

TOWARDS AUTOMATED SELF-OPTIMISATION OF CONTINUOUS HETEROGENEOUS CATALYSIS IN SUPERCRITICAL CO₂

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INTRODUCTION

Supercritical fluids (SCFs) have been extensively investigated as alternative solvents for chemical reactions, due to their lower environmental impact and the possibility of tuning their properties by changing the reaction conditions.[1, 2] Using SCFs with continuous heterogeneous catalytic reactions enables facile separation of products from the catalyst and avoids the hazards normally associated with traditional liquid catalysts.[3-5] Continuous reactors can also achieve the same productivity as much larger volume batch reactors; improving safety, allowing for just-in-time manufacture and potentially reducing costs. The reaction factors such as temperature, pressure and residence time can be varied almost independently of each other in a continuous flow process allowing the optimum conditions to be more readily achieved than in the analogous batch process.[3, 6-8]

Over the past 5 years, our group at Nottingham has developed an automated reactor for finding the optimal conditions for heterogeneous catalytic reactions in supercritical CO₂ (scCO₂).[9] This technique relies on using relatively small scale continuous reactors, equipped with in-line monitoring, typically by gas chromatography (GC). The small scale allows steady state to be re-established rapidly after a system perturbation is introduced and in-line monitoring enables the effect of this perturbation on the outcome of the reaction to be determined quickly, without any sample preparation. A typical experiment involves setting several reaction factors to a constant value, and then gradually varying a single factor (e.g. reactor temperature) and taking GC samples periodically to establish the effect of this factor on the reaction. The control of the varied factor and collection of the GC samples are all automated, allowing unattended experiments and the screening of potentially many hundred different conditions without human intervention. This methodology has been applied successfully to several different types of reaction including etherifications,[9-11] aldol condensations[12] and hydrogenations.[13] Figure 1 shows an example of the results which can be obtained from this automated system, as can be seen it is easy to identify the region where the settings for the varied factor maximise the composition of the desired product.

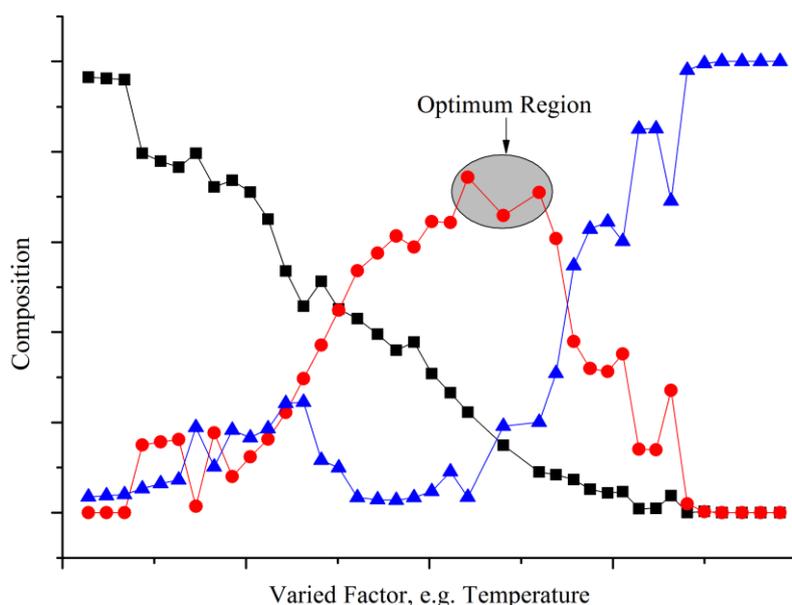


Figure 1. Example results from a typical automated experiment, all conditions are held constant apart from one factor which is changed gradually and its effect on the composition emerging from the reactor bed analysed. \blacksquare Represent the starting material, \bullet and \blacktriangle represent the desired and undesired products respectively, hence the optimal setting for the varied factor is within the shaded region shown as this maximises the composition of the desired product.

