Electronic Supplementary Material (ESI) for Chemical Communications

Rhodium / Phospholane-phosphite Catalysts give Unusually High Regioselectivity in the Enantioselective Hydroformylation of Vinyl Arenes.

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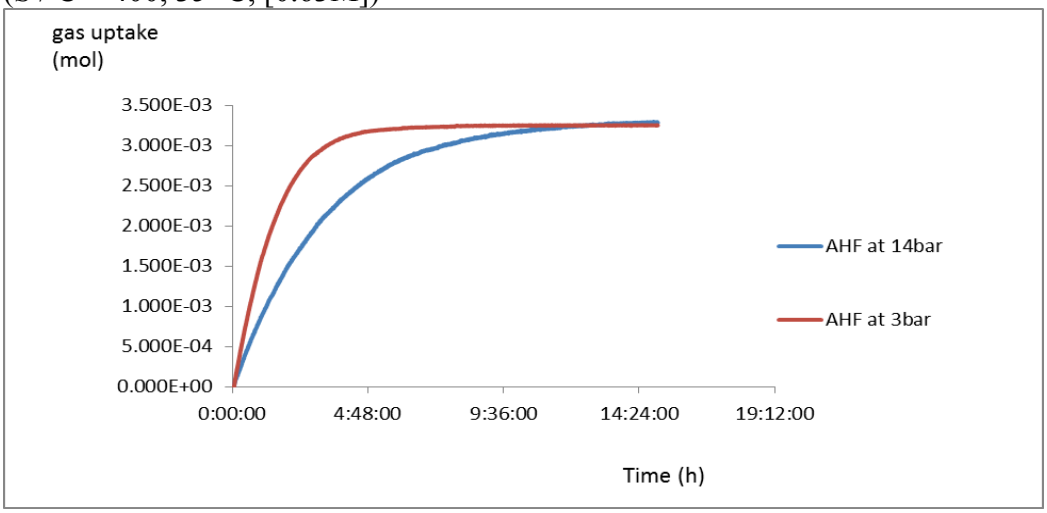
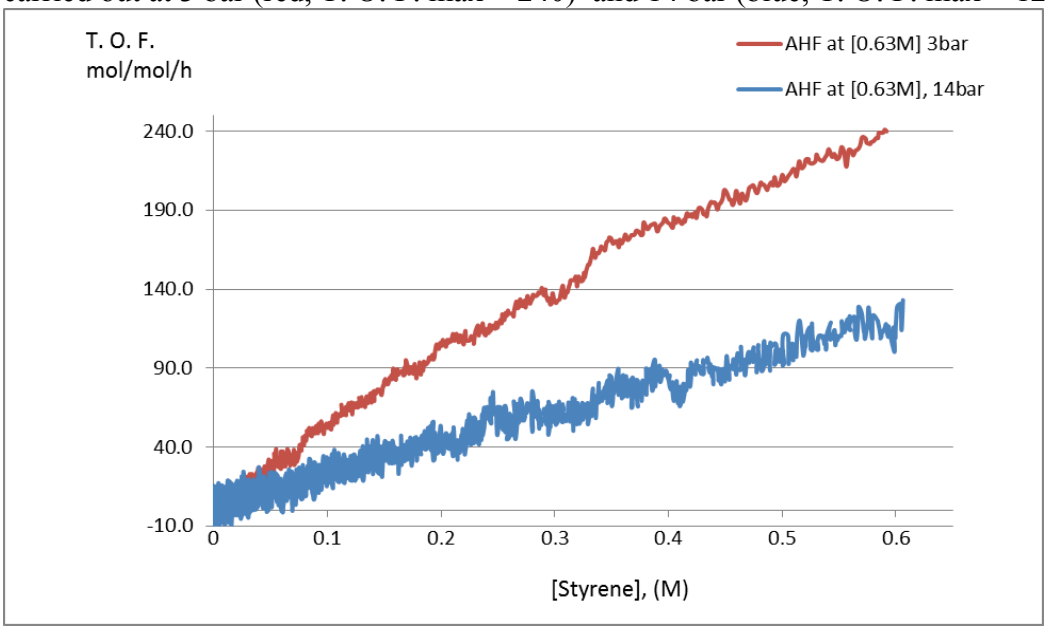
Supporting information:

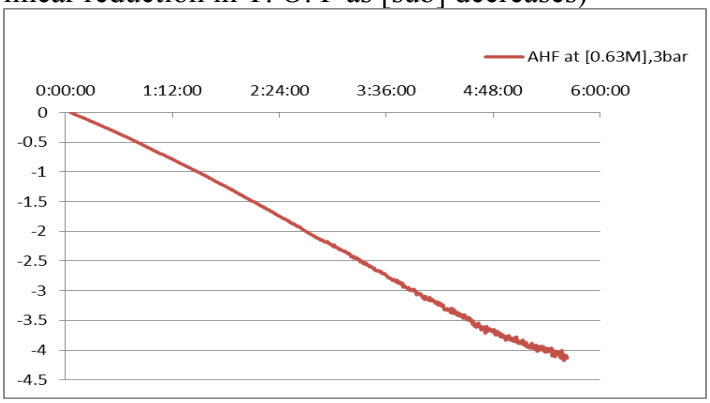
Kinetics of the hydroformylation reaction:
Catalysts are pre-activated as shown in the experimental, and substrate is added at the reaction temperature. (A short time for stabilisation (c. 1 minute) occurs before the machine starts recording data).
Effect of pressure, and order in substrate.
Plot of gas uptake vs. time: Comparison of hydroformylation of styrene at 3 bar (red) and 14 bar (blue), (S / C = 400, 35 ^{o}C, [0.63M])



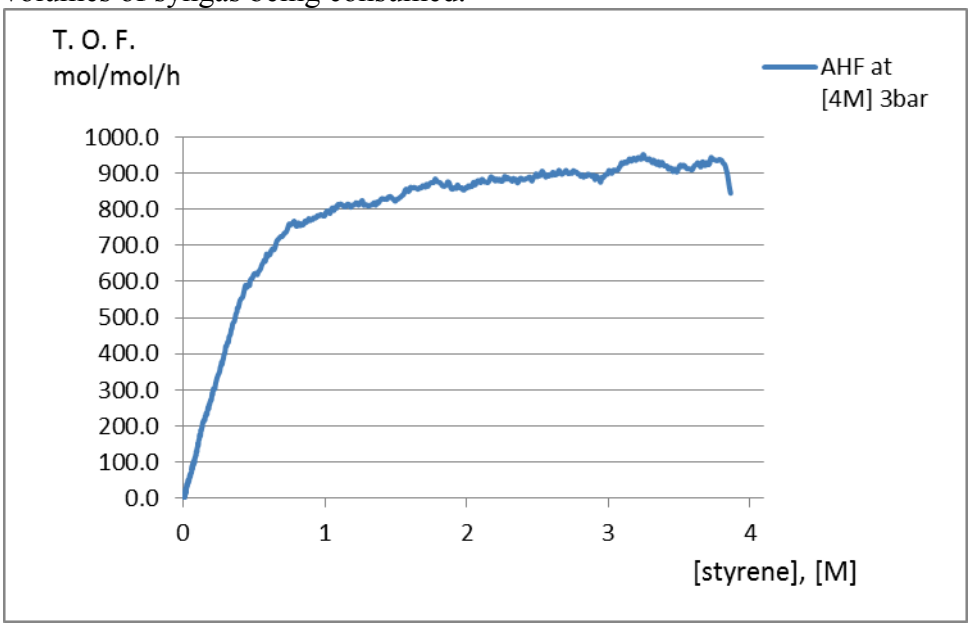
A plot of TOF in mol/mol/h vs. [substrate], calculated from gas uptake in 10 minutes periods for reactions carried out at 3 bar (red, T. O. F. max = 240) and 14 bar (blue, T. O. F. max = 125).



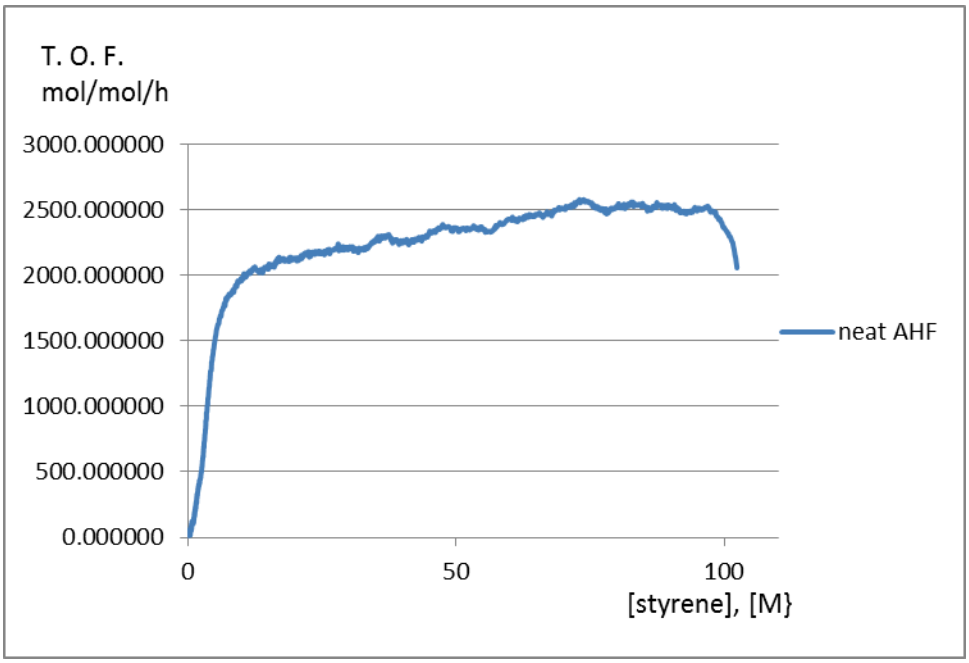
Plot of Ln[substrate] versus time for reaction at 3 bar: (confirms first order in substrate that is implied by the linear reduction in T. O. F as [sub] decreases)



Styrene AHF at [4M] concentration, S / C = 2000, 3 bar pressure, 50 °C.
A plot of TOF in mol/mol/h vs. [substrate], calculated from gas uptake in 10 minutes periods. T. O. F. max = 940. (diffusion controllled). There is less noise than the graphs on the previous page due to the larger volumes of syngas being consumed.

