Cobalt Hydroformylation of Olefins in a Biphasic System Using Ionic Liquids - Development and Reaction Optimization by a Design Experiment Approach.

Lionel Magna, Stephane Harry, Abdelaziz Faraj, Hélène Olivier-Bourbigou

Dossier

Discovery and Optimization of Catalysis and Solvents for Absorption Using High Throughput Experimentation
Découverte et optimisation de catalyseurs et d'absorbants par expérimentation haut débit

Cobalt Hydroformylation of Olefins in a Biphasic System Using Ionic Liquids – Development and Reaction Optimization by a Design Experiment Approach

L. Magna*, S. Harry, A. Faraj and H. Olivier-Bourbigou

IFP Energies nouvelles, Rond-point de l'échangeur de Solaize, BP 3, 69360 Solaize - France
e-mail: lionel.magna@ifpen.fr - stephane.harry@ifpen.fr - abdelaziz.faraj@ifpen.fr - helene.olivier-bourbigou@ifpen.fr

* Corresponding author

Résumé — **Hydroformylation des oléfines par le cobalt en milieu liquide ionique – Développement et optimisation de la réaction par plans d'expériences** — Ce document décrit l'utilisation des plans d'expériences en association avec des équipements d'expérimentation haut débit, pour le développement et l'optimisation de la réaction d'hydroformylation des oléfines par le cobalt en milieu liquide ionique. L'objectif principal de ce travail était d'identifier la manière dont les différents paramètres de réaction ($[Co]_{LI}$, L/Co, Ph_{org}/Ph_{NAIL}, pression et température) interagissent les uns avec les autres et d'évaluer leur influence sur l'activité et la sélectivité du catalyseur. Sur la base d'un plan d'expériences D-Optimal, cette étude fait ressortir la température et dans une moindre mesure le ratio "$Phase_{orga}/Phase_{NAIL}$" comme étant les paramètres critiques du procédé. Ces conclusions confirment dans une certaine mesure, les hypothèses formulées initialement pour décrire le principe de fonctionnement du procédé mis en œuvre. Cette stratégie permet de prédire rapidement les performances du système dans l'ensemble du domaine expérimental avec la possibilité d'identifier un optimum de fonctionnement.

Abstract — *Cobalt Hydroformylation of Olefins in a Biphasic System Using Ionic Liquids – Development and Reaction Optimization by a Design Experiment Approach* — *The present paper describes the use of experimental designs (DoE) in association with high throughput experimentation devices for the optimization of cobalt hydroformylation of olefins in a biphasic system using ionic liquids. The main goal of the study was to gain insight into the various factors ($[Co]_{NAIL}$, L/Co, Ph_{org}/Ph_{NAIL}, pressure and temperature) and how they interact and influence the activity and selectivity of the catalyst. On the basis of a D-Optimal design, the study pointed out that temperature and to a less extend "$Phase_{orga}/Phase_{NAIL}$" ratio are the most critical parameters. These conclusions confirm to a certain extend, the initial hypothesis formulated to describe the process operation. Furthermore, this strategy in association with high throughput experimentation devices, allows to predict catalytic results in the major part of a cubic space (representing the experimental domain) giving us the opportunity to determine the most suitable catalysts composition and optimal reaction conditions.*

INTRODUCTION

Hydroformylation reaction is one of the most important homogeneous transition metal catalyzed process in industry today [1, 2]. This reaction consists formally in the transformation of olefins under carbon monoxide and hydrogen pressure to linear and branched aldehydes as primary products (*Fig. 1*). The interest of such a reaction resides in the formation from an olefin to a new carbon-carbon bond with the introduction of a carbonyl functionality, which can be easily transformed in different products of industrial interest like detergents, plasticizers and pharmaceutical intermediates.

Several metals have been used to catalyse this reaction [1, 2], but only systems based on cobalt and rhodium are industrially applied. On a commercial scale, rhodium catalysts have become the catalysts of choice for hydroformylation for small alkenes (C3-C5). Nevertheless, a significant number of aldehydes are produced *via* cobalt catalysts especially when C8-C9 olefins feedstocks are used. However, in the actual industrial oxo processes, the separation of the catalyst from the products and its recycling is still a major concern. In the case of cobalt catalyst, this recycling on industrial scale is operated following three variants:

– alteration of the oxidation state of cobalt by hydrothermal treatment or oxygen treatment in acidic medium, followed by regeneration of the active species;
– extraction of the cobalt catalyst with aqueous caustic and reformation of the active species by subsequent acidification;
– ligand modification and thus stabilization of cobalt carbonyl, followed by product separation by distillation and recycling of the catalyst phase.

In recent studies, we described an original approach to perform cobalt catalyst recycling using ionic liquids in a biphasic mode [3, 4]. This approach is based on the well known chemistry on cobalt carbonyl species in the presence of Lewis base derived from pyridine [5-14]. The addition of pyridine to $[Co_2(CO)_8]$ yields generally to the formation of ionic species, mainly $[Co(Py)_6]^{2+}$ $[Co(CO)_4]_2^-$ and $[PyH]^+[Co(CO)_4]^-$. In the presence of ionic liquids, we can assume that these species remain soluble and immobilized in the ionic liquid phase. Under

Figure 2
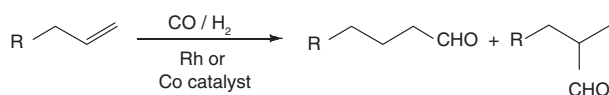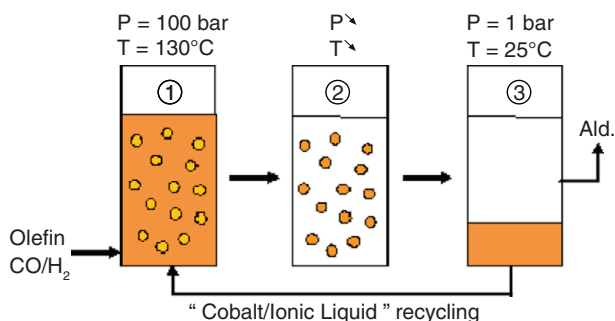
Simplified process (1-Reaction, 2-Cobalt recovery in the ionic liquid, 3-Separation).

reaction conditions such as CO/H_2 pressure (100 bar) and when the temperature is raised (130°C), the active species $[HCo(CO)_4]$ is generated. Owing to its high solubility in heptane, we can expect that $[HCo(CO)_4]$ is extracted in the upper organic phase, where the reaction takes place, without any mass transport limitation. The change in the operating conditions from 100 bar of CO/H_2 and 130°C to atmospheric CO/H_2 pressure and room temperature decreases the stability of $[HCo(CO)_4]$. Under the latter conditions $[HCo(CO)_4]$ tends to dimerize into $[Co_2(CO)_8]$ or reacts with pyridine to form $[PyH]^+[Co(CO)_4]^-$ by direct acido-basic neutralization. Furthermore, $[Co_2(CO)_8]$ can react with free pyridine to produce another ionic $[Co(Pyr)_6]^{2+}[Co(CO)_4]_2^-$ species. Because of their high affinity for the ionic medium, both these ionic species are extracted and immobilized in the ionic phase. Therefore, the product is easily separated by decantation and the ionic liquid containing the cobalt catalysts is recycled into the reaction section (*Fig. 2*) [15, 16].

