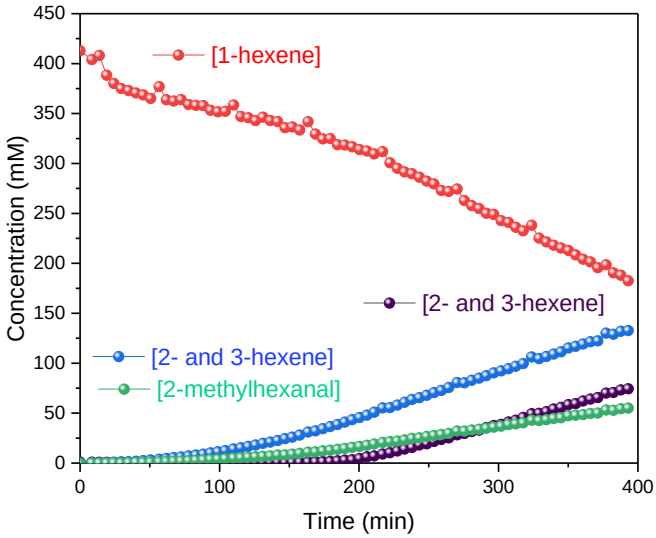

Figure S24. Concentration profiles of hydroformylation reactions at 50 °C under 12 bar of syngas (1:1 H_2/CO) using [$Rh(CO)_2(acac)$] = 2.5 mM, [1-hexene] = 500 mM, [TMB] = 100 mM and [PPh_3] = 2.5 mM. [PPh_3] /[$Rh(CO)_2(acac)$] used is 1.

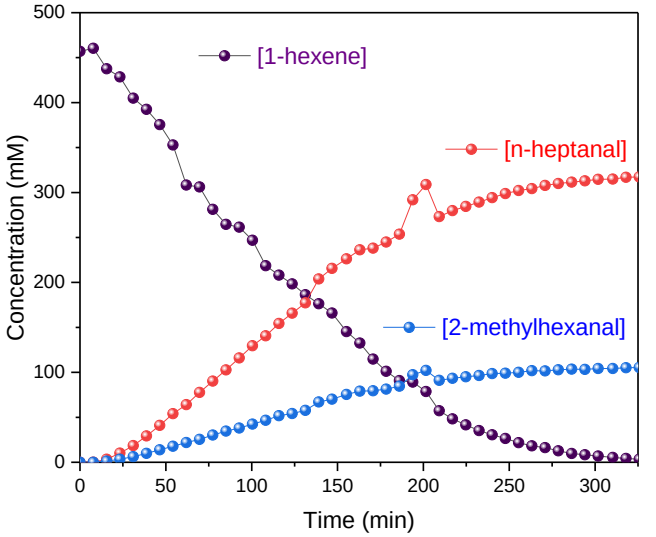

Figure S25.Concentration profiles of hydroformylation reactions at 50 °C under 12 bar of syngas (1:1 H_2/CO) using [$Rh(CO)_2(acac)$] = 2.5 mM, [1-hexene] = 500 mM, [TMB] = 100 mM and [PPh_3] = 7.5 mM. [PPh_3] /[$Rh(CO)_2(acac)$] used is 3.