Whilst this method gives good information for the factor that is been varied and we have shown that the results are scalable,[14] the information is only valid at the set conditions for the other factors. It is important to also optimise the reaction for the other factors even if a good yield has already been achieved. This is because it allows conditions to be identified which may allow for the same or better yield, but under better process conditions e.g. lower temperature or higher throughput. Also even modest improvements ($\leq 1\%$) to each single step in a multi-step process can have considerable impact upon the overall yield of the target compound, resulting in significant reductions to the amount of wasted material and the cost per mass of final product.[15] The traditional approach to identify these optimal conditions is to run a series of experiments varying one factor at a time. For example, taking the best temperature from Figure 1 and then to set the temperature to this value and vary another factor (e.g. pressure) until the best value for this factor has been found and hold at this value and vary another factor, and so on until all the factors have been investigated as illustrated by Figure 2.

However this “single factor at a time” approach ignores factor interaction, as changes in one factor (e.g. pressure) will affect the response (outcome of the chemical reaction) from changes in another factor (e.g. temperature), as demonstrated by Figure 2. Therefore, to find the true optimum for the system, a multi-factorial approach is required.[16, 17] Evolutionary operation is common way for multi-factorial experiments to be conducted, the general procedure is to conduct a number of experiments at varied conditions and analyse the results. An algorithm is then used to determine which experiments gave the best responses and how to combine characteristics of these conditions to generate new conditions which should give an improved response, further conditions are then generated

by analysing these new conditions and so on until an optimum region of response is found.[16] The simplex optimisation is one of the most efficient, well understood and simplest to calculate evolutionary operation.[17]

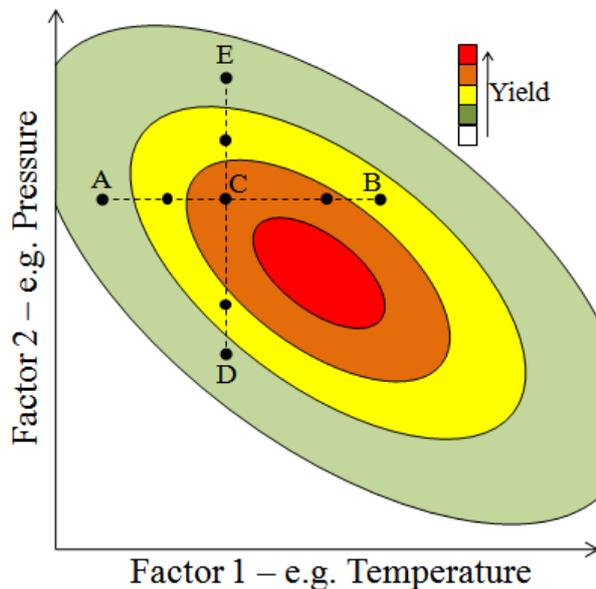


Figure 2. Experimental Path Using a Single Factor at a Time Approach, Based on Walters *et al.*^[16] First factor 2 is set to constant and factor 1 varied between point A and B and point C is identified as the best condition for this Factor. Factor 1 is then set to this value and factor 2 varied between points D and E, which identifies C as the best condition for factor 2. However this method ignores factor interaction and does not investigate the true optimal region in the centre of the figure.

A simplex is a geometric figure which has $f+1$ vertices, where f is the number of experimental factors, therefore if there are two factors then the simplex has three vertices and is a triangle. The response from the system is measured at each of these vertices and then they are ranked from worst to best response. The vertex with the worst response is rejected and the average of the remaining vertices is used to calculate a midpoint, a new point to investigate is then generated by reflecting away from the worst point through this midpoint. The new point and the remaining vertices then make up a new simplex, the response at the new point is measure and the whole process is repeated so that series of simplexes are generated, Figure 3 shows an example of how a two factor simplex is applied. This method forces the process to constantly move in the direction of increasing response and hence move toward the optimum condition.^[16-18] Such a procedure is also useful for dynamic systems where the optimum may change with time, for example if a catalyst was gradually deactivating a simplex procedure could be used to modify the conditions so that the yield is maintained, e.g. by increasing the temperature.^[19]