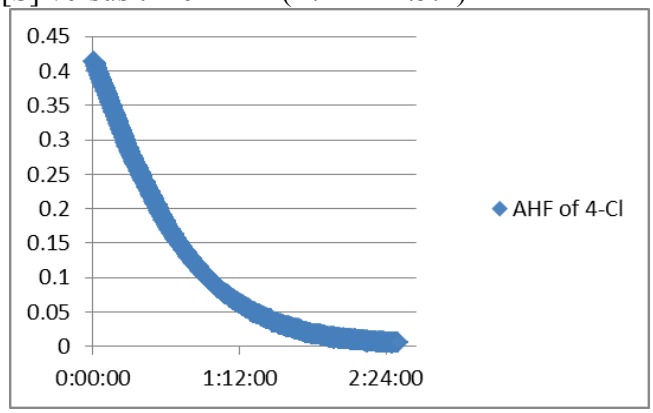


Styrene AHF neat, S / C = 10000, 12 bar pressure, 65 °C.
A plot of TOF in mol/mol/h vs. [substrate], calculated from gas uptake in 10 minutes periods. T. O. F. max = 2530. (diffusion controllled). We note here that in contrast to any of the other graphs, this graph includes an activation period. No data is collected in the 1-2 minutes waiting for the autoclave to heat up. The data from the very first minutes of the reaction where concentration will not be representative.

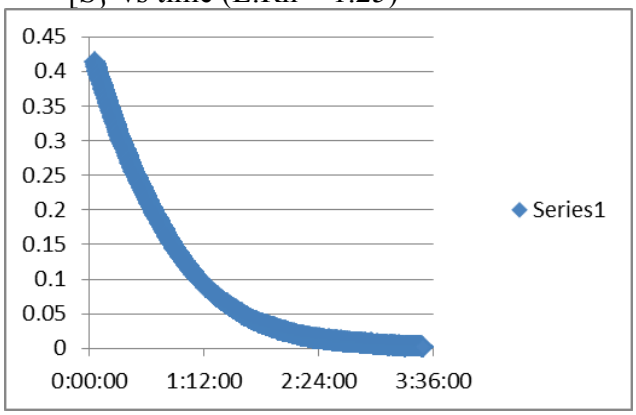


Plots of [substrate] versus time for AHF of 4-chloro-styrene using S/ C = 200, 0.4 M, 30 °C, 3 bar. On the left is shown reaction profile for reaction run using L: Rh of 2.5:1; right is shown the reaction using L / Rh of 1.25:1. There is little difference in reaction profile and both are first order in substrate, although the reaction run with excess ligand appears to go faster. The origin of this behaviour is not known, but could relate to inhibiting inactive catalyst resting states. For a reproducible and robust process using in situ catalysts, it is convenient that a small excess of ligand has no negative effects on the reaction.

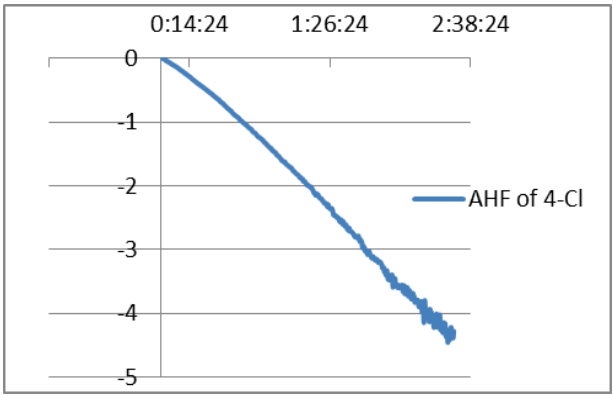
[S] versus time (L:Rh = 2.5:1)



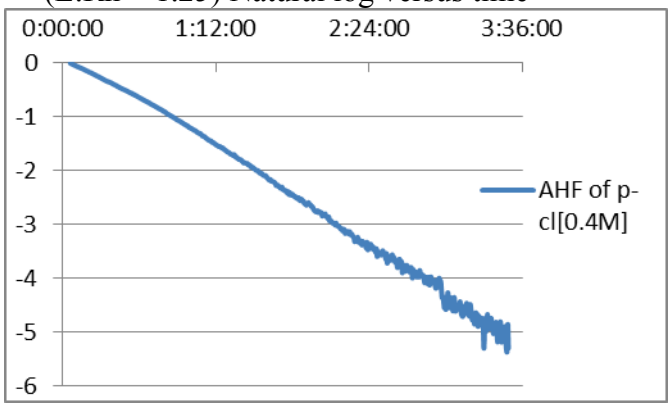
[S} vs time (L:Rh = 1.25)



Natural log versus time



(L:Rh = 1.25) Natural log versus time



A note on desired isomer yields.

In the main paper we refer to desired isomer yields as a useful measure of synthetic utility. This is especially true in asymmetric hydroformylation since chiral aldehyde regioisomers are often difficult to purify.
For the main systems noted, all of the catalysts are known to produce aldehydes with high or near perfect chemoselectivity and complete conversion. (some other papers only report their best e.e. at low conversion and we have not quoted from these where selectivity often drops off at high conversion). However, none of these would improve on the desired isomer yields found using the Landis ligands or (*S,S,S*)-BOBPHOS. Some papers quote 100%, 99%, >95% or a specific value above 95% for full conversions, so we elected to normalise these as 100%. We have also selected the best-published results for the desired isomer yields (the Landis catalysts in particular needed optimisation to achieve these). All of this ensures our values are not artificially inflated by our own measuring system.
The yields are therefore determined as in
Landis Rh catalyst: (*R,R,S*)-1 in paper: 93% e.e. = 96.5% e.r. x 100% conversion (actually 96% quoted in ref. 2f) x 98.2% regioselectivity (B:L = 55:1) = 94.8%
[For 4-Methoxystyrene: 95.2 e.r. % x 100% x 85% regioselectivity = 81%.]
Rh / Yanphos catalyst: 98% e.e. = 99% x 87.8% (B:L = 7.2:1) = 86.9%.
Rh / (*S,S,S*)-BOBPHOS catalyst: 92% e.e. = 96% e.r. x 100% conversion (>99% quoted) x 98.7% regioselectivity (B:L = 75:1) = 94.7%.

Experimental:

General:

Solvents were obtained from commercial sources. Dry solvents (toluene, tetrahydrofuran, diethyl ether and dichloromethane) were used directly from Grubbs system Braun MSB 8000 still without degassing unless stated otherwise, or purchased as anhydrous and used as received. Degasification of solvents where necessary was carried out using freeze-pump-thaw cycles. Distilled water was used in work-up procedures. Well known reagents were obtained from commercial suppliers and used without further purification unless stated otherwise. Synthesis gas (H_2:CO, 1:1) was obtained from BOC. Purification and separation by column chromatography was conducted with Silica Flash P60 by SILICYCLE unless otherwise stated. Chromatography on neutral alumina was carried out using Brockman I standard grade ~ 150 mesh, 58 angstrom neutral alumina. Thin layer chromatographic (TLC) analyses were carried out using POLYGRAM SIL G/UV_{254} plastic plates. TLC plates were visualised using a UV visualiser or alternatively stained using potassium permanganate or anisaldehyde dips, followed by gentle heating. ^{1}H and ^{13}C NMR analysis were carried out using either Bruker Avance 300 or 400 MHz NMR spectrometers at room temperature. The symbols s, d, t, q, and m used to assign ^{1}H NMR spectra refer to singlet, doublet, triplet, quartet and multiplet respectively. The abbreviation Ar is used to denote aromatic, C_{quat} denotes quaternary carbon. All NMR shifts are quoted in ppm and coupling constants (*J*) are quoted in Hz and refer to $^{3}J_{H\text{-}H}$ unless stated otherwise. ^{1}H NMR spectra referenced to tetramethyl silane, ^{31}P and ^{19}F were recorded with respect to external references.
Infrared spectroscopy: thin film on NaCl plates unless otherwise stated. Electrospray Mass Spectrometry (ESMS) and high-resolution mass spectrometry were carried out on a Micromass LCT orthogonal acceleration time of flight (TOF) mass spectrometer with the ionisation method indicated for each measurement. MS and HRMS refer to mass spectrometry and high-resolution mass spectrometry respectively. Optical rotation data were measured on a Perkin-Elmer Polarimeter (Model 341).

(*S,S,S*)-BOBPHOS and (*R,S,S*)-BOBPHOS were prepared according to: G. M. Noonan, J. A. Fuentes, C. J. Cobley, and M. L. Clarke, *Angew. Chem. Int. Ed.* 2012, **51**, 2477.

Hydroformylation using Argonaut Endeavour (AE) parallel autoclave system

Procedure 1: (used for Table 1 entries at S/C of 400, 30 and 60 ^{o}C)

Prior to carrying out the reaction the vessels of the AE were purged, initially with nitrogen then with CO:H_2 (1:1). The required amount of a stock solution of [Rh(acac)$(CO)_2$] in toluene (Concentration= 1mg/mL) was injected into each well of the AE (typically 1mL of stock solution added). This was followed by the required amount of each ligand (L:Rh= 1.25:1), also added as a stock solution in toluene. The mixture was then placed under 5 bar CO:H_2 (1:1) and heated to 50 °C for ~ 40 min in order to 'pre-activate' the catalyst prior to substrate addition. The pressure was then vented and the apparatus allowed to cool to room temperature. The required amount of substrate was then added (1 mmol) as a stock solution in toluene (Note: the total volume of liquid in each well was 3.5 mL). The apparatus was then purged three times with CO:H_2 (1:1) , placed under the required pressure and heated to the required reaction temperature for the required time (i.e.~ 20 h, reactions stopped short if gas uptake curves were observed to flatten indicating complete conversion. The crude reaction mixtures were then analysed by capillary GC, equipped with a chiral column and ^{1}H NMR spectroscopy.