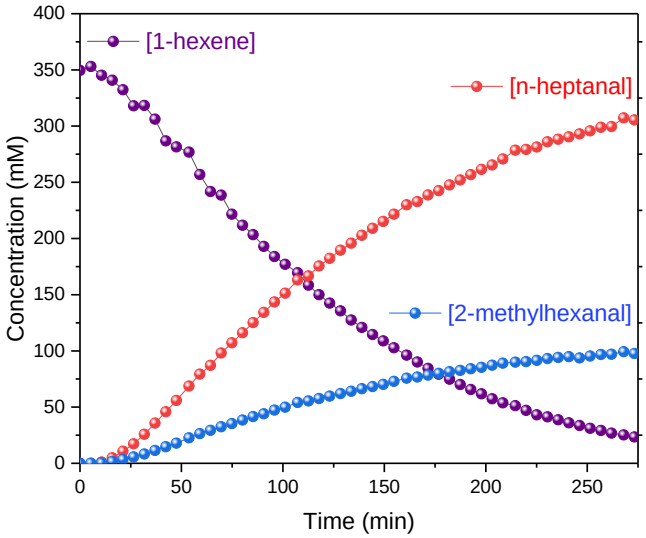

Figure S26. Concentration profiles of hydroformylation reactions at 50 °C under 12 bar of syngas (1:1 H_2/CO) using [$Rh(CO)_2(acac)$] = 2.5 mM, [1-hexene] = 500 mM, [TMB] = 100 mM and [PPh_3] = 15 mM. [PPh_3] /[$Rh(CO)_2(acac)$] used is 6.

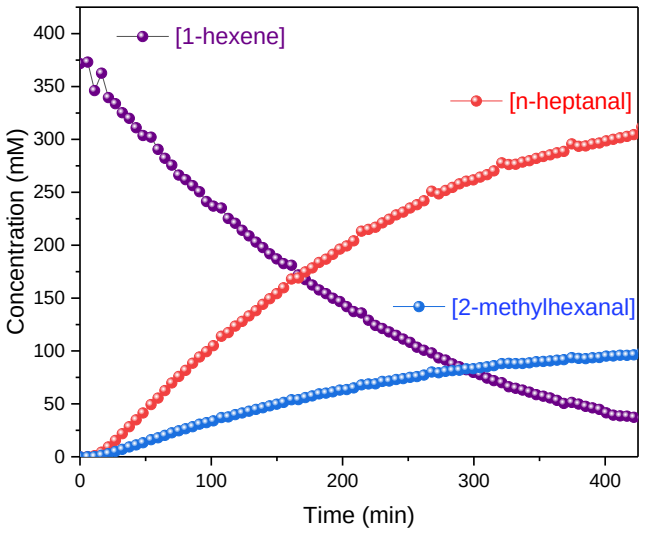

Figure S27. Concentration profiles of hydroformylation reactions at 50 °C under 12 bar of syngas (1:1 H_2/CO) using [$Rh(CO)_2(acac)$] = 2.5 mM, [1-hexene] = 500 mM, [TMB] = 100 mM and [PPh_3] = 25 mM. [PPh_3] /[$Rh(CO)_2(acac)$] used is 10.

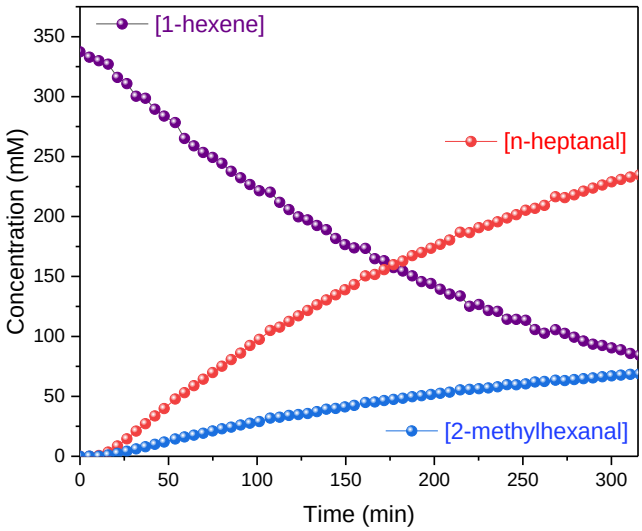

Figure S28. Concentration profiles of hydroformylation reactions at 50 °C under 12 bar of syngas (1:1 H_2/CO) using [$Rh(CO)_2(acac)$] = 2.5 mM, [1-hexene] = 500 mM, [TMB] = 100 mM and [PPh_3] = 50 mM. [PPh_3] /[$Rh(CO)_2(acac)$] used is 20.