Even though simplex can be an efficient method, a large number of experiments are still required before the optimum region can be identified, therefore to find this optimum within a useful timeframe and with high enough accuracy a system which can automatically conduct the simplex optimisation procedure is desired.^[15, 20] This paper describes how we

have adapted the automated continuous reactor so that all of the steps of the simplex procedure can be automated, allowing the effect of changing several reaction factors simultaneously to be determined. Using this methodology the reaction optimum can be identified even more rapidly than with our previous techniques.

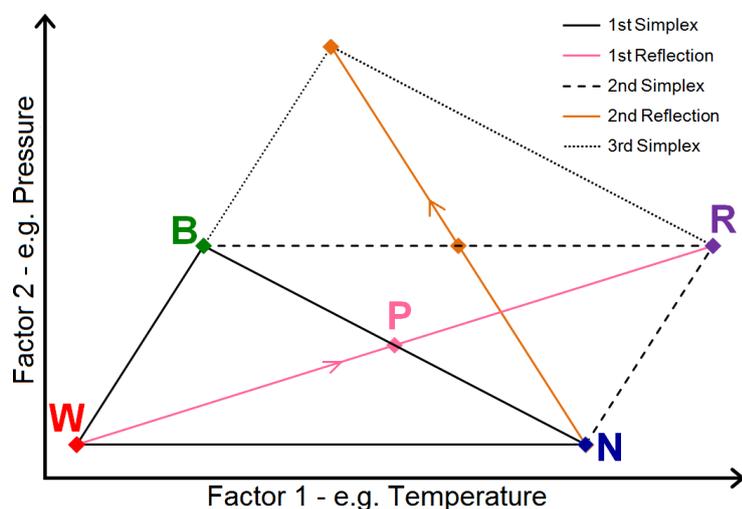


Figure 3. Illustration of a Two Factor Simplex. The initial simplex is made of three vertices which are then ranked in terms of response (e.g. yield), the worst response, **W**, the next worst, **N**, and the best response, **B**. **W** is rejected and a midpoint, **P**, is calculated as the average of the remaining vertices **N** and **B**. A new point to investigate, **R**, is then generated by reflecting away from **W** through **P**. A new simplex is then formed from the vertices **B**, **N** and **R** and the calculation procedure is repeated several times to drive the process towards the optimum conditions.

MATERIALS AND METHODS

Figure 4 shows a simplified schematic of the automated supercritical flow reactor, which is a modified version of the system previously described,[9] it consists of a HPLC CO₂ pump (Jasco PU-1580-CO₂) and HPLC pump (Jasco PU-980) which were connected via a 1/4 inch cross-piece to a 10 mL 316 stainless steel tube (156 mm × 12 mm OD) packed with sand, this tube acts as a mixer and pre-heater, heated by cartridge heaters within aluminium heating blocks. This pre-heater tube is connected to another identical 10 mL tube, also heated by aluminium heating blocks, which was packed with NWA-150 γ -alumina (Supplied by SI group; powder, 150 m²/g surface area and containing trace impurities of SiO₂, Fe₂O₃ and Na₂O). The temperature of the aluminium heating blocks was controlled *via* electronic heating controllers (Eurotherm 2216). The pressure of the system is controlled by a back pressure regulator (BPR) (Jasco BP-1580-81). An inline two position high pressure sample loop (HPSL) (VICI EPCI4W.06, 0.06 μ L, micro-electronically actuated, 250 ms switching time) which was positioned upstream of the expansion system to allow direct sampling of the product stream *via* GC analysis using a Shimadzu GC-14B equipped with a CP-Sil 8 CB column (Varian, 30m, 0.25 mm I.D., 0.25 μ m F.T.) using H₂ carrier gas and a flame ionisation detector. This sampling provides a method to obtain an

instantaneous ‘snapshot’ of the reaction products at the current reactor conditions. The identity of compounds was confirmed by injection of authentic samples and by GC-MS using a Thermo-Finnigan Polaris-Q instrument fitted with a RTX-1MS column (Restek, 30m, 0.25 mm I.D., 0.25 μ m F.T.). Reaction conditions are monitored using a data logger (Picotech TC-08) connected to thermocouples positioned internally and externally on the reactor and to the pressure transducers located within both the HPLC pumps and the BPR.