Hydroformylation using Argonaut Endeavour (AE) parallel autoclave system

Procedure 2: (used for other reactions in solvent, and for kinetics studies)

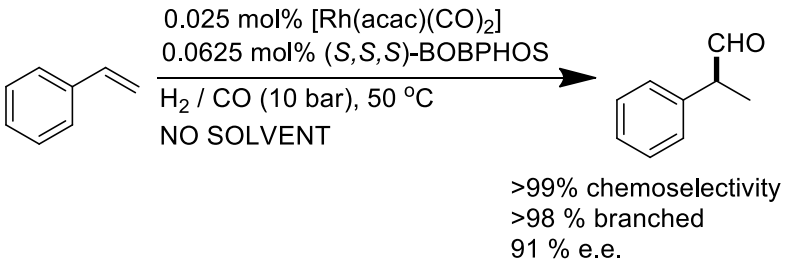
The reactor vial was charged with of [Rh(acac)$(CO)_2$] and (*S,S,S*)-BOBPHOS as dry powders in air. The vessels of the AE were purged with nitrogen, before the addition of dry toluene (1.6 mL used for 1 x 10^{-5} mols catalyst). A further three nitrogen purges were carried out, then three further purges with CO:H_2 (1:1, 10 bar). The mixture was then placed under 10 bar CO:H_2 (1:1) and heated to 50 °C for 60 min in order to 'pre-activate' the catalyst prior to substrate addition. The vessel was then cooled to 30 ^{o}C and vented. The required amount of substrate was then added (between 2.07 mmol and 16 mmol) as a solution in toluene (2.5 mL). The apparatus placed under the required pressure and heated to the required reaction temperature for the required time. Reactions were stopped short if gas uptake curves were observed to flatten indicating complete conversion. The crude reaction mixtures were then analysed by capillary GC, equipped with a chiral column and ^{1}H NMR spectroscopy. The products were isolated by removal of toluene solvent and found to be of high purity as shown by the illustrative NMR spectra shown later on. The aldehydes do not appear any purer after column chromatography on silica, and this resulted in degradation of e.e. The aldehydes could be stored as reactions mixtures, or neat in the freezer for 1-2 weeks in air with no or limited losses of enantioselectivity (c. 2-5 %) or oxidation. On some occasions, the substrate solution also contained cyclooctane as NMR internal standard. This along with NMR spectra obtained after removal of toluene demonstrates that the reactions using Rh / (*S,S,S*)-BOBPHOS were essentially chemoselective, and hence further experiments omitted this in order to directly obtained pure aldehydes simply be removing solvent. The NMR spectra of the products, all of which are well known compounds, were compared with authentic samples made using Rh / PPh3 catalyst systems or obtained commercially.

Hydroformylation using Argonaut Endeavour (AE) parallel autoclave system

Procedure 3: (used for other reactions without solvent)

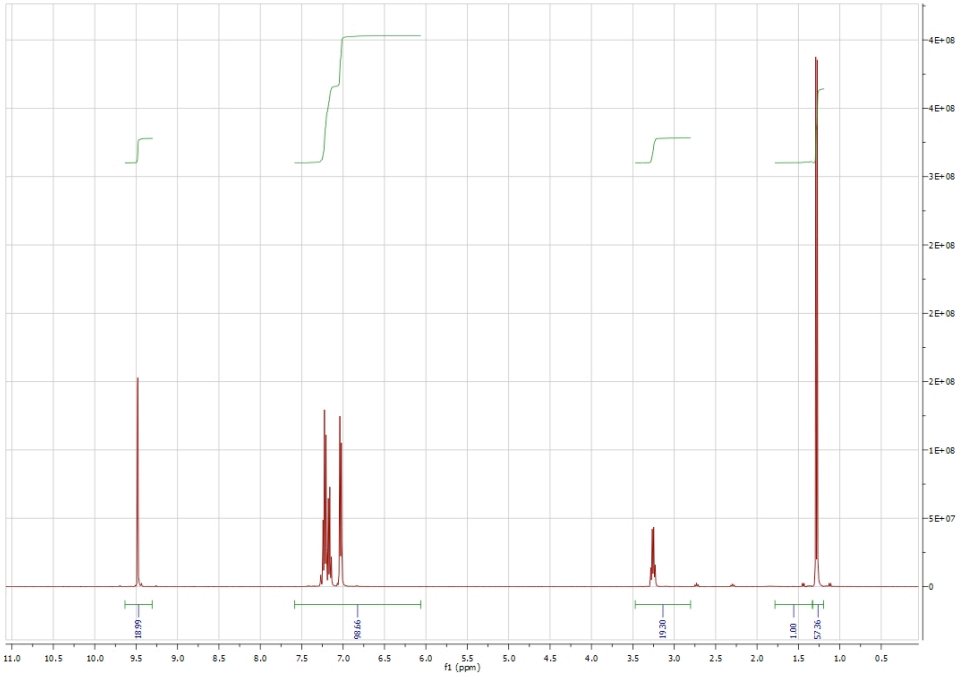
The reactor vial was charged with of [Rh(acac)$(CO)_2$], (*S,S,S*)-BOBPHOS as dry powders in air. The substrate was then added by syringe in air, and the vessels assembled immediately. The vessels of the AE were purged with nitrogen. (3x 10 bar). A further three purges with CO:H_2 (1:1, 10 bar) were carried out. The apparatus was placed under the required pressure and heated to the required reaction temperature for the required time. The crude reaction mixtures were then analysed by capillary GC, equipped with a chiral column and ^{1}H NMR spectroscopy. This gives pure branched aldehyde products (contaminated with ppm level of Rh), which were compared to commercial or authentic samples.

Selected NMR spectra from hydroformylation experiments.

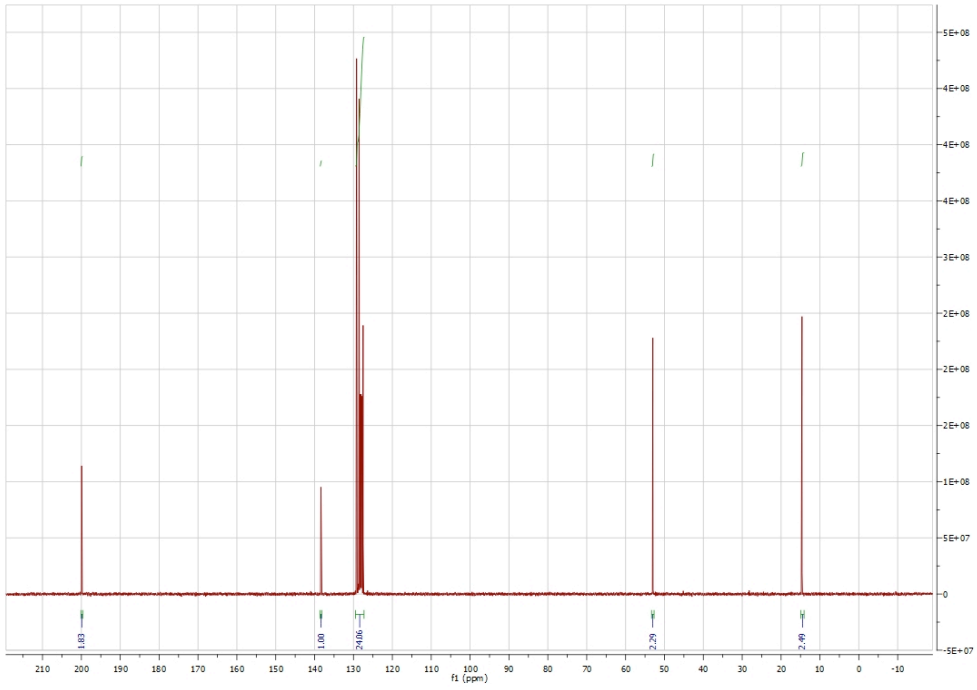


>99% chemoselectivity
>98 % branched
91 % e.e.

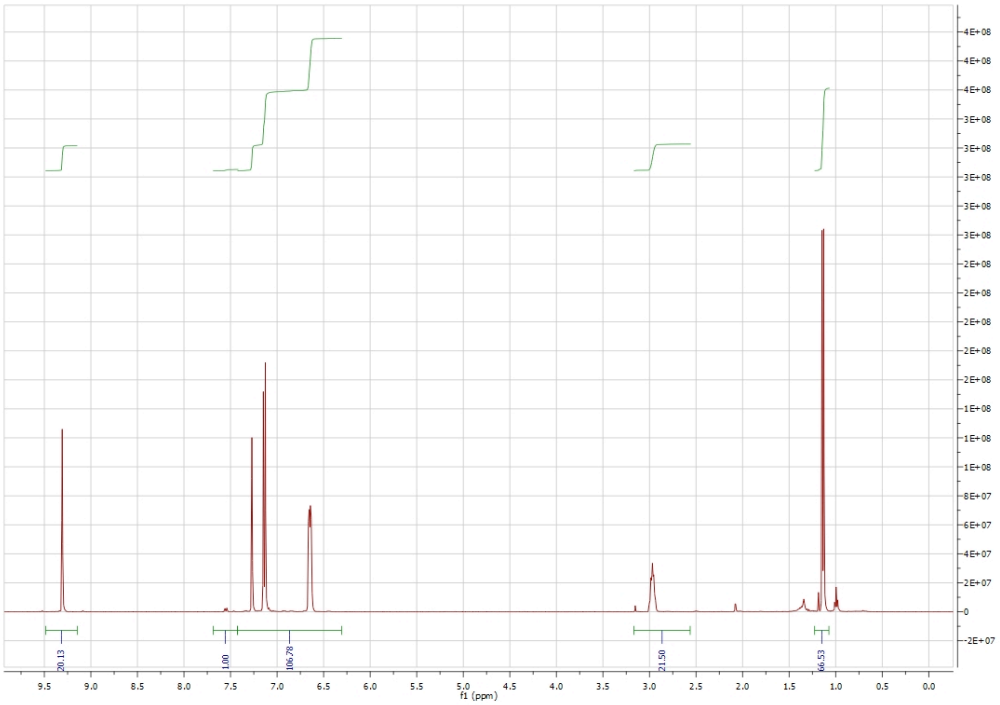
ESI. Fig. 1 1H NMR Spectra of reaction 'mixture' diluted in C_6D_6 (essentially pure (*S*)-2-phenylpropanal)