^{13}CO experiments for identification of acyl Rh complex

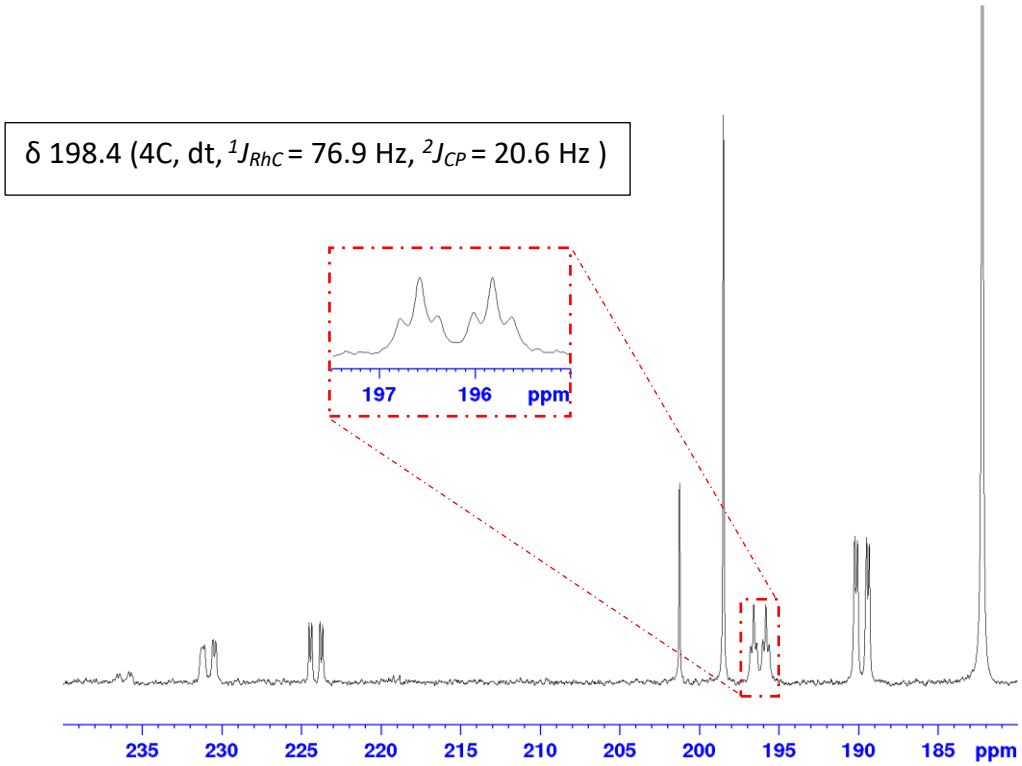

*Figure S29. {^{1}H} ^{13}C NMR spectrum of [$RhH(CO)(PPh_3)_3$] (25 mM) and 1-hexene (500 mM) under 5 bar of ^{13}CO in toluene at -90° C. The terminal carbonyl signals of **O/P** become a doublet of triplets due to $^2J_{CP}$.*