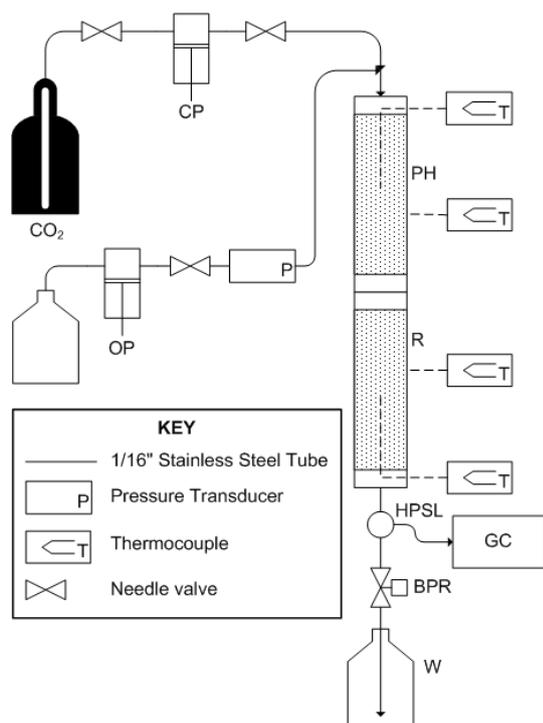


Figure 4. Schematic of the automated supercritical flow reactor developed at the University of Nottingham. The reactant solution and CO₂ are pumped by a HPLC pump (OP) and a chilled CO₂ pump (CP) respectively. The two streams are then mixed in a heated mixing unit (PH) and passed over a heated fixed catalyst bed (R). The system pressure is controlled by a BPR and the products are collected once the pressure is released in a collection vessel (W). Whilst the product stream is flowing from the exit of R to the BPR, the HPSL can remove aliquots of the product mixture and introduce them directly into the carrier gas stream of the GC for analysis.

The major modification from our previous system,[9] is that all the pumps, BPR, heating controllers and the HPSL have all been equipped with RS-232 serial connections. This allowed the development of software within the Matlab (The MathWorks) software environment which can communicate with all the control equipment of the supercritical flow reactor. Therefore it is now possible to monitor and control the reactor over very long time periods and program much more sophisticated experiments. This also enables for the first time with this equipment the possibility of feedback control.

In a typical experiment, the catalyst was loaded in the reactor and sealed into the apparatus. The first of the initial conditions for the first simplex were set at the pumps, BPR and

temperature controllers and the system was allowed to equilibrate over at least 30 minutes. The parameters for the simplex operation were entered into the user interface developed to control the simplex optimisation operations, these parameters include: the initial conditions to test, the system boundaries (usually set by the maximum operating temperature and pressure of the equipment), length of time to wait for steady state, maximum number of calculation, etc. The software would then check if these parameters are valid, for example checking that the test conditions are within the system boundary and do not possess a collinear relationship (tested using a convex hull function within Matlab). This is important because experiments with more than 3 factors it becomes very difficult to visualise the shape of the starting simplex.