Taking into account the equilibria involved in such process, it seems clear that optimization of the reaction conditions in order to achieve high activity and selectivity for aldehydes and high cobalt recycling will be quite challenging. For example, to optimize catalyst recycling, ionic species must be favoured. This can be achieved by using pyridine derivatives presenting high basicity and high coordination ability to the metal centre or by increasing their concentration with respect to cobalt. On the other hand, highly active systems will need harsh pressure and temperature conditions.

In this paper, we describe how to optimize this system in which a large number of parameters such as nature of the pyridine, ratio pyridine *versus* cobalt, pressure, temperature are able to influence the course of the catalytic reaction. More precisely, this strategy has enabled us to

Figure 1

Olefins hydroformylation.

*L. Magna et al. / Cobalt Hydroformylation of Olefins in a Biphasic System Using Ionic Liquids –
Development and Reaction Optimization by a Design Experiment Approach*

417

TABLE 1

The constraints of the system

Variables in the model	Definition	Unit	Minimum	Average	Maximum
Z_1	Cobalt concentration in the ionic liquid phase	mol/L	0.078	0.135	0.195
Z_2	Molar ratio "ligand/ cobalt"	-	2	6	10
Z_3	"Orga. phase/Ion. liq. phase" volume ratio	-	1.5	3	4.5
Z_4	Reaction pressure	bar	60	80	100
Z_5	Reaction temperature	°C	100	125	150

gain insight into how the various reaction parameters cooperate and influence the activity and selectivity of the catalyst.

1 RESULTS AND DISCUSSION

Considering the large number of parameters that needs to be evaluated for the optimization of this reaction we envision that a Design of Experiment (DoE) approach will be a valid strategy to find the optimum catalytic conditions. DoE methodologies [17-20] can be considered more efficient than traditional methods, which involving the consecutive optimization of the various reaction parameters. Instead, our approach makes possible to maximize the amount of information while minimizing the number of experiments. The DoE methodology consists in building a mathematical model (here a second degree polynomial model), with a predicting variance as small as possible, that links up a response Y_i (or output variable) with J factors Z_J (or input variables), etc., starting from a small number of experiments. This model is valid inside the domain D of feasible experiments. Hypercubes and hyperspheres are normally chosen as representing experimental regions D. Generally the number of feasible experiments is very high, so it is important to appropriately choose them in order to limit costs and time of execution. In our approach, we prefer to use optimal designs instead of standard classical ones[1].

---

[1] As standard classical designs, we refer to methods currently used and reported in classic books and experiments planning software. In particular, they include screening designs (Hadamard matrix, two-level or more factorial designs), designs for response surfaces (composite design, Box-Behnken, Doehlert, etc.).

In addition, in this study, we limit our methodology to designs for response surfaces. Even though traditional methods are well-known and currently used in industry, in some cases they can show great limitations. On the other hand, the use of classical DoE is not always attractive (not realistic factor levels, some of the experiments are difficult or impossible to be realized, experimental domain constrained, need to integrate experiments already done, etc.). By optimal experimental design we can overcome these limitations in order to find the best custom-made solution to a given problem.

The determination of an optimal design starts from N candidate points (or potential experiments) inside the relevant experimental domain D, among which we are searching for a subset of n experimental runs to carry out (with or without repetitions). For this purpose some optimization algorithms called "exchange algorithms" (Fedorov [21] or Mitchell [22] algorithms) are needed. Starting from an initial design (randomly chosen), which will be improved by repeated iterations, we exchange a run of the design with another not chosen. The exchange algorithms do not necessarily converge to the optimum of D-optimality criterion. It is usually recommended to build multiple designs where numbers of experiments are varied and to select the best design in accordance with several other criteria. Only the experiments of this last design are then carried out.

1.1 Definition of Factors and Construction of the Experimental Matrix

The use of a DoE strategy requires as first step the compilation of all potentially important parameters, based on previous experiences, literature or chemical intuition and knowledge. The initial research space

TABLE 2
Experiment matrix with 40 points

Test Nr.	Nature	$[Co.]_{LI}$	L/Co	Ph_{ORGA}/Ph_{LI}	Pressure	Temperature
1	Plan	0.199	2	1.5	60	100
2	Plan	0.081	2	1.5	60	150
3	Plan	0.199	11	1.5	60	150
4	Plan	0.08	2	1.5	100	100
5	Plan	0.081	10	1.5	100	100
6	Plan	0.199	2	4.5	100	100
7	Plan	0.199	2	1.5	100	150
8	Plan	0.081	2	4.5	100	150
9	Plan	0.199	10	4.5	100	150
10	Plan	0.081	6	1.5	60	100
11	Plan	0.14	10	1.5	60	100
12	Plan	0.081	2	4.5	60	100
13	Plan	0.199	10	4.5	60	100
14	Plan	0.199	6	4.5	60	125
15	Plan	0.199	2	3	60	150
16	Plan	0.082	9.8	4.5	60	150
17	Plan	0.199	10.4	1.5	80	100
18	Plan	0.081	9.9	1.5	80	150
19	Plan	0.199	6	1.5	100	100
20	Plan	0.081	6	4.5	100	100
21	Plan	0.08	10.1	4.5	100	125
22	Plan	0.14	10	1.5	100	150
23	Plan	0.082	6	3	100	150
24	Plan	0.14	6	4.5	80	150
25	Center	0.139	6	3	80	125
26	Center	0.14	6	3	80	125
27	Center	0.139	6	3	80	125
28	Center	0.139	6	3	80	125
29	Center	0.14	6	3	80	125
30	Test	0.2	10	3	100	125
31	Test	0.082	2	3	80	100
32	Test	0.12	5	2.5	70	115

(continued)

L. Magna et al. / Cobalt Hydroformylation of Olefins in a Biphasic System Using Ionic Liquids –
Development and Reaction Optimization by a Design Experiment Approach

419

TABLE 2 (*continued*)

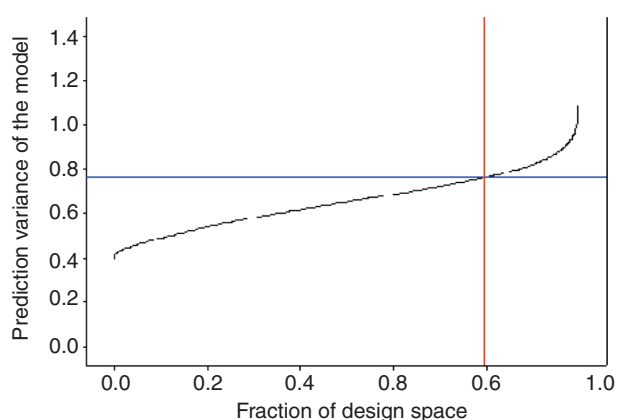| Test Nr.	Nature	[Co.] $_{LI}$	L/Co	Ph$_{ORGA}$/Ph$_{LI}$	Pressure	Temperature
33	Test	0.16	5	2.5	70	115
34	Test	0.159	8	2.5	70	115
35	Test	0.16	6	4	70	115
36	Test	0.161	6	3	70	140
37	Test	0.159	6	3	90	125
38	Test	0.199	2	4.5	80	150
39	Test	0.141	9.9	4.5	100	100
40	Test	0.14	2	1.5	100	125

Figure 3

Fraction of Design Space (FDS) graph for the selected design of 29 points. This curve indicates that 80% of the design space has a prediction standard error equal or lower than 0.76 for an experimental standard error equal to 1.