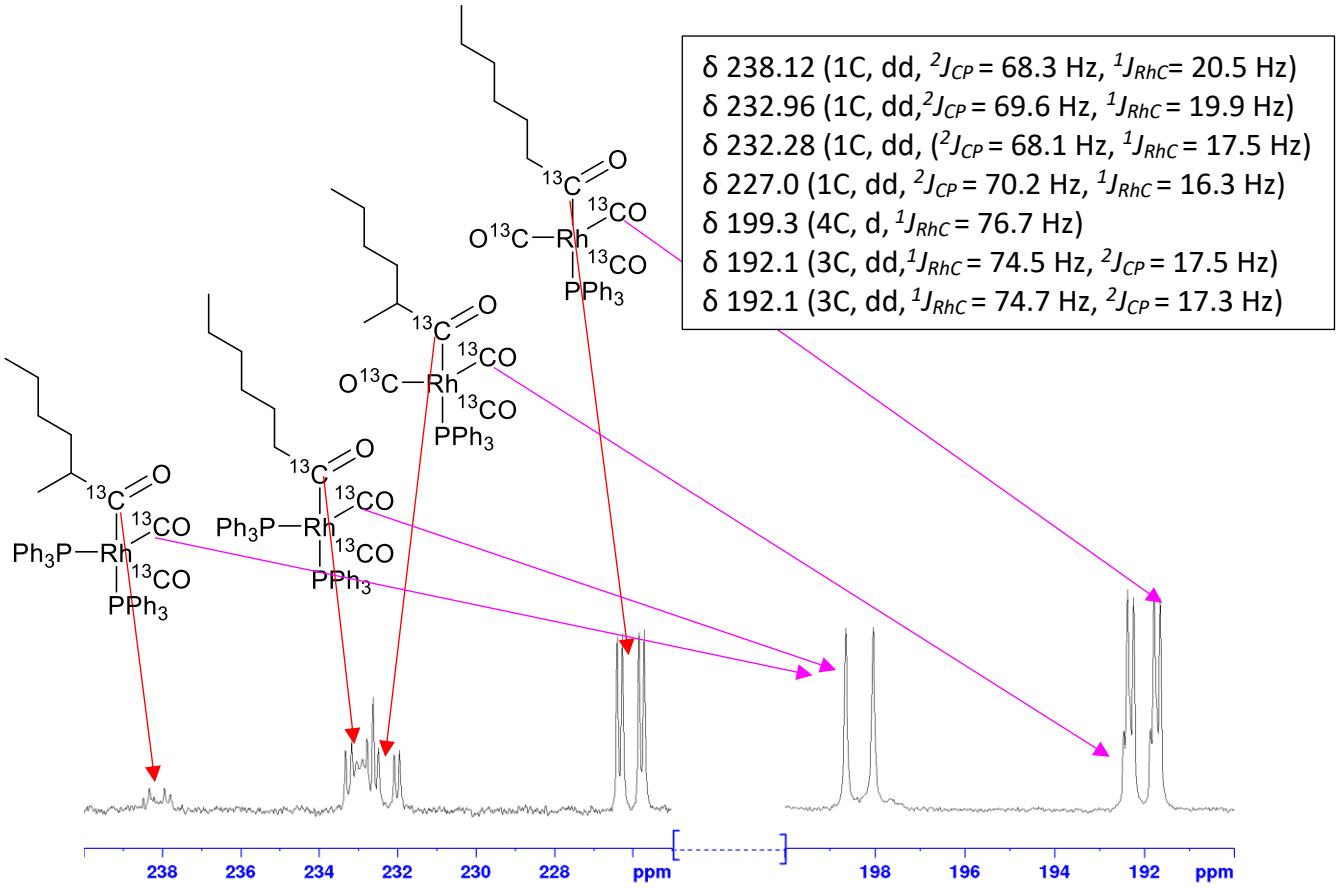

Figure S30. {^{1}H} ^{13}C NMR spectral regions of the acyl complexes formed from [RhH(CO)(PPh$_3$)$_3$] (25 mM) and 1-hexene (500 mM) under 5 bar of ^{13}CO in toluene at -40° C.