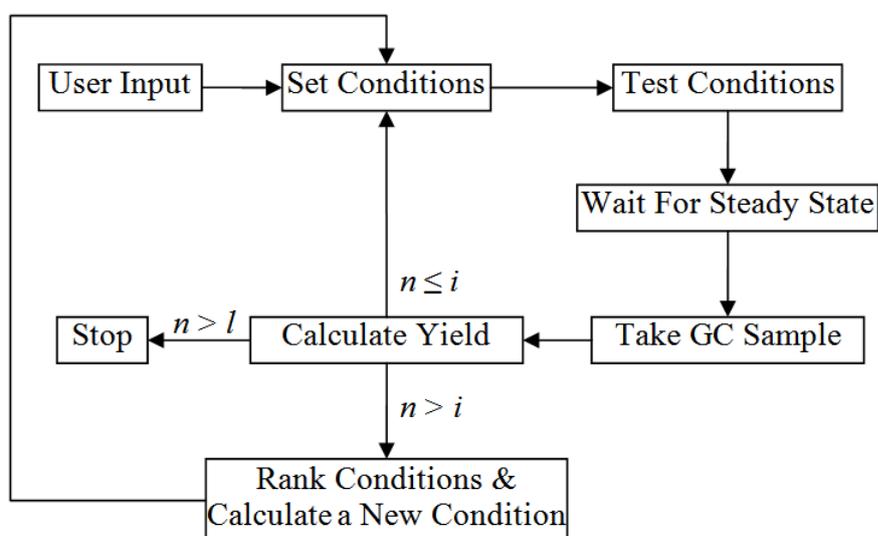


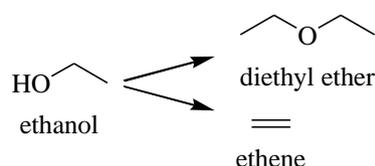
Figure 5. Block Diagram Representing the Automated Simplex Program. First the user inputs the initial conditions and other calculation parameters; the program then sets the first condition to all of the equipment and begins to monitor the process to determine when the system has reached the set conditions. Then the program waits for steady state, after which a GC sample is taken and the yield of the desired compound calculated. If there are more initial conditions then these are set until the first simplex can be formed and a new conditions generated, the process loops until it reaches a preset number of iterations. n is the number of the current iteration, i is the number of initial conditions (equal to $f+1$) and l is the maximum number of iterations.

The automation would then start as illustrated in Figure 5; first the system changes all the setting to those specified and waits until the system reaches these conditions (for the first initial condition this was nearly instant as these conditions used to set up the reactor). The point at which the system reaches the set conditions was determined by the software by monitoring the equipment and determining when the actual process values were within a preset limit away from the actual set point and had been stable for a preset amount of time (preset at the user interface discussed above). The software then would wait the preset steady state time before turning the HPSL to inject a sample onto the GC, simultaneously triggering the temperature program, separately programmed using GCsolution (Shimadzu). The results of that GC sample would be read out from the ASCII file generated by GCsolution into Matlab and the yield of the desired compound determined. This process is

repeated until all of the initial conditions had been tested, the conditions are then ranked and a simplex calculation (as described above) was performed to generate a new condition to be tested. The automation would then continue until either a user interrupted it or the maximum number of simplex calculations had been reached.

RESULTS

To prove the concept of the automated simplex optimisation a series of experiments were conducted to attempt to find the optimum condition for the bimolecular dehydration of ethanol to form diethyl ether over γ -alumina in $scCO_2$, Scheme 1, a reaction we have studied previously in the automated supercritical reactor^[9] and is a well known reaction over this catalyst.^[21, 22] The major by-product from this reaction is ethene which is formed *via* the unimolecular dehydration of ethanol.



Scheme 1. The Dehydration of Ethanol Over γ -Alumina. There are two major products the desired diethyl ether and the undesired ethene.

The first few experiments were used to determine how well the algorithm used to implement the simplex optimisation method performed when applied to a two factor optimisation of temperature (between 100-345 °C) and ethanol flow rate (between 0.05-1 mL/min), with the CO_2 flow set to 1 mL/min and the pressure maintained at 100 bar. These experiments highlighted some improvements to the algorithm which would be necessary before the longer multi-factorial optimisation experiments could be conducted including:

- A method for the size of the simplex to gradually shrink (how far away from the worst vertex the new reflected vertex is), important for converging on the optimum region without an unrealistic amount of experimental conditions.^[16, 17]
- A method to introduce random movements if the calculations get stranded, e.g. if all of the simplex vertices have the same value for one of the factors. This can happen if the new condition is calculated to be set to outside of the boundary set by the user for that factor and therefore has to be rounded up/down to maintain safe operation.