(*i.e.* experimental domain) should be broad enough to assure that the real optimum of the reaction is included. In the course of our investigations on the nature of the ligand and the nature of the ionic liquid used for this process [3, 4], we have demonstrated that a good compromise can be obtained with the use of 2-methoxypyridine in [BuMePyrr][NTF$_2$]$^{(2)}$.

While these two parameters are fixed, we also defined five other parameters influencing the course of the reaction (*Tab. 1*). These parameters were identified through one-variable-at-a-time experiments prior to the launch

of this study. Each factor can take three values (minimum, average and maximum). These three values are selected on the basis of their relevance and their experimental feasibility (we can accurately reach the established levels without generating too much experimental constraints).

As reported above, we made use of optimal designs instead of standard classical ones. In this respect, we generated several designs with different numbers of experiments and selected among them the one with the best statistical quality. These designs were computed by the exchange algorithm among 243 candidates (feasible experiments) that represent the whole possible combinations in the experimental domain. The selected design contains 25 runs including an experiment replicated 5 times in the centre of the experimental domain (*Tab. 2*). The repeated experiments allow us to calculate the experimental variance of responses. The final selected design contains 29 experiments. To these experiments, we added 11 runs, which were used as test points for the validation of the computed models. It should be noticed that the selected design suggests only 25 different trials (24 + 1 centre point) while classical designs require more trials. For example, for 5 factors, a full half-fraction central composite design suggests 27 trials (26 + 1 centre point) and a Box-Behnken design suggests 41 trials.

The quality of an optimal design is usually evaluated by using numerous alphabetic criteria, such as D-, G- or V-optimality [23-25]. However, these criteria, which are single numbers, do not completely express the prediction power of the design in question. To compare the experimental designs with each other, we used their Fraction of Design Space (FDS) graph. This graph represents the prediction standard error of a model built

---

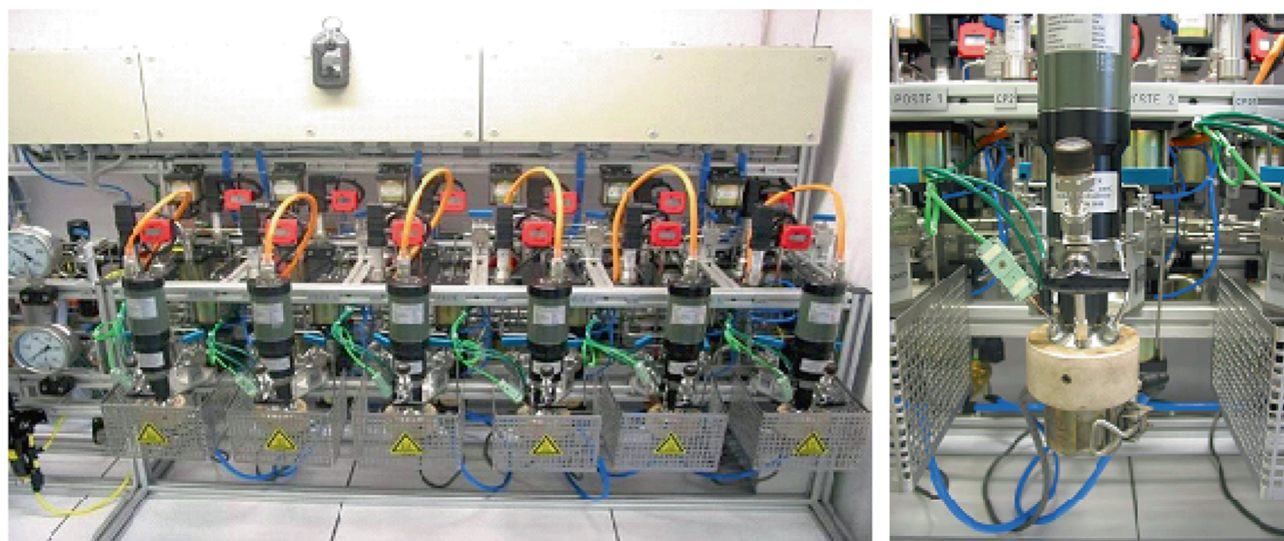^{2} [BuMePyrr][NTF$_2$] = N-butyl-N-methylpyrrolidinium bis(trifluoromethylsulfonyl)amide.

Figure 4

Hydroformylation unit.

TABLE 3

Responses definition

Code	Responses	Unit
Y_1	Turn Over Frequency (TOF)	mol/mol/h
Y_2	Aldehydes selectivity	wt %
Y_3	n/iso ratio for aldehydes	-

with the design of experiments *versus* the fraction of design space (*Fig. 3*). The FDS Graph is a curve showing the relationship between the fraction of the design space and the prediction standard error. It indicates the percentage (fraction) of the design space having a given prediction standard error or lower. Lower and flatter FDS curves are better.

1.2 High Throughput Catalyst Testing

To enhance catalyst testing, a High-Throughput Experimentation (HTE) device was used (*Fig. 4*). Combination of HTE with DoE has been successfully described in the literature in the fields of material science [26-30], heterogeneous [31-34] and homogeneous catalysis ([35, 36] and for review see [37]). The 40 experiments reported in

Table 2 were carried out in a multi reactor for parallel reactions (*Fig. 4*). This device can carry out up to 6 parallel catalytic tests. All reactors are completely independent and they can be operated simultaneously or in a staggered way. Sequences of tests are quite automated. Only the introduction of the catalyst solution is done manually.

In a typical run, the program starts with nitrogen "pressurization/depressurization" cycles. Each reactor is then charged with the desired amount of $[Co_2(CO)_8]/$ 2-methoxypyridine/ionic liquid solution. 1-hexene and heptane (co-solvent) are then added to the autoclave. The pressure is raised to 40 bar and the temperature adjusted to 90°C for a pre-activation period of 30 min. During this period no gas consumption was observed. Pressure and temperature were adjusted to the desired values in the second part of the catalytic test (*Tab. 2*). The reaction mixture was then stirred at 1 500 rpm for 1 h and the autoclaves maintained at constant pressure until the end of the reaction. The reactors were then rapidly cooled down to room temperature and the CO/H_2 pressure released to atmospheric pressure. Before opening the reactors, nitrogen "pressurization/depressurization" cycles were performed to release any traces of CO.