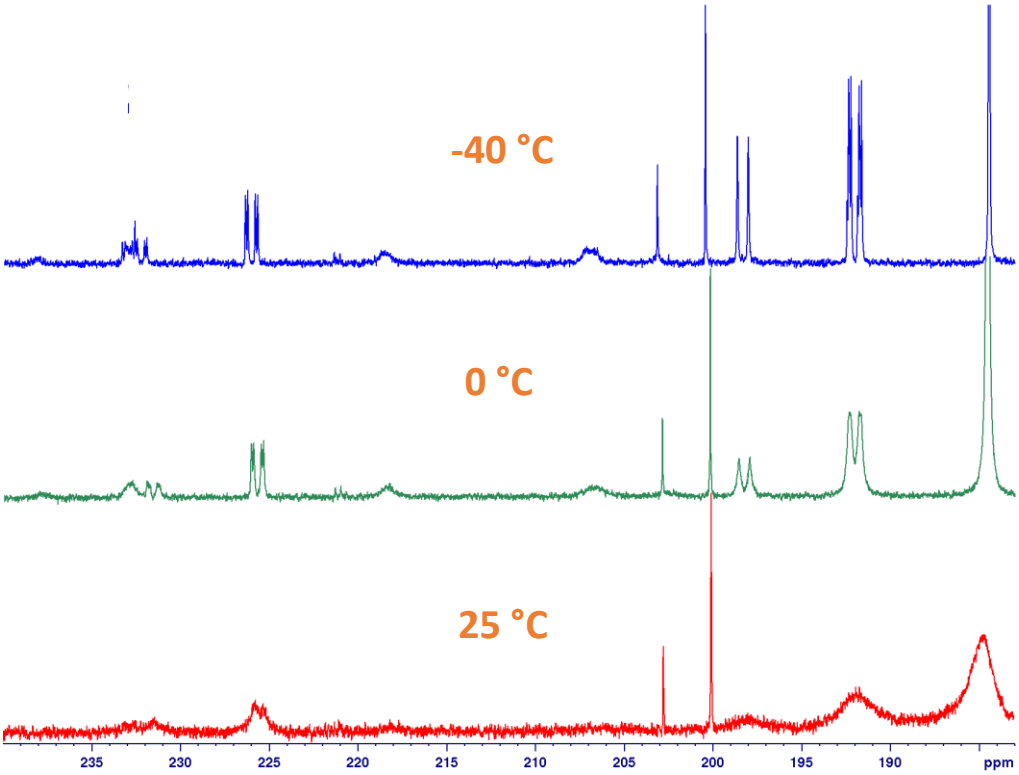

Figure S31. VT {^{1}H} ^{13}C NMR spectra of [RhH(CO)(PPh$_3$)$_3$] (25 mM) and 1-hexene (500 mM) under 5 bar of ^{13}CO in toluene at three different temperatures.