With this improved algorithm the simplex optimisation method was applied to a three-factorial experiment where pressure (70-240 bar), temperature (100-345 °C) and ethanol flow rate (0.05-0.7 mL/min) were optimised and the CO_2 flow rate set to 1 mL/min. The

initial conditions inputted are detailed in Table 1 and Figure 6 shows the results of the simplex procedure. The yield of diethyl ether increased from 0% at the first initial condition (entry A in Table 1) to 68% at 0.4 mL/min ethanol flow, 212 bar and 340 °C. An optimum region of $\geq 67\%$ yield was present between ethanol flow rates of 0.38-0.4 mL/min, pressure of 190-215 bar and temperatures of 335-340 °C.

Table 1. Initial conditions for The Three-Factorial Optimisation of Pressure, Temperature and Ethanol Flow Rate for the Production of Diethyl Ether Over γ -Alumina.

Condition	Ethanol Flow Rate (ml/min)	Pressure (bar)	Temperature (°C)	Yield of Diethyl Ether (%)
A	0.2	240	200	0
B	0.1	150	230	21
C	0.3	200	300	50
D	0.15	210	280	52

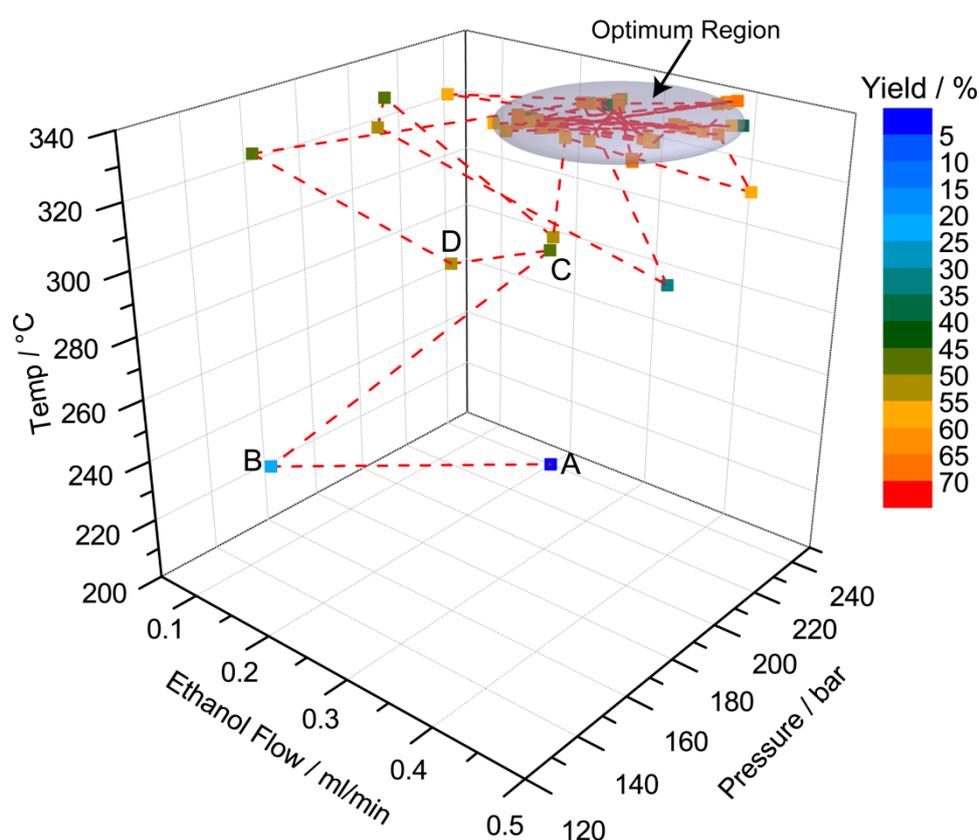


Figure 6. Three-Factorial Optimisation of Pressure, Temperature and Ethanol Flow Rate for the Production of Diethyl Ether Over γ -Alumina. Reactions were performed in continuous flow with a tubular reactor, internal volume 10 mL packed with catalyst. The flow rate of scCO₂ was set to 1.0 mL/min and the pressure, temperature and ethanol flow rate allowed vary between 70-240 bar, 100-345 °C and 0.05-0.7 mL/min respectively *via* computer controlled simplex operations. A, B, C and D mark the initial conditions set for the simplex calculations (see Table 1 for details) and the dashed line shows the experimental route taken by the automated simplex operation.

CONCLUSIONS

A method for automating simplex evolutionary operation optimisation on a continuous flow reactor has been developed. A software algorithm has been written which allows the control and monitoring of all of the process control equipment on the reactor, allowing different conditions to be set automatically, determine when these conditions have been met and then take a GC sample to determine the system response to the change in conditions (change in composition of reagents emerging from the reactor). This has been combined with a simplex calculation which takes the response from several conditions