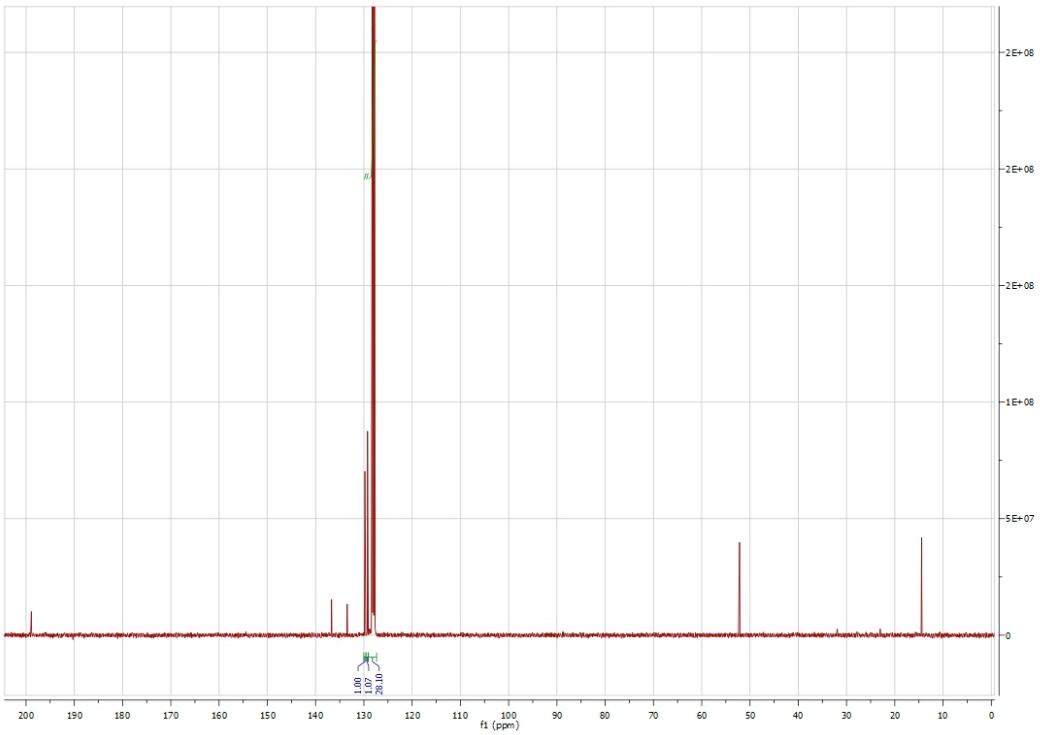
ESI. Fig. 2 13 C NMR Spectra of reaction 'mixture' diluted in C_6D_6 (essentially pure (*S*)-2-phenylpropanal)



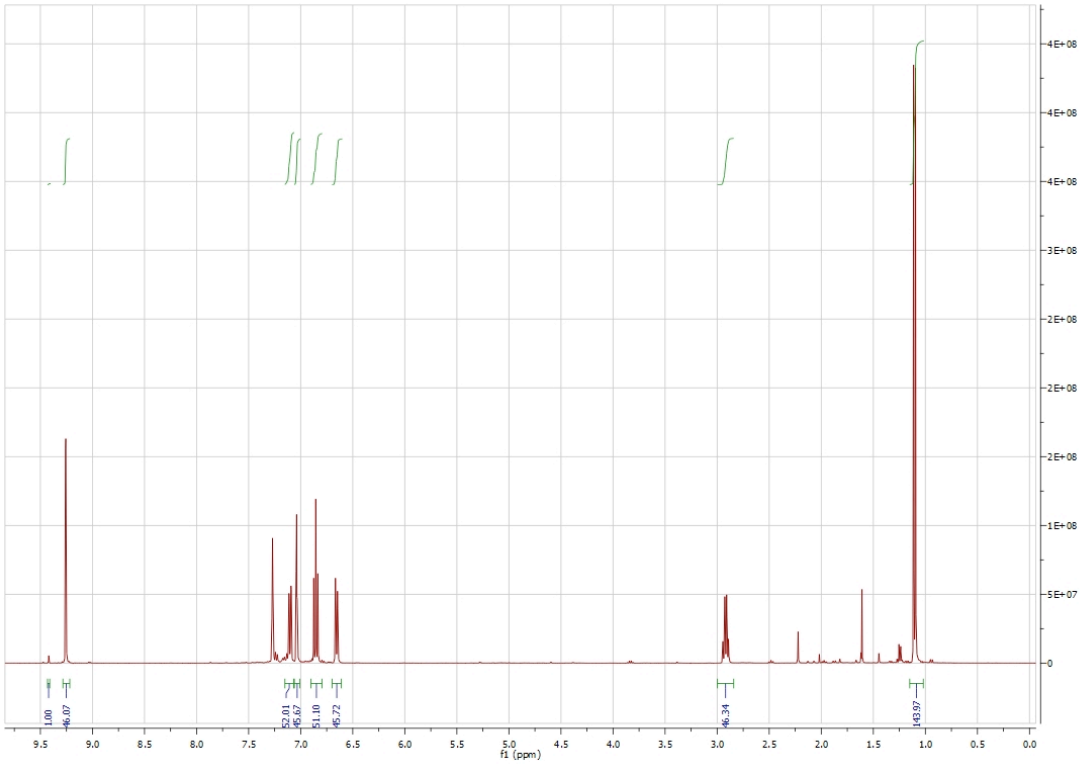
ESI. Fig. 3 1 H NMR Spectra of (*S*)-2-(4-chlorophenyl)propanal from 4-chlorostyrene hydroformylation. (300 MHz, C_6D_6)



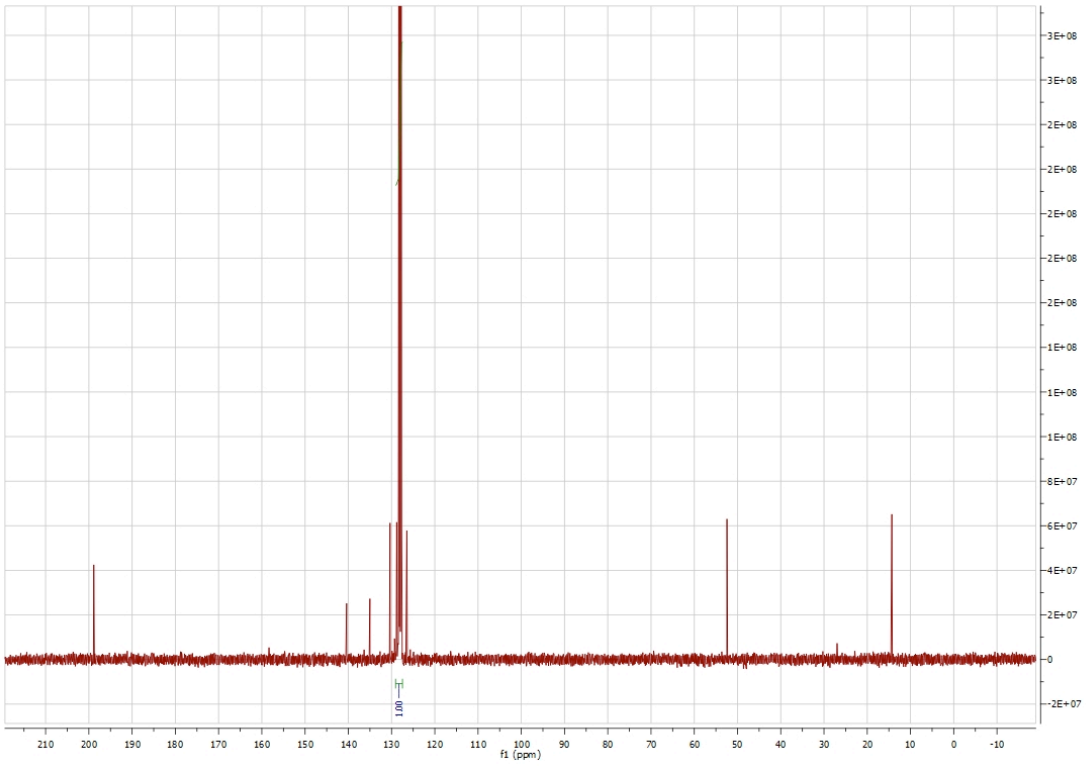
ESI. Fig. 4 13 C NMR Spectra of (*S*)-2-(4-chlorophenyl)propanal from 4-chlorostyrene hydroformylation.



