Continuous Flow Hydroformylation using Supported Ionic Liquid Phase Catalysts with Carbon Dioxide as a Carrier Ulrich Hintermair,^{a,b} Zenxing Gong,^a Mark J. Muldoon,^a Catherine C. Santini^b and David J. Cole-Hamilton^a

Supplementary data

Experimental

Estimating flow rates

The flow meter was actually calibrated for pure CO_2 only and thus the flow of a mixture of gases having a different density from that of pure CO_2 must be recalculated. Although the input rate for CO/H_2 and the total pressure are known, the ratio of CO/H_2 to CO_2 in the exiting stream depends on the conversion of 1-octene to aldehyde. At a starting flow ratio of syngas:substrate of 10:1, 100 % conversion would consume 10 % of the syngas. Since the conversion is not known at the start of the reaction, it must be estimated in order to set the appropriate flow rate. The calculation started from the assumptions that there was negligible substrate (or product) concentration in the gas phase and a linear correlation between mole fraction and density. The calculation of flow rate was as follows:

It was assumed that, at 1 bar, CO, H_2 and CO₂ are ideal gases and that 1:1 CO:H₂ was consumed during the reaction.

d = density, m = mol fraction, f = flow

f(meas) is the flow rate obtained from the graph of float travel in the flow meter against flow rate, assuming that the flowing gas is purely CO_2 .

f(act) is the actual flow rate

f(syn) is the syngas flow rate at the flow meter

 $d(act) = [d(syn) \times m(syn)] + [d(CO_2) \times m(CO_2)]$

 $f(act) = [f(meas) \times d(CO_2)] / [d(syn) \times m(syn) + d(CO_2) \times m(CO_2)]$

rearranging and remembering that

 $[f(act) \times m(syn)] = f(syn) \text{ and } [f(act) \times m(CO_2)] = f(CO_2)$

 $[d(syn) \times f(syn)] + [d(CO_2) \times f(CO_2)] = d(CO_2) \times f(meas)$

Since all the terms in this equation were known, $f(CO_2)$ could be calculated.

Here $f(CO_2)$ was calculated from the amount of syngas and conversion of aldehyde, which was initially guessed on the basis of previous reactions under similar conditions. The flow travel required for the desired flow rate was calculated and used in the reaction. The actual flow rate was calculated once the products had been analyzed by GC.

The detailed steps were the following:

The partial pressure of CO_2 and of syngas required in the experiment were decided upon

The total flow rate and the dosimeter settings which would give the desired partial pressures were calculated Knowing the catalyst and substrate concentration an expected conversion was estimated. This gives the amount of syngas, which should be consumed by the reaction

It is then possible to calculate the amount of syngas left at the end of the reaction and hence the expected density of the gas mixture after the reaction.

This density was used to calculate the real flow and the float travel setting for the flow meter.

Once the conversion was known, the actual flow rate was recalculated.

Catalytic reactions – Statistical Experimental design

Initial factor screening

Initial screening of several reaction parameters was carried out using statistical experimental design. For these reactions the Syngas/substrate ratio was 10, the temperature 100 °C and the pressure 100 bar.

As known from the gas phase reaction, the IL loading is believed to have a significant influence on the performance of the SILP catalysts (see above).²⁴ A preliminary factor screening with a fractional factorial model without centre points was used to investigate the linear influence of IL loading, substrate injection rate and volumetric flow (~ residence time) on the activity (Table S1). The flow factor in the screening

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model was the measured float travel on the flow meter which was recalculated to the real volumetric flow of mixed gas after determination of conversion (see Experimental).

Table S1. Experimental matrix for the fractional factorial linear model for testing the influence of flow rates (substrate and total) and IL loading on the hydroformylation of 1-octene over a SILP catalyst.

Exp. number	IL loading [wt%]	Substrate injection rate [ml/min]	Float travel [mm]	Volumetric flow [nmL/min] ^a	
1	14	0.2	50	1580	
2	44	0.2	30	940	
3	14	0.36	30	1175	
4	44	0.36	50	1830	

^a nmL = ml at NTP.

As a result of different IL loadings the mass of SILP catalyst and thus content of Rh introduced into the reactor varied slightly from run to run. In order to eliminate this fault and to account for shorter contact times at higher flow velocities the activity optimization was performed on the turnover frequency. The full experimental results are shown in Tahle S2.