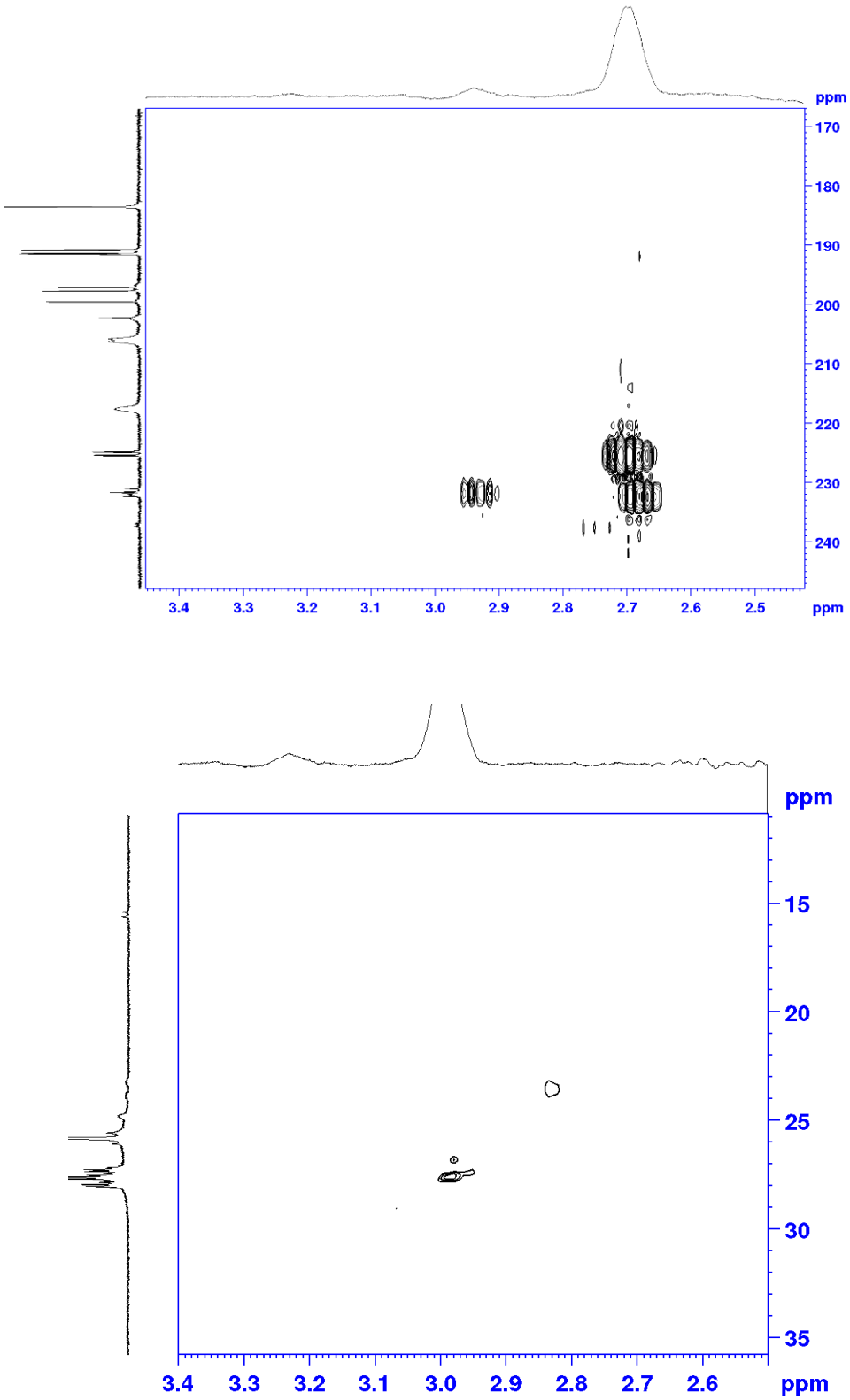

Figure S32. ^{1}H-^{13}C HMBC (upper) and ^{1}H-^{31}P HMBC (lower) spectra of $[RhH(CO)(PPh_3)_3]$ (25 mM) and 1-hexene (500 mM) under 5 bar of ^{13}CO in toluene at -40°C.

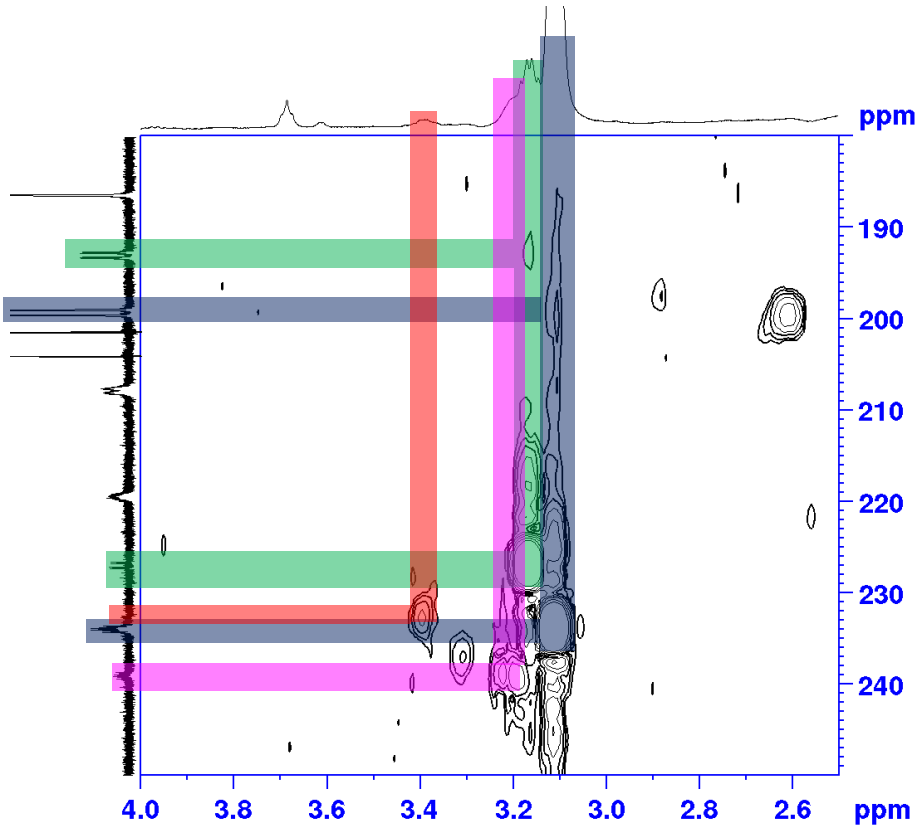

Figure S33. ^{1}H-^{13}C HMBC spectrum of $[RhH(CO)(PPh_3)_3]$ (25 mM), 1-hexene (500 mM) and PPh_3 (25 mM) under 5 bar of ^{13}CO in toluene at -20°C.