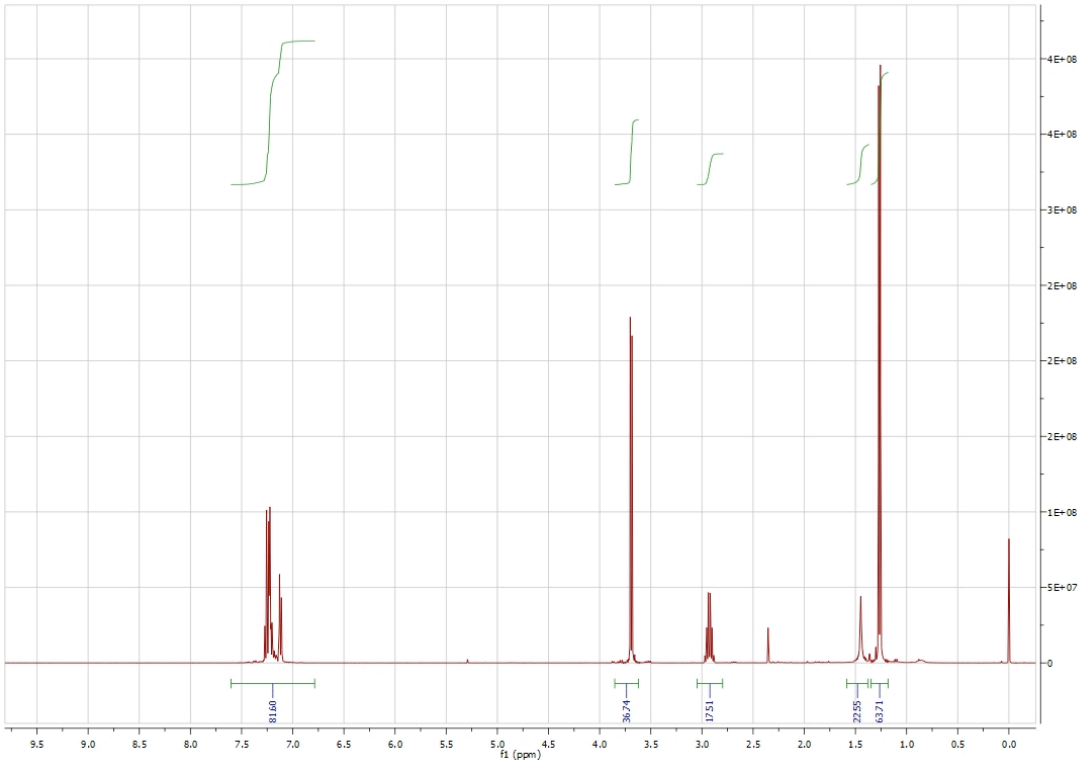
ESI. Fig. 5 1 H NMR Spectra of (*S)*-2-(3-chlorophenyl)propanal produced by hydroformylation of 3-chlorostyrene. .(Product purified using chromatography with some racemisation (37% e.e., 62.5 % yield. (300 MHz, C_6D_6)



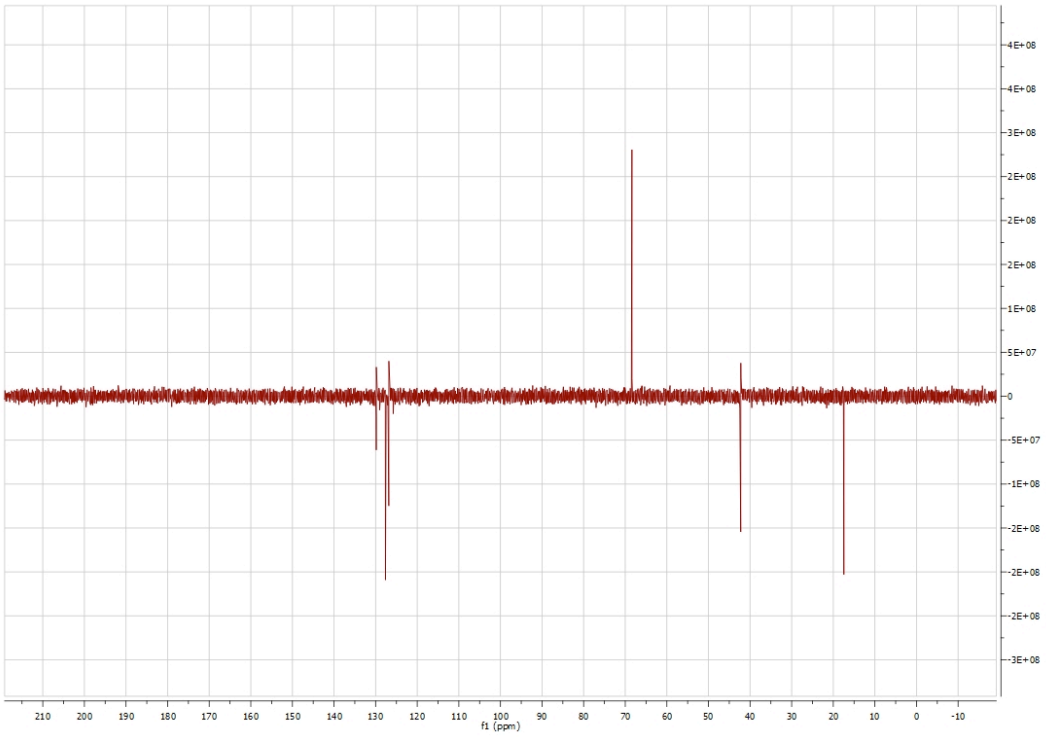
ESI. Fig. 6 13 C NMR Spectra of (*S)*-2-(3-chlorophenyl)propanal produced by hydroformylation of 3-chlorostyrene.



ESI. Fig. 7 1 H NMR Spectra of (*S*)-2-(3-chlorophenyl)propanol produced by hydroformylation of 3-chlorostyrene followed by reduction using $NaBH_4$ (75% yield from alkene, 89% e.e. (full retention of stereochemistry). (300 MHz, C_6D_6)

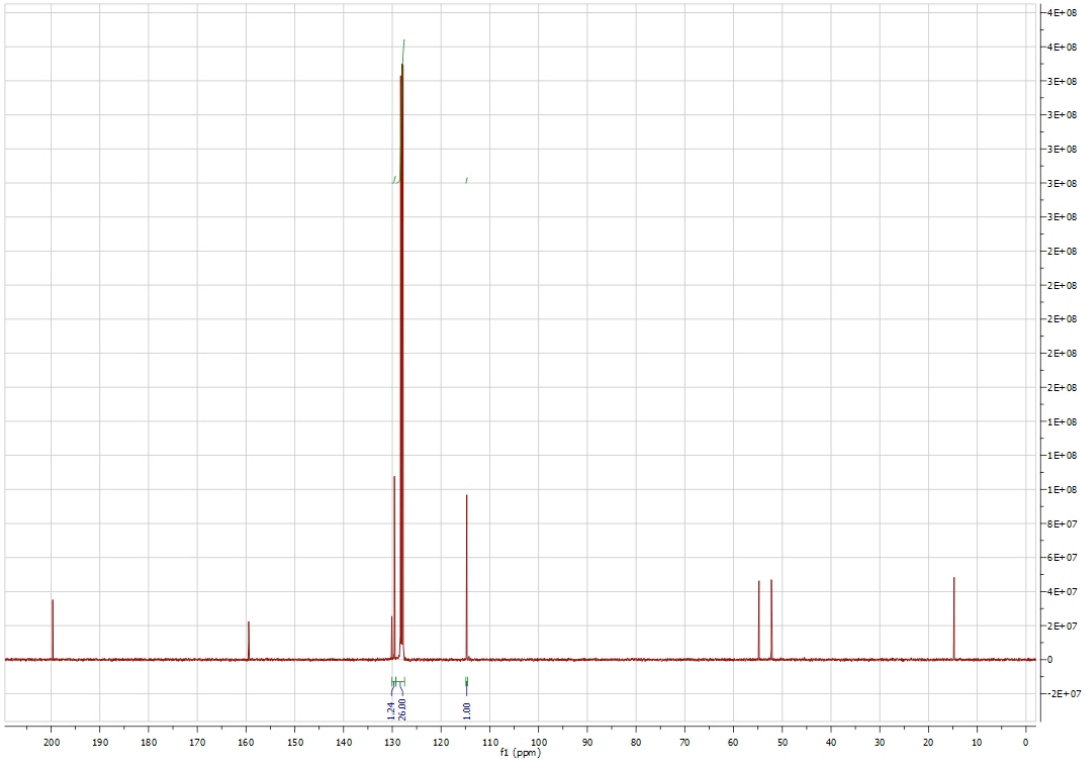


ESI. Fig. 8 13 C NMR Spectra of (*S*)-2-(3-chlorophenyl)propanol produced by hydroformylation of 3-chlorostyrene followed by reduction using $NaBH_4$ (75% yield from alkene, 89% e.e. (full retention)

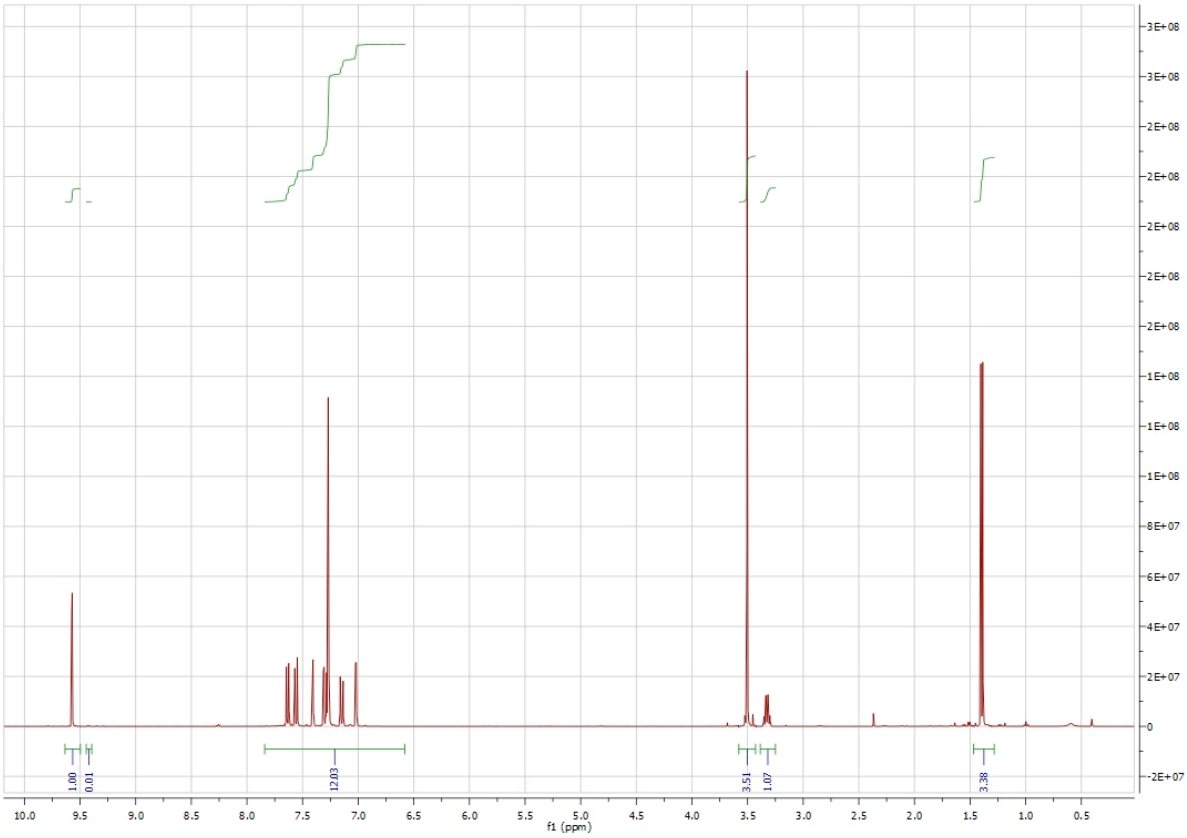


ESI. Fig. 9 1H NMR Spectra of reaction 'mixture' diluted in C_6D_6 (essentially pure 3-(4-methoxy-phenyl)propanal) (300 MHz, C_6D_6)