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Exp	Exp.	Run	Incl/excl	IL	Substrate	Overall	Conversion
No.	Name	order		Loading	flow rate	Flow	(mmol Rh^{-1})
				% w/w	./ cm ³	rate	
					min ⁻¹	Normal	
						L min ⁻¹	
1	UH03	1	Incl	14	0.2	50	103.7
2	UH02	2	Incl	44	0.2	30	496.1
3	UH05	4	Incl	14	0.36	30	490
4	UH04	3	Incl	44	0.36	50	224.1

Table S2. Full results from preliminary screening experiments.

The model could successfully be fitted with multilinear regression (MLR), as shown on Figure S1.



IL mass loading

total volumetric flow

Fig. S1. Normalized linear influence of IL loading, substrate flow, and total flow on the TOF of the hydroformylation of 1-octene over a Rh - SILP catalyst in compressed CO_2 .

The IL loading shows a slight negative effect on the TOF, hence the less IL the more activity per time. This may reflect minor mass transfer limitations, but the influence is small in comparison to the other factors. This is in line with the observation that mass transfer is not rate limiting under similar conditions by comparison wit data from the bulk SCF-IL system.^[31]

As expected, the substrate flow shows a positive influence on the performance of the SILP catalyst. The fact that the order is different from 1 arises from the non-linearity of product formation over time due to the kinetics of homogeneous hydroformylation, meaning that the true reaction rate is more underestimated by the TOF the higher the conversions.

Less volumetric flow resulting in longer residence times turned out to be the crucial parameter for the activity here; a reasonable dependence in continuous flow catalysis. The factor of -0.7 indicates that not all active centres participate in the catalysis at higher flow velocities; otherwise an influence of -1 would be expected.

In another test run beyond the matrix, a variation of the Syngas/substrate ratio, which was kept constant before, showed a distinct influence on the activity, but not on the selectivity of the catalysts. In order to investigate this effect in more detail the influence of Syngas/substrate ratio was included in further optimization studies. The total volumetric flow was changed proportionally to the substrate flow such as the alkene concentration over the SILP catalyst remained constant and the different experiments kinetically comparable. Using a quadratic model the parameters were investigated for potential interactions and a response surface modelling was performed.

Optimisation studies

A quadratic model based on the Box-Benhken design with one single centre point was used to create the experimental matrix on the following factor levels:

•	Ionic liquid loading:	14 wt% – 44 wt%
•	Substrate injection rate:	0.12 ml/min - 0.36 ml/min
•	Syngas/substrate ratio:	10 - 20

The responses studied were Selectivity (l:b ratio), Turnover Frequency and conversion to aldehydes. Chemoselectivity usually was > 98 % for *n*- and *iso*-nonanal with minor amounts of hydroformylation products of isomerized substrate in some

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cases, and traces of heavy side products arising from aldol condensation of hydrogenated aldehydes when conversions exceeded 40 %. The comparison of conversion and TOF reflects the influence of different residence times and allows for a judgement of substrate-catalyst contact. For the quantitative analysis, the responses for conversion were referred to aldehydes per mmol Rh to eliminate fluctuations from different reactor loadings.

Knowing the time needed for reaching equilibrium from previous experiments, all experiments sharing the same catalyst could be grouped together and carried out in series without changing the catalyst or stopping the flows. The other factors were varied according to the experimental matrix (Table S2) after a minimum of two hours of equilibration time respectively.

Exp. Number	IL loading [wt%]	Substrate injection rate [ml/min]	Syngas/substrate ratio	
1	14	0.12	15	
2	14	0.24	10	
3	14	0.24	20	
4	14	0.36	15	
5	29	0.12	10	
6	29	0.12	20	
7 ^a	29	0.24	15	
8	29	0.36	10	
9	29	0.36	20	
10	44	0.12	15	
11	44	0.24	10	
12	44	0.24	20	
13	44	0.36	15	

Table S2. Grouped experimental matrix for Box-Benhken designed quadratic model.

a = centre point

The raw data collected in Table S4 and are summarised in the Figures S2-S5 where vertical lines indicate when reaction conditions were changed respectively. The arithmetic means of the last two values for each period under constant conditions were used for the statistical analysis.