For each experiments, three different characteristics were studied (*Tab. 3*): Y_1 (TOF), which is calculated based on the monitoring of synthesis gas consumption when theoretical olefin (1-hexene) conversion reached 25%. Others responses (Y_2 and Y_3) are extracted from

*L. Magna et al. / Cobalt Hydroformylation of Olefins in a Biphasic System Using Ionic Liquids –
Development and Reaction Optimization by a Design Experiment Approach*

421

TABLE 4

Responses values for 40 experiments

Test Nr.	Nature	TOF (mol/mol/h)	Ald. sel. (wt %)	n/iso ald.
1	Plan	40	79	2.7
2	Plan	550	57.9	1.1
3	Plan	207	68.1	1.1
4	Plan	47	68.8	3.4
5	Plan	15	68.8	3.2
6	Plan	50	77.9	3.5
7	Plan	488	45.5	1.4
8	Plan	971	78.6	1.6
9	Plan	800	77.7	1.6
10	Plan	35	77.5	2.5
11	Plan	20	76.1	2.3
12	Plan	41	61.3	2.4
13	Plan	41	76.9	2.5
14	Plan	220	83.7	1.7
15	Plan	478	55.1	1.1
16	Plan	741	80.1	1.2
17	Plan	9	74.6	2.7
18	Plan	416	76.7	1.4
19	Plan	22	80.7	3.2
20	Plan	54	63.9	3.4
21	Plan	251	88	2.3
22	Plan	337	76.9	1.5
23	Plan	842	75.9	1.6
24	Plan	692	78.3	1.4
25	Center	230	80.2	2
26	Center	228	85.1	2.1
27	Center	237	84.8	2
28	Center	227	81.2	2
29	Center	236	83.6	2
30	Test	197	88.5	2.2
31	Test	43	62.8	3
32	Test	140	85.1	2.1

(continued)

TABLE 4 *(continued)*

Test Nr.	Nature	TOF (mol/mol/h)	Ald. sel. (wt %)	n/iso ald.
33	Test	140	86.5	2.1
34	Test	143	86.1	2
35	Test	127	84.8	2.2
36	Test	411	83.4	1.5
37	Test	234	89.8	2.2
38	Test	750	64.9	1.3
39	Test	45	73.7	3.4
40	Test	216	77.7	2.3

TABLE 5

Experimental standard deviation of responses

	TOF	Ald. sel.	n/iso ald.
Std dev.	9.06	2.48	0.0284

gas chromatographic analysis of organic phase after 1h reaction time.

Following the procedure described above, highly reproducible experiments were obtained. It was possible to verify that results obtained in the same reactor were reproducible and that it was possible to compare the results between different reactors. The values for each response of the 40 experiments are listed in Table 4. Instead, Table 5 specifies the experimental variance for each response.

1.3 Correlations Between Responses Y_1 to Y_3

In Figure 5, we report the crossplots of the 3 responses against each other. Every point is associated with an experiment in the 2-responses plot. Red points (•) indicate the 11 test experiments and cross-marked (✕) indicate experiments repeated in the center of the domain. Their dispersion displays the "repeatability" of measurements performed in the domain center.

In Figure 5, numeric values presented above and below each response indicate their relative minimum and maximum values. Hence, the TOF (Y_1) varies from 9 to 971 mol/mol/h, aldehydes selectivity (Y_2) from 45 to 89.8 wt%, and finally n/iso ratio for aldehydes (Y_3) varies from 1.1 to 3.5. These intervals are obtained from experimental data, but the values
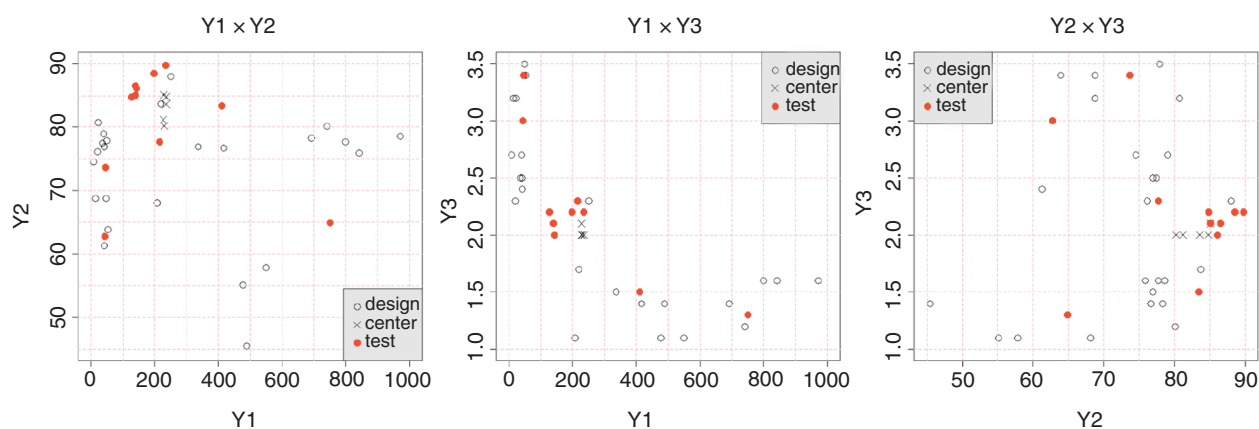
Figure 5

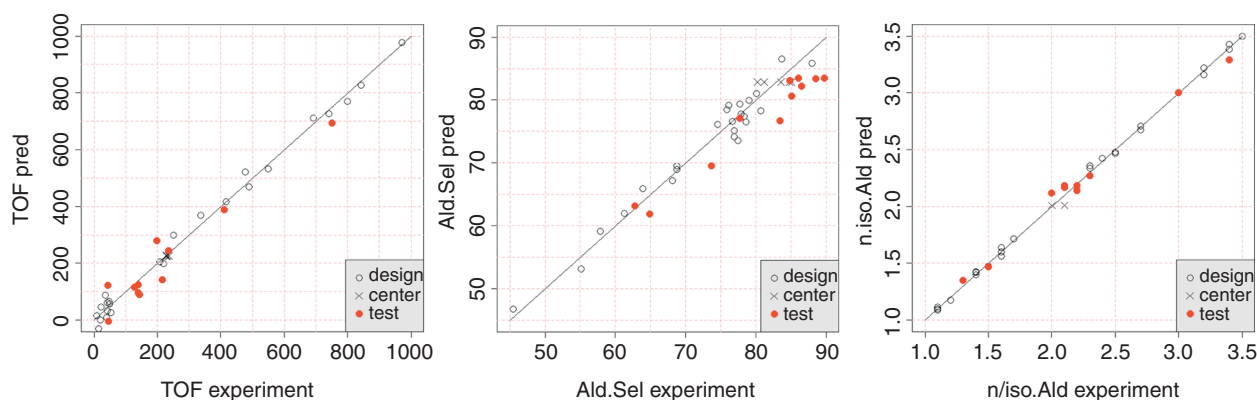Responses crossplotted with test points (•) and points repeated in domain center (×).