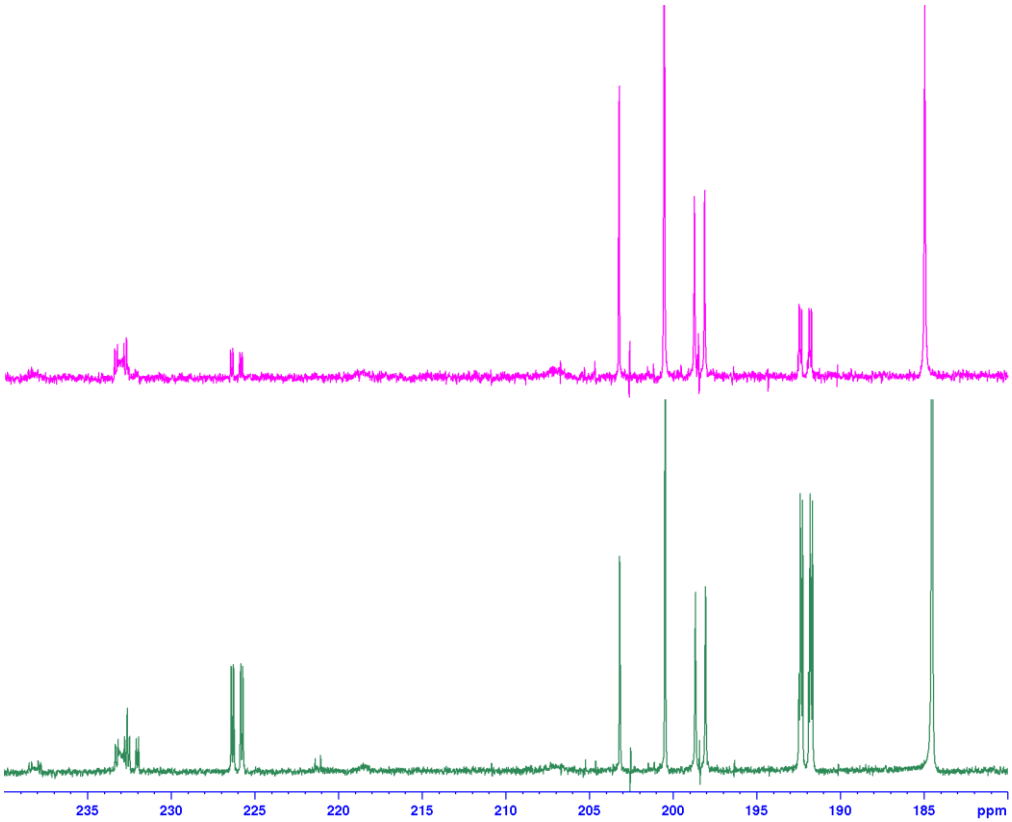

Figure S34. $\{^{1}H\}$ ^{13}C NMR spectra of $[RhH(CO)(PPh_3)_3]$ (25 mM), 1-hexene (500 mM) and 5 bar of ^{13}CO in toluene at -40° C. Green spectrum was recorded under 5 bar ^{13}CO and the pink one at atmospheric pressure after venting the NMR tube.