Table S4 Full experimental results for optimisation studies

Exp	Exp	Run	Incl/	IL	Substrate	Syngas/Substrate	Turnover	Selectivity	Cc
No	Name	Order	Excl	loading	rate		Frequency		/ n
1	UH 10A	1	Incl	14	0.12	15	292.5	3.03	63
5	UH 10B	2	Incl	14	0.24	10	590.6	3.06	53
7	UH 10C	3	Incl	14	0.24	20	479	3.01	52
3	UH 10D	4	Incl	14	0.36	15	543.3	3.03	39
9	UH 11A	5	Incl	29	0.12	10	319	2.92	69
11	UH 11B	6	Incl	29	0.12	20	331.3	2.72	71
13	UH 11C	7	Incl	29	0.24	15	606.1	2.77	66
10	UH 11D	8	Incl	29	0.36	10	686.5	2.97	49

Comment [MSOffice1]: In fact, the assumption to have fixed alkene concentration is not 100% true as the real residence time varied from the adjusted one due to mix-gas density variation from catalytic conversion. However, I don't see a possibility to correct for this now and from the comparison of conv. vs. TOF effects the error is not too big.

Comment [djch2]: Should we say something about the total flow rate?

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12	UH 11E	9	Incl	29	0.36	20	606	2.92	44
2	UH 12A	10	Incl	44	0.12	15	332.2	3.05	72
6	UH 12B	11	Incl	44	0.24	10	485.3	3.15	52
8	UH 12C	12	Incl	44	0.24	20	584.6	3	63
4	UH 12D	13	Incl	44	0.36	15	539.7	3.1	39



Fig. S2 Conversion to aldehydes of the 14 wt% and the 44 wt% SILP catalysts (experiment numbers refer to the conditions in Table 3).



Fig. S3 Conversion to aldehydes of the 29 wt% SILP catalyst (experiment numbers refer to the conditions in Table 3).



Fig. S4 Turnover frequencies of the 14 wt% and the 44 wt% SILP catalysts (experiment numbers refer to the conditions in Table 3).



Fig. S5 Turnover Frequencies of the 29 wt% SILP catalyst (experiment numbers refer to the conditions in Table 3).



Fig. S6 Regioselectivity as ratio of *n*- to *iso*-nonanal (linear to branched) of all SILP catalysts under different conditions.

Besides the statistical analysis, a number of interesting observations can be made from the data shown in Figures 4-8. In particular, under most of the conditions studied, the reaction rates are high corresponding to turnover frequencies up to 800 h⁻¹. In the bulk SCF-IL system, rates higher than 600 h⁻¹ were not accessible, partly because the rate of removal of the product under conditions where the rates were highest was insufficient to remove all of the product as it formed so the autoclave filled up and the entire mixture was flushed from the reactor over time.^[31] In some cases using the SILP catalysts, the conversion of aldehydes was > 95 %, despite the catalyst bed only being 8 cm³ in volume. Under these conditions, 7.2 cm³ of alkene is converted per hour, giving a liquid hourly space velocity (LHSV) close to 1.

The 1:b ratio shows little variation in all samples analysed. This invariability is expected given that the phosphine remains constant and there always is a 10 fold excess present. L:b ratios in hydroformylation reactions usually depend on the steric demand of the phosphine and the P:Rh ratio. However, changes in p_{CO} can also have an effect as can the conversion, 1:b ratio decreasing at high conversion because isomerised alkene is hydroformylated more slowly than terminal alkene.^[37]

Quantitatively, the model could successfully be fitted on all responses with partial least squares (PLS) regression (Figure S7).

The R^2 factors representing the fraction of response variation explainable by the model through variation of the factors studied ^[38] are high for catalytic activity (0.8 for TOF, 0.9 for conversion) demonstrating a good fit. The small variations in selectivity can barely be described by the factors included in the model, but they are not expected to be significant anyway.

The Q^2 factor representing the fraction of response variation predictable by the model on basis of the factors included ^[38] might still be acceptable for the conversion, but less reliable for the TOF. Selectivity trends are not predictable at all, proving that the small variations observed are random fluctuations. Consequently, only the activity was analyzed further. The linear impacts of the single factors as well as their binary interaction impacts are shown in the following overview plot (Figure S8).



Fig. S7 Summary of Fit on a 95 % confidence level for all responses (dark gray = R^2 , light gray = Q^2).



Fig. S8 Normalized overview plot of linear and mixed quadratic factor influences on the hydroformylation activity of Rh – SILP catalysts.

Opposed to the screening investigation using a simple linear model, in the quadratic model the IL loading shows a slight positive effect on the activity. The low influences in both cases suggest that the film thickness does not significantly hinder nor accelerate the catalysis, however.