Figure 6

Correlations of predicted and experimental values for Y_1, Y_2 and Y_3.

obtained from models can exceed them. Therefore, this indicates that the responses are not correlated with each other.

1.4 Construction and Validation of Models

The experimental design methodology allows to make an approximation of the studied of physical-chemical phenomenon with a response surface. In real conditions, the phenomenon is much more complex to be globally described by a polynomial model, but because of the restriction of the relevant experimental domain to a specific region, a polynomial is most of the times sufficient to model it.

For each response Y_1 and Y_3, respectively TOF and n/iso ratio, correlation between predicted and experimental values can be considered very accurate/reliable. For Y_2 (aldehydes selectivity), some deviations for high selectivity values are observed. Nevertheless, the estimation of the values of aldehydes selectivity in this domain is still good enough. Furthermore, the predicted values for tests points (•, *Fig. 6*) validate the quality of the models for Y_1, Y_2 and Y_3 responses.

Once validated, this polynomial allows to predict the studied phenomenon in every point of experimental domain. This forbids, of course, any extrapolation outside the domain. For "practical" interpretation and concrete visualization of theses responses, it is possible to

L. Magna et al. / *Cobalt Hydroformylation of Olefins in a Biphasic System Using Ionic Liquids –*
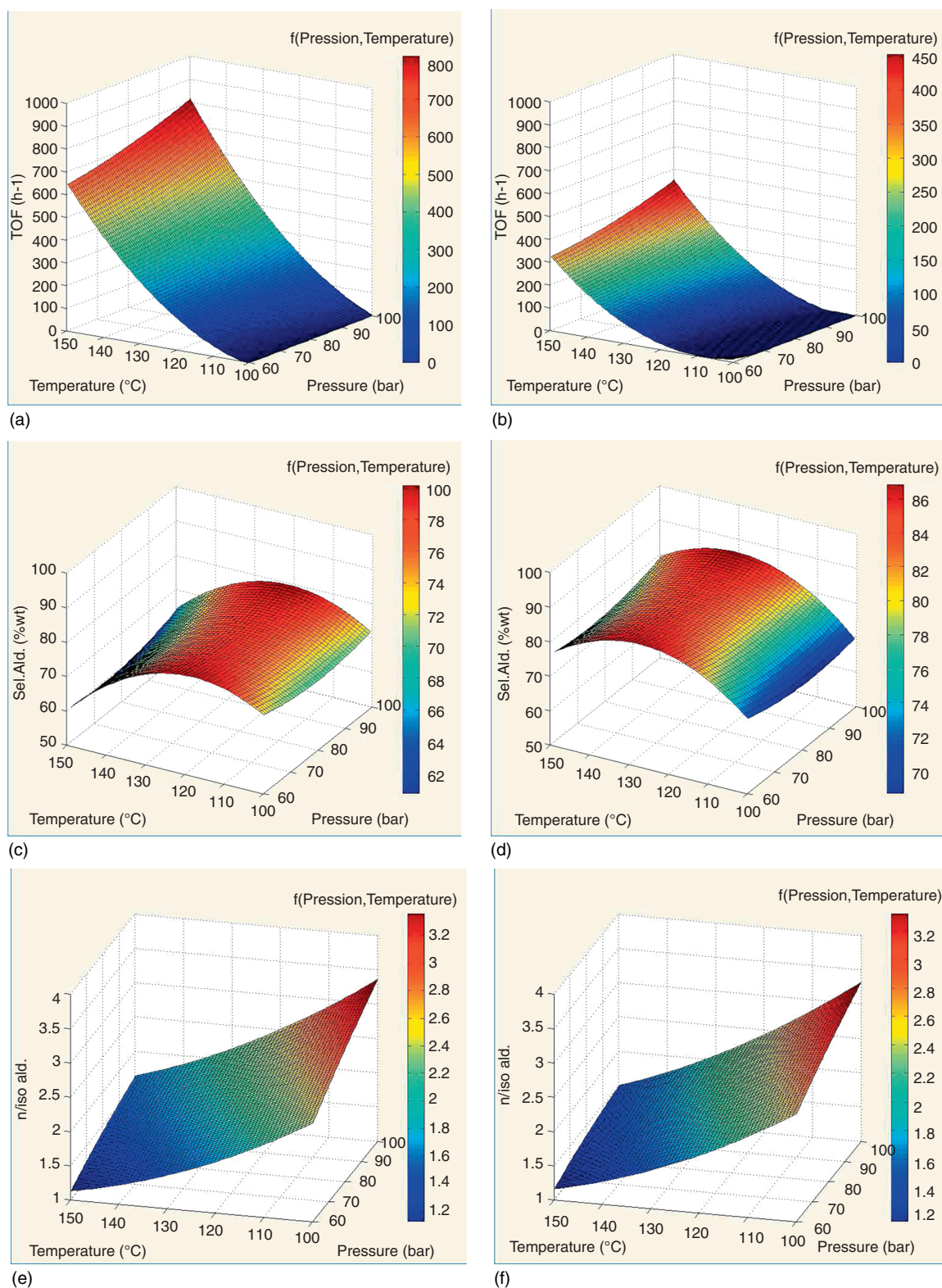*Development and Reaction Optimization by a Design Experiment Approach*

423

Figure 7

3D-plans for Y_1, Y_2 and Y_3. Calculated a) TOF with $Z_1 = 0.135 / Z_2 = 6 / Z_3 = 1.5$; b) TOF with $Z_1 = 0.135 / Z_2 = 6 / Z_3 = 4.5$; c) Ald. Sel. with $Z_1 = 0.135 / Z_2 = 2 / Z_3 = 3$; d) Ald. Sel. with $Z_1 = 0.135 / Z_2 = 10 / Z_3 = 3$; e) n/i Ald with $Z_1 = 0.077 / Z_2 = 2 / Z_3 = 3$; f) n/i Ald. with $Z_1 = 0.196 / Z_2 = 10 / Z_3 = 3$.
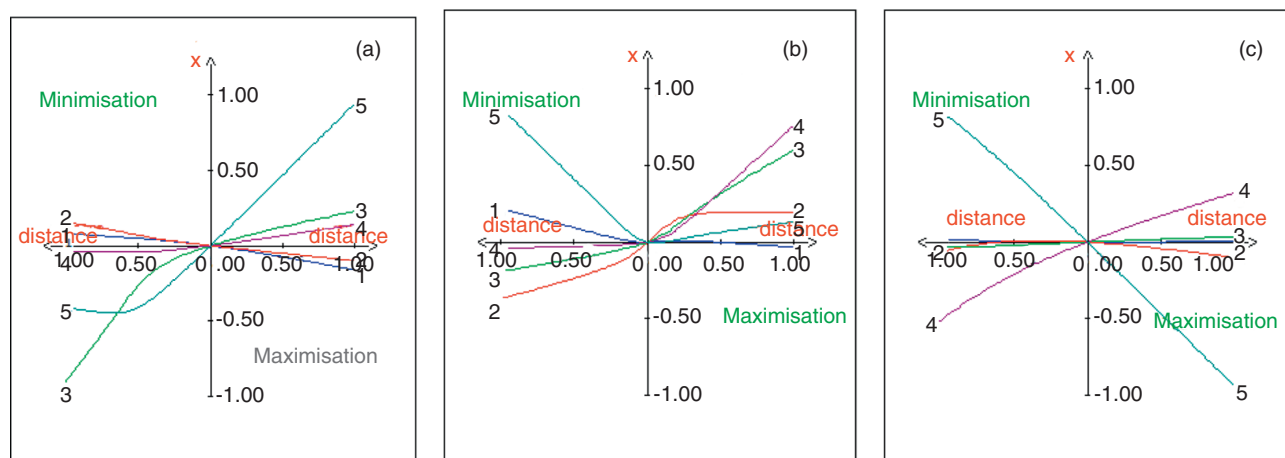
Figure 8