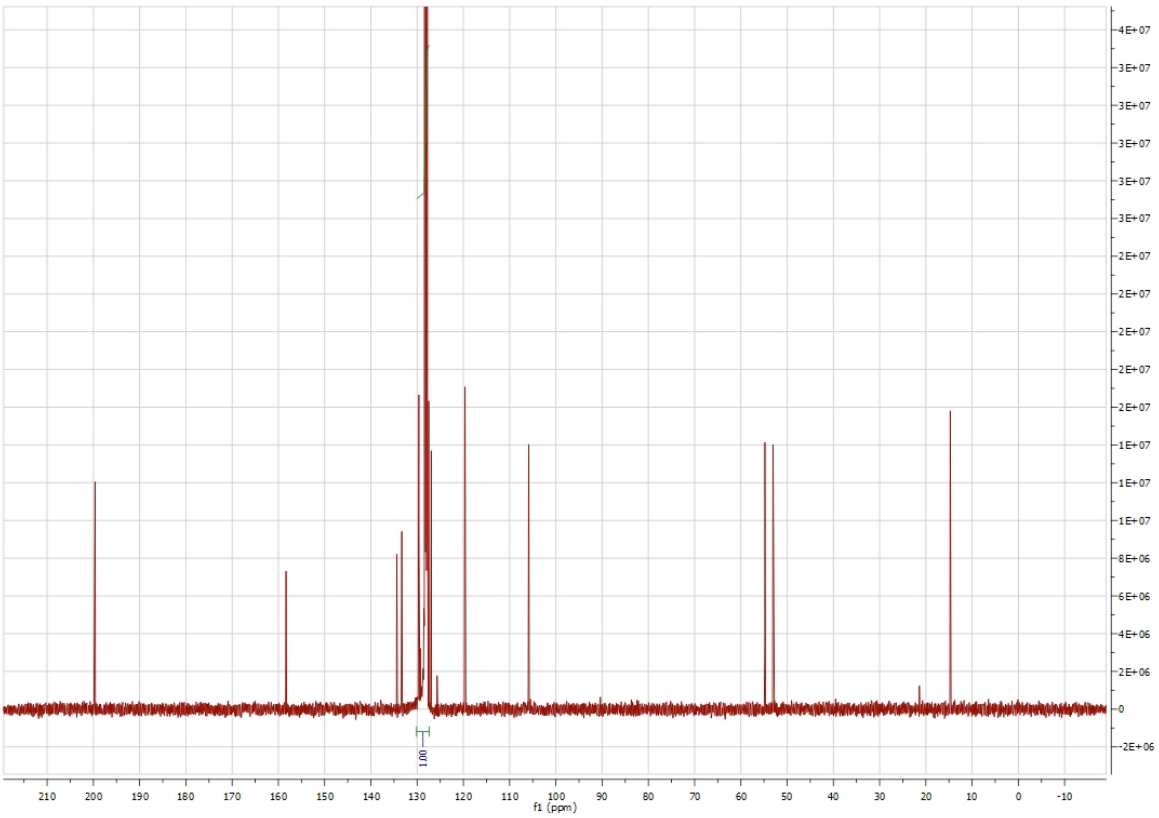
ESI. Fig. 10. 13 C NMR Spectra of reaction 'mixture' diluted in C_6D_6 (essentially pure 3-(4-methoxy-phenyl)propanal)



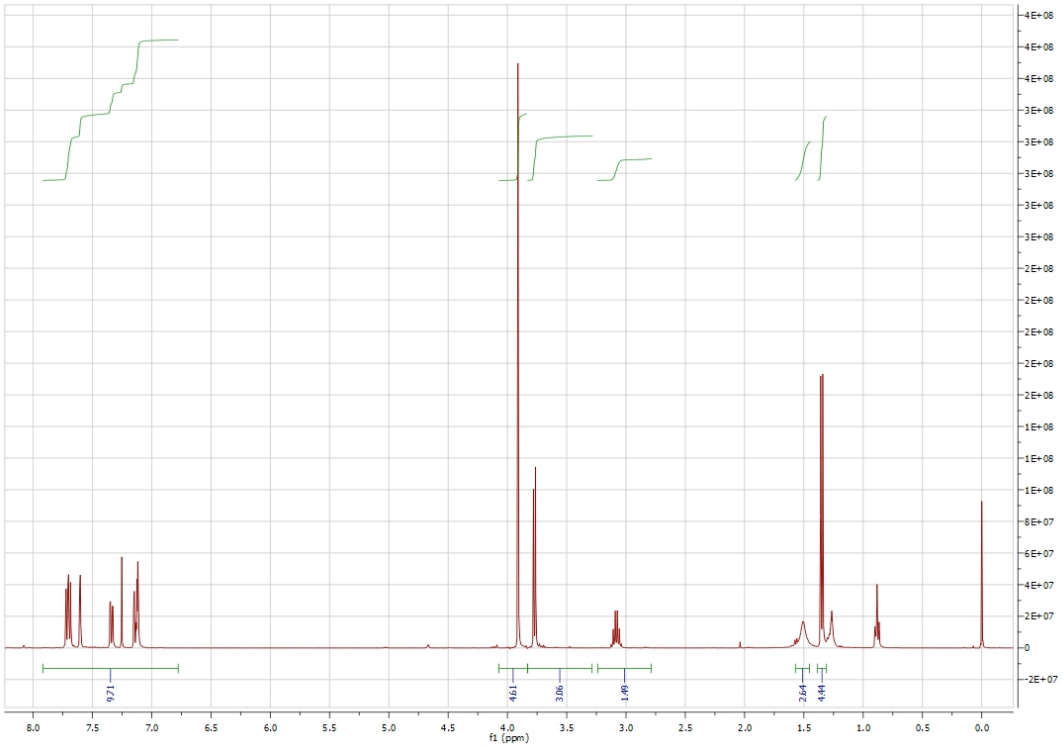
ESI. Fig. 11. 1 H NMR Spectra of (*S)*-2-(6-methoxynaphthalen-2-yl)propanal produced by hydroformylation of 2-methoxy-6-vinylnaphthalene. (300 MHz, C_6D_6).



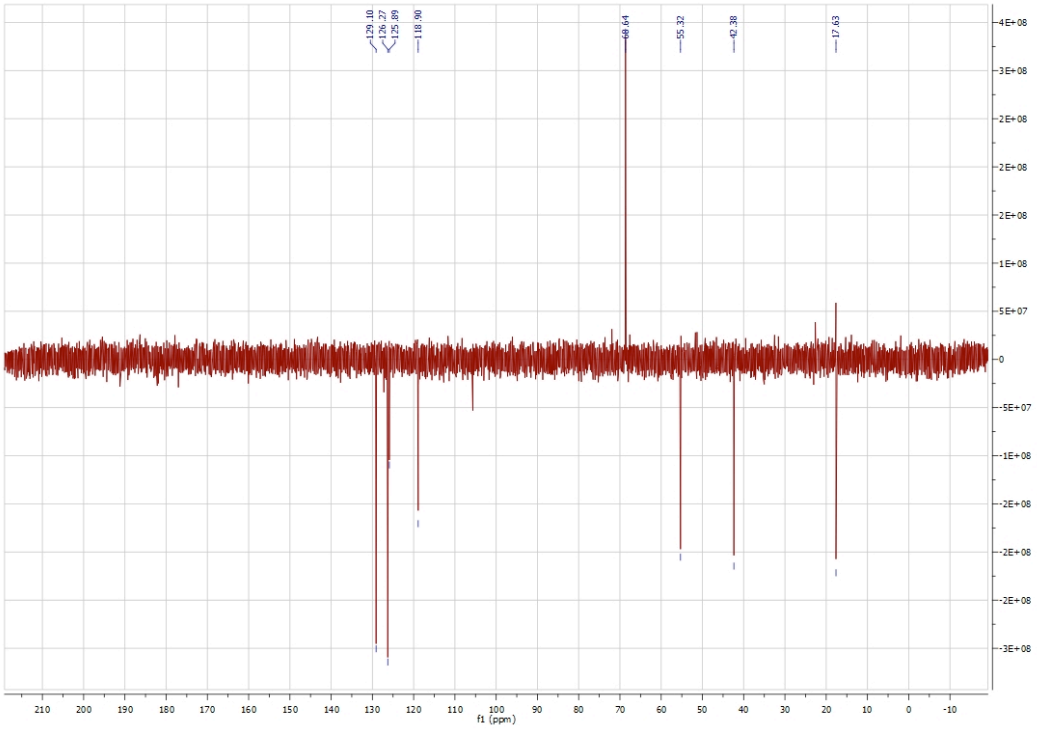
ESI. Fig. 12. 13 C NMR Spectra of (*S)*-2-(6-methoxynaphthalen-2-yl)propanal produced by hydroformylation of of 2-methoxy-6-vinylnaphthalene.