The Syngas to substrate ratio seems to slow down the catalysis very slightly at higher partial pressures. Mechanistically this would be in accordance with the general kinetics for phosphine modified Rh hydroformylation,^[37] where the positive order in H_2 is supposed to be smaller than the negative CO influence above the critical CO concentration for active complex formation, globally resulting in a slight negative order for a 1:1 syngas mixture.

As found previously, the substrate injection rate most strongly affects the activity (confer Figure S1). The fact that the influences are almost exactly opposed for TOF (+0.86) and conversion (-0.9) reflects that the adjustment of the total volumetric flow (residence time) to the substrate flow resulted in constant alkene concentrations over the SILP catalyst as intended, and that in the range of total volumetric flows good substrate-catalyst contact is ensured.

Most interesting are, however, the interactions between the factors. Interaction effects are easily overlooked by traditional (usually strictly linear) optimization studies; a common approach is to fix all reaction parameters except one and then analyze the effect of the latter on a chosen response such as conversion or selectivity. In order to test the influence of the variable on all different levels of the other factors a large number of experiments would be necessary, and usually this effort is not taken also because chemists are intuitively less aware of such interaction effects. Statistical design of experiment (DoE) systematically probes these effects (within a given matrix) and allows for quantification on a chosen confidence level, revealing potentially important effects which often remain unexplored. The dimension and trends of factor interactions can be derived from the non-parallelism of the linear impacts on different levels.^[38] As it can be seen from Figure S8, all three interactions (hatched bars) show the same trends for both TOF and conversion which means that they do not depend on residence time. Figures S9 - S11 break the interaction effects down to both levels respectively. For clarity, the levels have been denoted as "high" or "low" where the absolute values can be found in Table S1.

Figure S9 shows the influence of IL loading at high and low substrate flow levels on the TOF. At higher flows the film thickness barely affects the reaction, while at lower substrate flows more IL seems to slightly enhance the rate. As the concentration of 1-octene over the SILP catalyst was kept constant by adjusting the residence time accordingly these (admittedly small) effects are still unclear at present.



Fig. S9 Interaction between IL loading and substrate injection rate on the TOF of 1octene hydroformylation over Rh - SILP catalysts with compressed CO_2 .

The interaction between the amount of substrate and the Syngas/substrate ratio is more pronounced (Figure S10). At higher flows more Syngas decreases the activity while at lower flows it slightly enhances the catalysis. This difference in dependence may originate from two different phenomena; a physical and a kinetic one. As in the bulk SCF-IL system, the amount of Syngas will affect the partition of the substrate between CO₂-phase and the SILP. A higher partial pressure of CO/H₂ pushes the substrate more into the IL phase because it acts as an anti-solvent for CO₂. At low substrate flows more Syngas thus intensifies catalyst-substrate contact leading to enhanced activity. At higher flows the contact is more intimate anyway, and increasing the amount of Syngas lowers the rate due to the global negative order of syngas explained above.



Fig. S10 Interaction between Syngas/substrate ratio and substrate injection rate on the TOF of 1-octene hydroformylation over Rh – SILP catalysts with compressed CO₂.

The most pronounced interaction is the mutual impact of IL loading and Syngas/substrate ratio on the performance of the catalyst Catalysts with low IL loadings react with a decrease in activity when more syngas is present, while catalysts with higher IL loadings show increased activity when more syngas is delivered (Figure S11).

These observations are again in line with the interplay of local alkene vs. Syngas concentration. In the case of relatively thick IL layers, more Syngas leads to better alkene-catalyst contact and therefore higher activity. Thin IL layers are more

accessible anyway, and higher CO/H_2 delivery lowers the reaction rate due to the global negative order of syngas.

With a fitted model at hand response surface modelling can be performed on conversion and TOF (Figure 9 published paper), visualising all factor influences (both linear and interactions) on the performance of the SILP catalysts. The respective maxima of the two responses are opposite in all three factors. While highest conversion is located at high IL-loadings, high Syngas/Substrate ratios at low flow rates the opposite is true for the TOF. Highest rates (at the expense of conversion) are found for low IL loading, low Syngas/Substrate ratio at high substrate flow.



Fig. S11 Interaction between IL loading and Syngas/substrate ratio on the TOF of 1-octene hydroformylation over Rh – SILP catalysts with compressed CO₂.