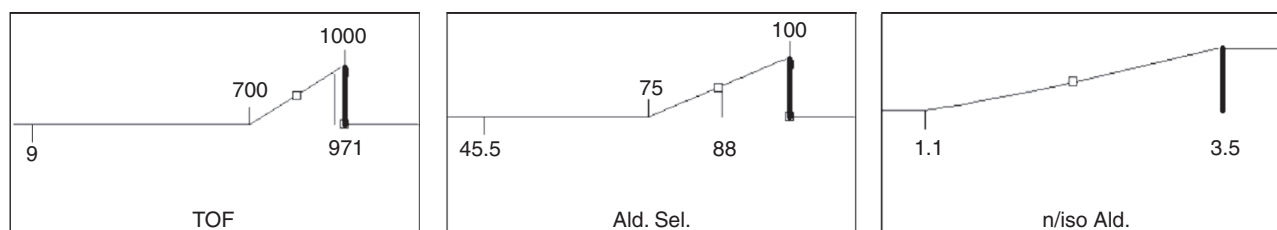Ridge analysis for a) TOF, b) Aldehydes selectivity and c) *n*/iso ratio.

Figure 9

Definition of desirability functions D_1, D_2 and D_3.

represent the Y_1 to Y_3 variation curves in different 3D-plans composed by factors. Some examples are shown in Figure 7.

1.5 Highlighting of the Critical Parameters

Once built, these models can be used to understand the underlying physical-chemical phenomenon: searching for an optimum, identifying influent factors, etc. Depending on whether this optimum is inside or outside the experimental domain, it is often necessary to take a sequential approach carrying out successive design of experiments to reach the optimum [38].

As soon as the number of factors becomes important (3 or more) the use of contour plots or representation presented in Figure 7, becomes unfruitful. Therefore, more direct methods are needed to search for the optimum – "ridge analysis" – and to determine which factors

direction to follow to reach the optimum [20]. These methods also enable to find the most influent factors. These approaches are well known in optimization but their use was standardized in experimental design approach. The algorithms allowing their implementation depend on nature of the used method and/or his degree, if polynomial.

Thanks to ridge analysis we can detect the factors direction along which a progression is possible in order to carry out optimal experiments. It is possible to use the "increasing slope" method to reach the maximum (or "decreasing slope" to reach the minimum). This method enables to move in the response rapid increase (or decrease) direction. In Figure 8, ridge analysis for TOF, aldehydes selectivity and *n*/iso ratio are presented.

As Figure 8a shows, the TOF can be maximized by increasing factor Z_5 (temperature). Decreasing factor Z_5 (temperature) or Z_3 (Phase (orga.) / Phase (ion liq)

TABLE 6

Maximum coordinates and characteristics

Constraints

Name	Goal	Lower Limit	Upper Limit
A:[Co.] LI	is in range	0.078	0.195
B:"L/Co"	is in range	2	10
C:"PhORGA / PhLI"	is in range	1.5	4.5
D:Pressure	is in range	60	100
E:Temperature	is in range	100	150
TOF	is target = 1 000	700	1 000
Ald. Sel.	is target = 100	75	100
n/iso Ald.	Maximize	1.1	3.5

Solutions

Number	Z_1 [Co.]$_{LI}$	Z_2 L/Co	Z_3 Ph$_{ORGA}$/Ph$_{LI}$	Z_4 Pressure	Z_5 Temperature	TOF	Y_2 Ald. sel.	Y_3 n/iso ald.
1	0.08	8.02	4.50	100.00	150.00	889.02	87.68	1.70
2	0.08	8.02	4.48	99.96	150.00	887.70	87.56	1.70
3	0.08	8.37	4.46	100.00	149.76	875.08	87.85	1.71
4	0.08	8.09	4.48	99.39	150.00	884.01	87.35	1.70
5	0.08	7.33	4.46	100.00	150.00	889.43	86.84	1.69
6	0.08	6.02	4.50	99.99	150.00	925.89	85.35	1.67
7	0.08	7.35	4.36	100.00	150.00	896.81	86.34	1.69
8	0.08	5.73	4.50	100.00	150.00	930.77	84.91	1.66
9	0.08	6.05	4.38	99.99	150.00	924.43	84.78	1.67
10	0.08	9.22	4.36	100.00	149.44	847.54	87.99	1.73

volume ratio) will also affect the TOF. The effects of others factors towards the TOF values are very limited. In particular, we can notice that the pressure does not have any significant impact on the TOF. This result is well known for hydroformylation reactions catalyzed by an unmodified cobalt catalysts in a conventional homogeneous system [39]. This result indicates to a certain extend that the reaction takes place with an unmodified cobalt catalyst. Reaction rate for hydroformylation reaction using an unmodified cobalt catalyst was indeed rationalized by Natta *et al.* [40] already in 1955 through Equation (1). According to Natta, the reaction rate is independent on the total pressure when CO/H$_2$ ratio is

1/1. This is due to opposite effect of CO and H$_2$ partial pressure.

$$\frac{d[\text{aldehyde}]}{dt} = k[\text{olefin}].[\text{Co}].\frac{P_{H_2}}{P_{CO}} \qquad (1)$$

We can also notice that ligand to cobalt ratio does not affect the TOF significantly. On the other hand, the role of pyridine type ligands as modifiers for cobalt catalysed hydroformylation was already reported several years ago [9]. It was demonstrated that hydroformylation reaction could be accelerated by small amount of pyridine (<2 eq./Co). If larger amount were used (2-8 eq./Co),

the effects became smaller. Very large amounts (> 30 eq./Co) hinder the reaction. This statement seems to be verified in our system too, under reaction conditions considered in the experimental matrix.

Concerning aldehydes selectivity, it appeared that depending on the location in the experimental domain, pressure, temperature and "Phase (orga.) / Phase (ion liq)" volume ratio have an impact. It is also noticeable that increasing the ligand to cobalt ratio improves the aldehydes selectivity. As this ratio has no impact on TOF, it appears important to maintain this value as high as possible in order to favour both aldehydes selectivity and catalyst recycling (it will indeed favour ionic species when pressure is released).

Finally, we can clearly notice the effect of temperature concerning the n/iso ratio. All the other factors do not have significant impact on this response. The higher the temperature is the lower the n/iso ratio. Once again, this phenomenon is an indication that an unmodified cobalt catalyst is acting in our process.