ESI. Fig. 13. 1 H NMR Spectra of (*S)*-2-(6-methoxynaphthalen-2-yl)propanol produced by hydroformylation of 2-methoxy-6-vinylnaphthalene, followed by $NaBH_4$ reduction. (300 MHz, C_6D_6).



ESI. Fig. 14. 13 C NMR Spectra of (*S)*-2-(6-methoxynaphthalen-2-yl)propanol produced by hydroformylation of hydroformylation of 2-methoxy-6-vinylnaphthalene, followed by $NaBH_4$ reduction. (C_6D_6).



GC spectra and experimental details.

Conversion and regioselectivity were determined by 1H NMR. The enantioselectivity of the reactions was measured on the crude aldehydes (containing branched and linear aldehyde generally dissolved in the reaction solvent, sometimes starting alkene, and sometimes cycloctane internal standard). When using the Rh / BOBPHOS catalysts, no by-products were detected above trace amounts by NMR ,GC or HPLC, hence the internal standard was not routinely included after this was established. Capillary Gas Chromatography was carried out on a Perkin Elmer Autosystem XL or an Agilent 6890 equipped with a chiral column. HPLC was carried out on an Agilent 1200 HPLC with DAD detector. Racemic standards were analysed first generally as reaction mixtures, prepared by hydroformylation using a Rh / PPh_3 catalyst system. (These show lower regioselectivity and tend to give less clean GC and NMR spectra relative to the Rh / BOBPHOS catalysts)

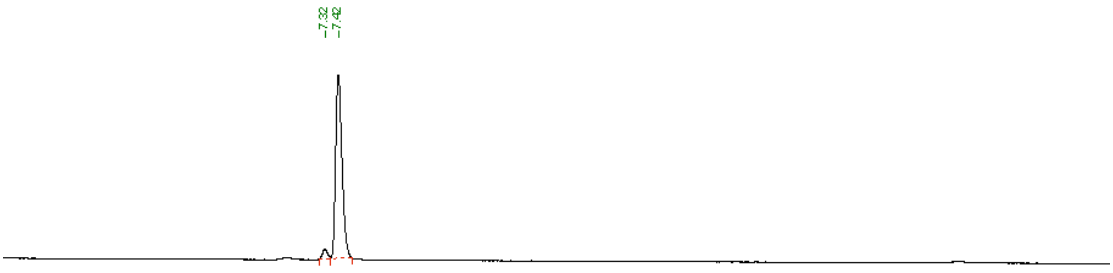
The following columns and methods were used:

Method: Betadex 225 column (30m x 0.25mm x 0.25µm)
115°C (hold 15 min) ramp at 15/min to 220°C (hold 1min)
Helium carrier gas at 20psi constant pressure
Injector/FID 200°C/220°C

Retention Times: 7.32 (*R)*-2-phenylpropanal; 7.42 (*S)*-2-phenylpropanal; 12.19 (Linear-3-phenylpropanal)

rac-2-phenylpropanal

(*S*)-2-phenylpropanal (92% e.e.)

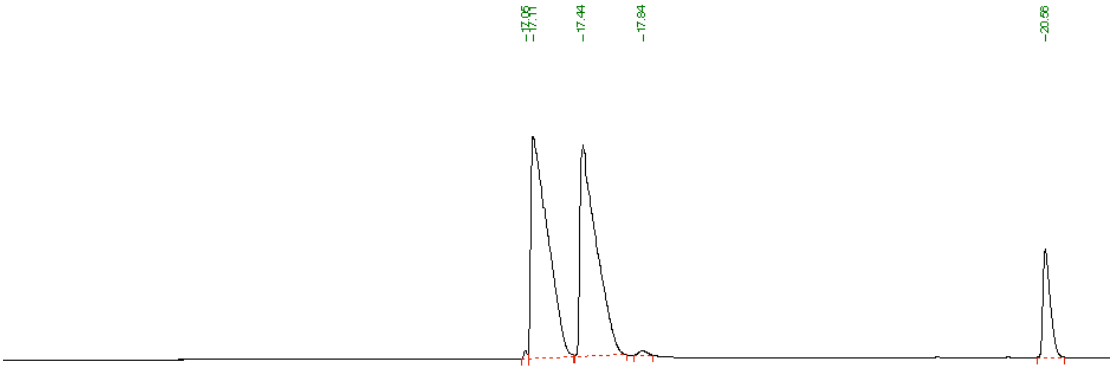


Peak #	Component Name	Time [min]	Area [uV*sec]	Height [uV]	Area [%]
1		7.319	7216.90	2493.41	4.13
2		7.423	167707.27	48325.21	95.87
			174924.17	50818.62	100.00

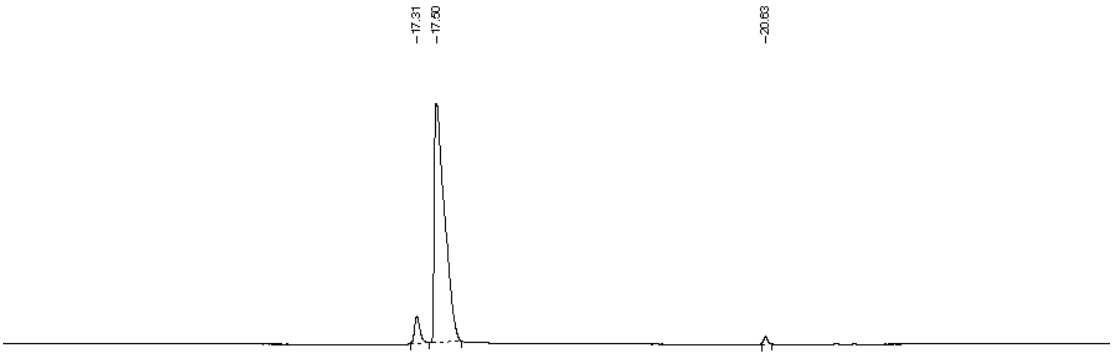
Method: : Betadex 225 column (30m x 0.25mm x 0.25µm)
125°C (hold 15 min) ramp at 10/min to 220°C (hold 1min)
Helium carrier gas at 20psi constant pressure
Injector/FID 200°C/220°C

Retention Times: 17.1 (*R)*-2-(4-chlorophenyl)propanal; 17.4 (*S)*-2-(4-chlorophenyl)propanal; 20.6 (Linear-3-(4-chlorophenyl)propanal)

rac-2-(4-chlorophenyl)propanal from 4-chlorostyrene hydroformylation



30 C (*S)*-2-(4-chlorophenyl)propanal (89% e.e.)

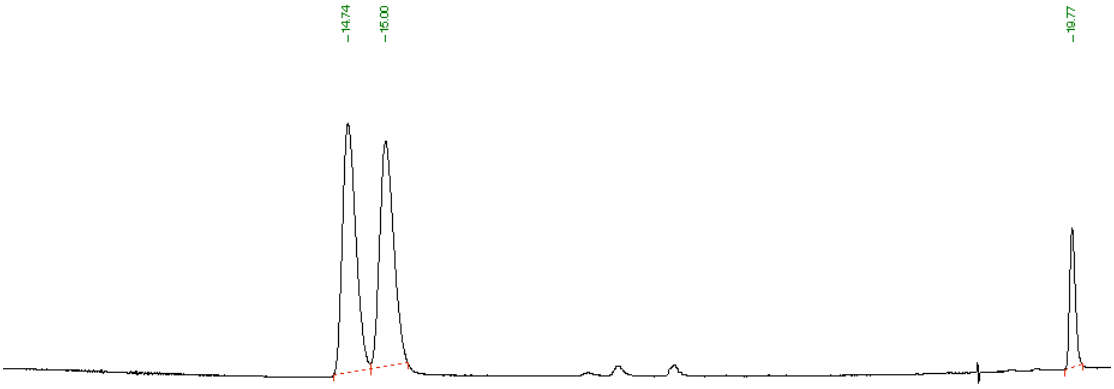


Peak #	Component Name	Time [min]	Area [uV*sec]	Height [uV]	Area [%]
1	Branched 1	17.306	54696.18	15581.88	5.49
2	Branched 2	17.498	931194.99	137481.67	93.48
3	Linear	20.625	10318.43	4321.20	1.04
			996169.59	157384.75	100.00

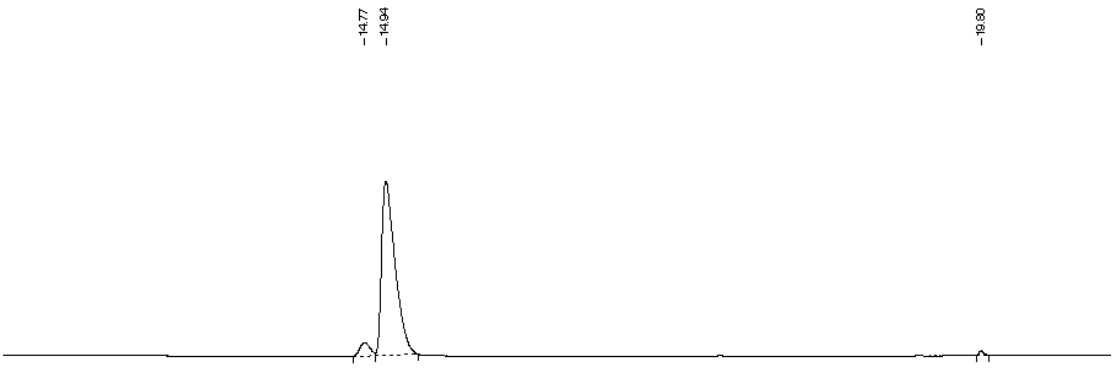
Method: Betadex 225 column (30m x 0.25mm x 0.25µm)
125°C (hold 15 min) ramp at 10/min to 220°C (hold 1min)
Helium carrier gas at 20psi constant pressure
Injector/FID 200°C/220°C

Retention Times: 14.7 (*R)*-2-(3-chlorophenyl)propanal; 15.0 (*S)*-2-(3-chlorophenyl)propanal; 19.8 (Linear-3-(3-chlorophenyl)propanal)

rac-2-(3-chlorophenyl)propanal from 3-chlorostyrene hydroformylation.