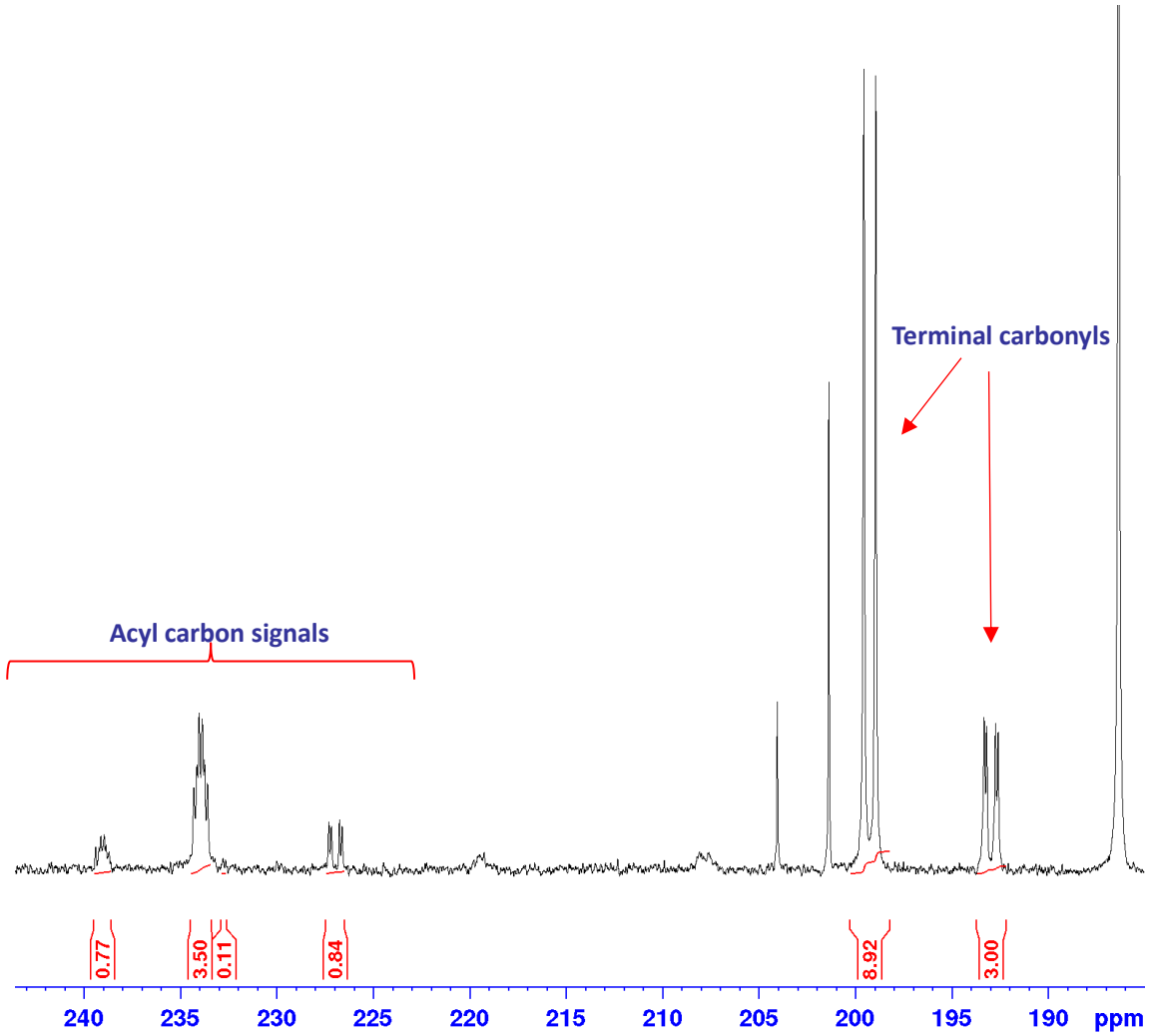

Figure S35. Quantitative {^{1}H} ^{13}C NMR spectra of [$RhH(CO)(PPh_3)_3$] (25 mM), 1-hexene (500 mM) and PPh_3 (25 mM) under 5 bar of ^{13}CO in toluene at -20° C with D1 = 70 sec.

References

1. A. M. R. Hall, J. C. Chouler, A. Codina, P. T. Gierth, J. P. Lowe and U. Hintermair, *Catal. Sci. Technol.*, 2016, **6**, 8406–8417.