In summary, high TOF with high aldehydes selectivity, high n/iso ratio and efficient catalyst recycling will be obtained using high pressure (for stability of the active species), moderate temperature (for activity) and large ligand to cobalt ratio (for cobalt recycling).

1.6 Searching for an Optimum

It is necessary to determine the point in the experimental domain (factor combination) that is optimal for overall the studied responses. A given absolute optimum for a response is not necessarily the absolute optimum for the others responses, therefore we would define a compromise satisfying at best the studied responses as a whole. This compromise is written like a combination of "desires" or "desirability functions D_i" associated to responses. First, we need to choose some performance objectives (goals) on responses Y_1 (TOF), Y_2 (aldehydes selectivity) and Y_3 (n/iso ratio). These performance goals are described respectively by the desirability functions D_1, D_2 and D_3 (*Fig. 9*).

According to desirability function D_1, we attempt to reach a TOF within 700 and 1 000 h^{-1} (abscises Y_1). Therefore, the optimum will reject the operational conditions that do not follow at least this minimum. Also, our "satisfaction" towards the operation point will be more important when the TOF value will approach 1 000 h^{-1}. In addition of a TOF within 700 and 1 000 h^{-1} (D_1), we will search for an aldehydes selectivity higher than 75% with a target of 100% (D_2) and a "n/iso" selectivity as high as possible (D_3). The setting of functions D_1, D_2 and D_3 is made starting from the

NemrodW software. After setting these functions one or more factors rounds (Z_1 to Z_5) are proposed. For each response, the software calculates our "*satisfaction rate*" related to initially fixed goal (*Tab. 6*). It is also possible to give a changing "weight" to these desired functions depending on the importance of each response. It can be seen in that optima proposed are in accordance with the analysis of critical parameters we have made earlier.

CONCLUSIONS

The present paper describes the use of experimental designs (DoE) in association with high throughput experimentation devices, for the optimization of the cobalt hydroformylation of olefins in a biphasic system using ionic liquids. The main goal of the study was to gain insight into how the various factors ([Co]$_{NAIL}$, L/Co, Ph$_{org}$/Ph$_{NAIL}$, pressure and temperature) interact and influence the activity and selectivity of the catalytic reaction. On the basis of a D-Optimal design, the study pointed out that temperature and to a less extend "Phase$_{orga}$/Phase$_{NAIL}$" ratio are the most important parameters and they determined the output of the hydroformylation reaction. These studies confirm the initial hypothesis that an unmodified cobalt catalyst is the active species in the process. Furthermore, this strategy in association with high throughput experimentation screening allowed to predict catalytic results in the major part of a cubic space (representing the experimental domain) giving us the opportunity to determine the most suitable catalysts composition and optimal reaction conditions.

In addition, DoE based on D-optimal design appeared as particularly adapted for optimization processes where the experimenter has to control the nature of tests to be carried out. In addition, it is possible to guide the model or even to impose some experiments. Suggested experiments must be worthwhile for the studied reaction without too hard experimental constraints. In this type of experimental design, experimenter remains the game master.

REFERENCES

1 Frohning C.D., Kohlpaintner C.W., Bohnen H.-W. (2003) *Carbon Monoxide and Synthesis Gas Chemistry*, in *Applied Homogeneous Catalysis with Organometallic Compounds*, Cornils B., Herrmann W.A. (eds), Wiley-VCH, Weinheim, Vol. **1**, pp. 31-103.

2 van Leeuwen P.W.N.M. (ed.) (2004) *Homogeneous Catalysis*, Kluwer Academic Press, Dordrecht.

L. Magna et al. / Cobalt Hydroformylation of Olefins in a Biphasic System Using Ionic Liquids –
Development and Reaction Optimization by a Design Experiment Approach

427

3 Magna L., Harry S., Proriol D., Saussine L., Olivier-Bourbigou H. (2007) *Oil Gas Sci. Technol.* **62**, 6, 775.

4 Hebrard F., Kalck P., Saussine L., Magna L., Olivier-Bourbigou H. (2007) *Dalton Trans.* **2**, 190.

5 Fachinetti G., Fochi G., Funaioli T. (1986) *J. Organomet. Chem.* **301**, 91.

6 Sisak A., Marko L. (1987) *J. Organomet. Chem.* **330**, 201.

7 Fachinetti G., Fochi G., Funaioli T., Zanazzi P.F. (1987) *Angew. Chem. Int. Ed Engl.* **26**, 680.

8 Fachinetti G., Funaioli T., Marcucci M. (1988) *J. Organomet. Chem.* **353**, 393.

9 Iwanaga R. (1962) *Bull. Soc. Chem. Japan* **35**, 6, 865.

10 Roos L., Orchin M. (1966) *J. Org. Chem.* **31**, 3015.

11 Moffat A.J. (1970) *J. Catal.* **19**, 322.

12 Matsuda A., Shin S., Nakayama J.-I., Bando K.-I., Murta K. (1978) *Bull. Soc. Chem. Japan* **51**, 10, 3016.

13 Vigranenko Y.T., Rybakov V.A., Fedorov V.S., Borisov R.B., Gavrilova V.M., Gvozdovskii G.N. (1996) *Petroleum Chem.* **36**, 1, 56.

14 Vigranenko Y.T., Rybakov V.A., Kashina V.V., Tarasov B.P. (1996) *Kinet. Catal.* **37**, 4, 524.

15 Magna L. (2005) Hydroformylation, Multiphase Homogeneous Catalysis, in: Cornils B., Herrmann W.A., Horvath I.T., Leitner W., Mecking S., Olivier-Bourbigou H., Vogt D. (eds.), Wiley-VCH, Weinheim, Vol. 2, pp. 477-494.

16 Haumann M., Riisager A. (2008) *Chem. Rev.* **108**, 1474.

17 Massart D.L., Vandeginste B.G.M., Buydens L.M.C., de Jong S., Lewi P.J., Smeyers-Verbeke J. (1997) *Handbook of Chemometrics and Qualimetrics, Part A*, Elsevier, Amsterdam, pp. 643-658 and 701-737.

18 Kirchhoff E.W., Anderson D.R., Zhang S., Cassidy C.S., Flavin M.T. (2001) *Org. Proc. Res. Devel.* **5**, 50-53.

19 Marchetti M., Guerzoni M.E. (1991) *Cerevisia Biotechnol.* **16**, 24-33.

20 Myers R.H., Montgomery D.C., Anderson-Cook C.M. (2009) *Response Surface Methodology: Process and Product Optimization Using Designed Experiments*, Wiley Series in Probability and Statistics.