(*S)*-2-(3-chlorophenyl)propanal (89% e.e.)

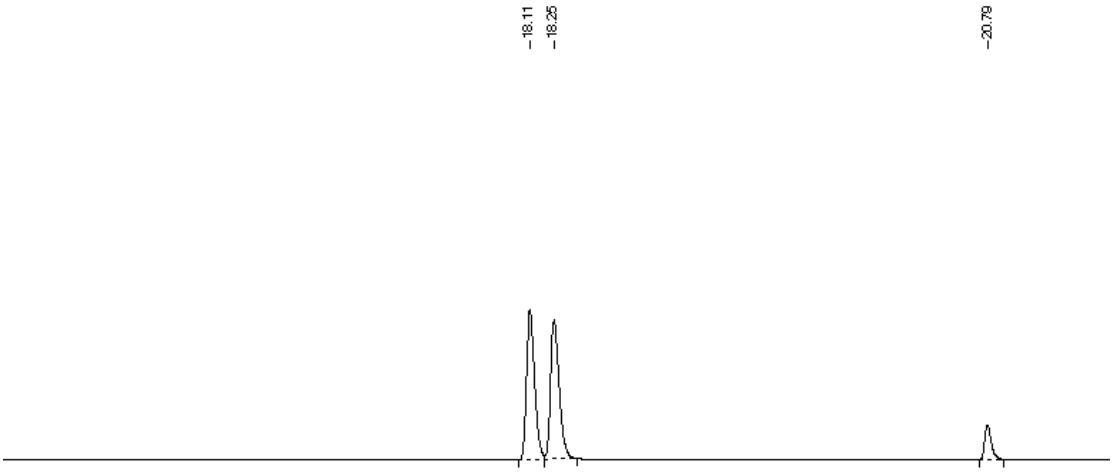


Peak #	Component Name	Time [min]	Area [uV*sec]	Height [uV]	Area [%]
1	Branched 1	14.769	50458.13	9046.11	5.30
2	Branched 2	14.943	893051.64	117093.89	93.85
3	Linear	19.802	8073.30	3045.43	0.85
			951583.07	129185.42	100.00

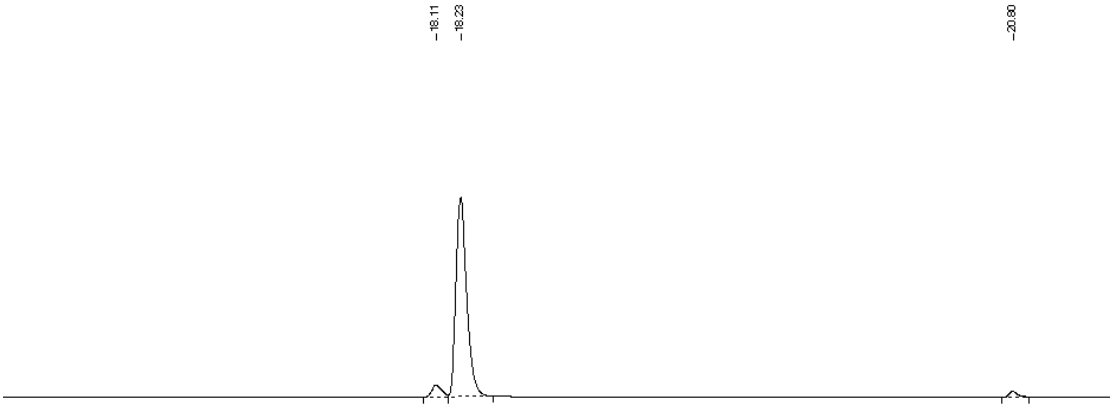
Method: Betadex 225 column (30m x 0.25mm x 0.25µm)
125°C (hold 15 min) ramp at 10/min to 220°C (hold 1min)
Helium carrier gas at 20psi constant pressure
Injector/FID 200°C/220°C

Retention Times: 18.1 (*R)*-2-(4-methoxyphenyl)propanal; 18.3 (*S)*-2-(4-methoxyphenyl)propanal; 20.8 (Linear-3-(4-methoxyphenyl)propanal)

2-(4-methoxy-phenyl)propanal



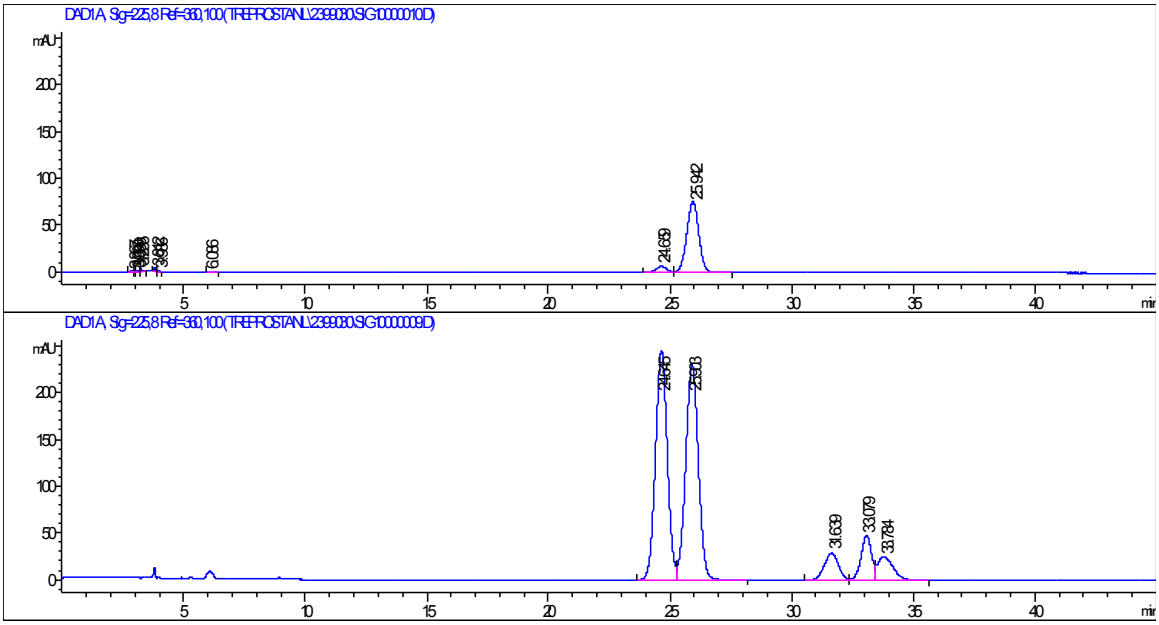
(*S*)-2-(4-methoxy-phenyl)propanal (90% e.e.)



Peak #	Component Name	Time [min]	Area [uV*sec]	Height [uV]	Area [%]
1		18.115	102674.35	32364.16	4.95
2		18.230	1916336.22	551764.47	93.18
3	Linear	20.796	37680.79	14349.22	1.83
			2056691.36	598477.85	100.00

Method: Lux Cellulose 4 column (250 x 4.6mm) at 40°C
Mobile phase: Hexane 75% : Hexane/IPA (9:1) 25%
Flow rate: 1mL/min
UV detector at 225nm

Top: (*S*)-2-(6-methoxynaphthalen-2-yl)propanol produced by hydroformylation of 2-methoxy-6-vinylnaphthalene, followed by reduction using $NaBH_4$. Bottom: Racemic 2-(6-methoxynaphthalen-2-yl)propanol (crude sample from hydroformylation using Rh / PPh_3 and $NaBH_4$ reduction). It was always our experience that the commercially applied benchmark achiral hydroformylation catalyst Rh / PPh_3 gave lower chemoselectivity than our chiral catalyst system.

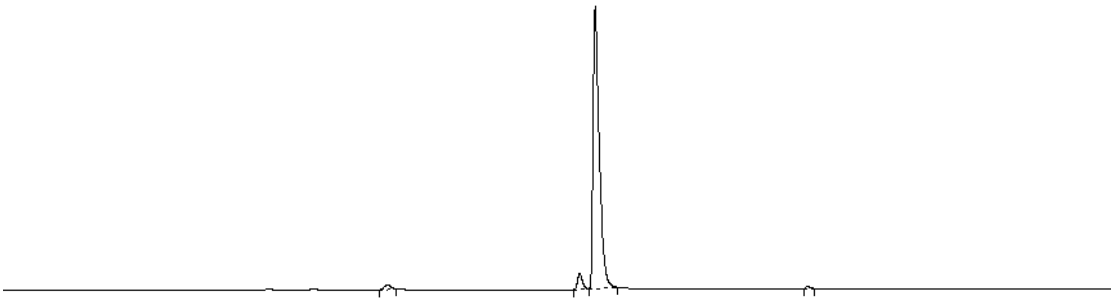


In order to confirm that reduction of the chiral aldehydes of this type doesn't cause racemisation, we also reduced (*S)*-2-(3-chlorophenyl)propanal (89% e.e.) to its alcohol and measured the e.e. as shown below.

Method: Betadex 225 column (30m x 0.25mm x 0.25µm)
125°C (hold 15 min) ramp at 10/min to 220°C (hold 1min)
Helium carrier gas at 20psi constant pressure
Injector/FID 200°C/220°C

rac-2-(3-chlorophenyl)propanol

(S)-2-(3-chlorophenyl)propanol (89% e.e. alcohol)
produced by hydroformylation of 3-chlorostyrene followed by reduction using $NaBH_4$ (75% yield from alkene, 89% e.e. (full retention of stereochemistry).



Peak #	Component Name	Time [min]	Area [uV*sec]	Height [uV]	Area [%]
1		17.663	21648.27	5722.78	1.60
2		19.309	54942.44	19371.44	4.07
3	Linear	19.443	1269844.93	346687.15	93.72
4		21.268	8260.00	3231.23	0.61
			1350495.63	375012.60	100.00