21 Fedorov V.V. (1972) *Theory of Optimal Experiments*, Academic Press, New York.

22 Mitchell T.J. (1974) *Technometrics* **16**, 203-210.

23 Liang L., Anderson-Cook C.M., Robinson T.J. (2006) *Quality Reliability Eng. Int.* **22**, 275-289.

24 Anderson-Cook C.M., Borror C.M., Montgomery D.C. (2009) *J. Stat. Plan. Infer.* **139**, 629-641.

25 Anderson-Cook C.M., Borror C.M., Montgomery D.C. (2009) *J. Stat. Plan. Infer.* **139**, 671-674.

26 Cawse J.N. (2003) Experimental Design for Combinatorial and High Throughput, Materials Development, Wiley, p. 338.

27 Harmon L. (2003) *J. Mater. Sci.* **38**, 4479-4485.

28 Webster D.C. (2008) *Macromol. Chem. Phys.* **209**, 237-246.

29 Cawse J.N. (2001) *Acc. Chem. Res.* **34**, 213-221.

30 Serra J.M., Baumes L.A., Moliner M., Serna P., Corma A. (2007) *Comb. Chem. High. Throughput Screening* **10**, 13-24.

31 Paul J.S., Janssens R., Denayer J.F.M., Baron G.V., Jacobs P.A. (2005) *J. Comb. Chem.* **7**, 407-413.

32 Paul J.S., Urschey J., Jacobs P.A., Maier W.F., Verpoort F. (2003) *J. Catal.* **220**, 136-145.

33 Maier W.F., Stowe K., Sieg S. (2007) *Angew. Chem. Int. Ed.* **46**, 6016-6067.

34 Corthals S., Witvrouwen T., Jacobs P., Bert S. (2011) *Catal. Today* **159**, 12-24.

35 Loch J.A., Crabtee R.H. (2001) *Pure Appl. Chem.* **73**, 119-128.

36 Hagemeyer A., Jandeleit B., Liu Y., Damodara M.P., Turner H.W., Volpe A.F., Weinberg W.H. (2001) *Appl. Catal. A* **221**, 23-43.

37 Potyrailo R., Rajan K., Stoewe K., Takeuchi I., Chisholm B., Lam H. (2011) *ACS Comb. Sci.* **13**, 579-633.

38 Coetzer R.L.J., Morgan D.H., Maumela H. (2008) *J. Appl. Statistics* **35**, 2, 131-147.

39 Cornils B. (1980) Hydroformylation. Oxo synthesis, Roelen reaction, New Syntheses with Carbon Monoxide, in: Falbe J. (ed.), Springer-Verlag, pp. 1-95.

40 Natta G., Ercoli R., Castellano S. (1954) *J. Am. Chem. Soc.* **76**, 4049.

41 Thomazeau C., Olivier-Bourbigou H., Magna L., Gilbert B., Lutz X. (2003) *J. Am. Chem. Soc.* **125**, 18, 5264-5265.

APPENDIX

Experimental part

General Considerations

All reactions were carried out using standard Schlenk techniques under an atmosphere of argon. Heptane and 1-hexene were dried and deoxygenated by distillation under argon using the appropriate drying agent. Other chemicals were purchased from commercial sources and used without further purification. The syngas (CO/H_2, 50/50, purity > 99%) used for hydroformylation experiments was purchased from Air Liquide. ^1H and ^{13}C NMR spectra were recorded on a Bruker AC 300 MHz spectrometer. The chemical shifts were measured in ppm relative to CD_2Cl_2 as internal standard. NMR solvent (CD_2Cl_2) was purchased from "Euriso-top" and used as received. The water content of ionic liquid was determined by Karl Fischer coulometry using a "METROHM 756 KF" apparatus. Anolyte and catholyte were "coulomat AG" purchased from Hydranal [41]. The [BuMePyrr][NTf$_2$] (99%) was obtained from Solvionic as a light yellow liquid and used as received. Water content < 50 ppm. The chloride content is given lower than 2 ppm.

Hydroformylation Experiments

In a typical experiment, the automated program starts with a series of nitrogen "pressurization/depressurization" cycles. Each reactor is then charged with desired amount of [$Co_2(CO)_8$] / 2-methoxypyridine / ionic liquid solution. 1-hexene and heptane (co-solvent) are then added to the autoclave. The pressure is raised to 40 bar and the temperature adjusted to 90°C for a pre-activation period of 30 min (no gas consumption was observed during this period). Pressure and temperature were adjusted to the desired values in a second step of the catalytic test. The reaction mixture was then stirred at 1 500 rpm for 1 h and the autoclave maintained at constant pressure until the end of the reaction. The reactor was then rapidly cooled down to room temperature and the CO/H_2 pressure released to atmospheric pressure. Before opening the reactors, nitrogen "pressurization/depressurization" cycles were performed to release any traces of CO. A typical reaction profile is given in Figure A1.
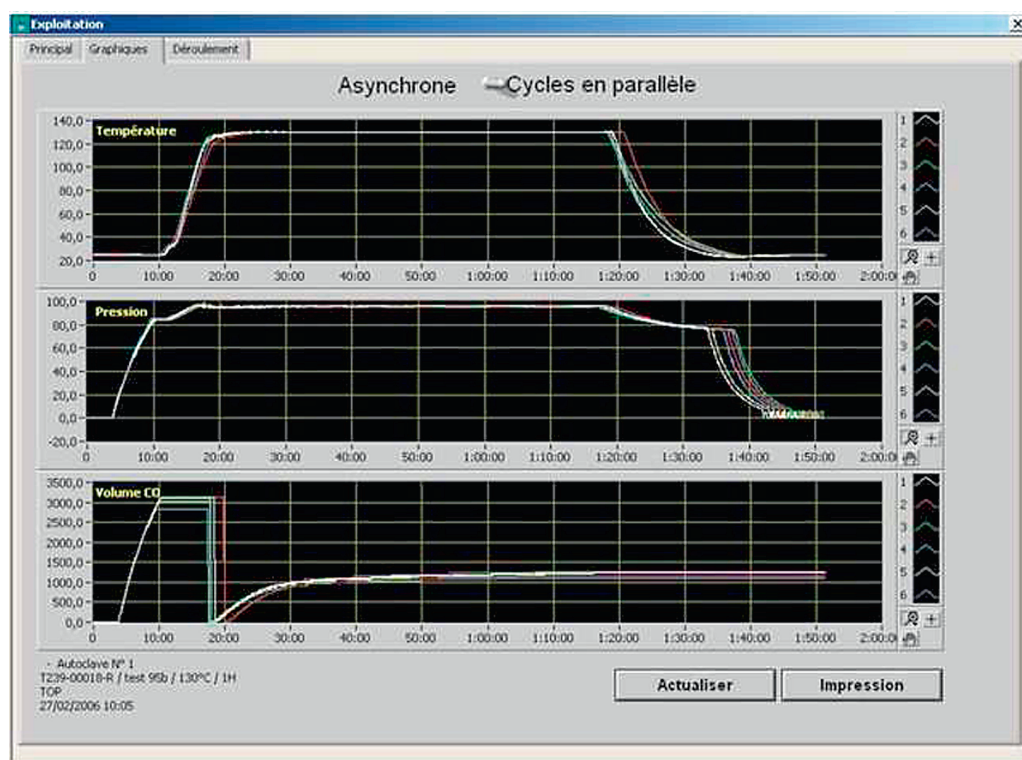

Figure A1

Typical reaction profile.