and calculates new conditions to test which moves the system towards an optimum region of response. The method was successfully applied to the two- and three-factorial optimisation of diethyl ether yield from the dehydration of ethanol over alumina, where the varied factors were pressure, temperature and ethanol flow rate with a set CO₂ flow rate.

Work is being currently conducted to apply this technique to more than 3 factors simultaneously and to apply the technique to more challenging chemistry, such as dehydrogenation reactions. The use of alternative evolutionary operations methods such as modified^[23] and super-modified simplex,^[24] which use alternative ways to change the size of the simplex step as the operation progresses, are also being investigated.

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REFERENCES

- [1] M. Araia, S. Fujitaa, M. Shirai, *Journal of Supercritical Fluids*, 47, **2009**, 351.
- [2] B. Subramaniam, C. J. Lyon, V. Arunajatesan, *Applied Catalysis B-Environmental*, 37, **2002**, 279.
- [3] A. Baiker, *Chemical Reviews*, 99, **1999**, 453.
- [4] M. A. Harmer, Q. Sun, *Applied Catalysis A-General*, 221, **2001**, 45.
- [5] P. Barbaro, F. Liguori, *Chemical Reviews*, 109, **2009**, 515.
- [6] R. Ciriminna, M. L. Carraro, S. Campestrini, M. Pagliaro, *Advanced Synthesis & Catalysis*, 350, **2008**, 221.
- [7] J. R. Hyde, P. Licence, D. Carter, M. Poliakoff, *Applied Catalysis A-General*, 222, **2001**, 119.
- [8] G. Jas, A. Kirschning, *Chemistry-a European Journal*, 9, **2003**, 5708.
- [9] B. Walsh, J. R. Hyde, P. Licence, M. Poliakoff, *Green Chemistry*, 7, **2005**, 456.

- [10] P. Licence, W. K. Gray, M. Sokolova, M. Poliakoff, *Journal of the American Chemical Society*, 127, **2005**, 293.
- [11] P. N. Gooden, R. A. Bourne, A. J. Parrott, H. S. Bevinakatti, D. J. Irvine, M. Poliakoff, *Organic Process Research & Development*, 14, **2010**, 411.
- [12] J. G. Stevens, R. A. Bourne, M. Poliakoff, *Green Chemistry*, 11, **2009**, 409.
- [13] R. A. Bourne, J. G. Stevens, J. Ke, M. Poliakoff, *Chemical Communications*, **2007**, 4632.
- [14] P. Licence, J. Ke, M. Sokolova, S. K. Ross, M. Poliakoff, *Green Chemistry*, 5, **2003**, 99.
- [15] M. Harre, U. Tilstam, H. Weinmann, *Organic Process Research & Development*, 3, **1999**, 304.
- [16] F. H. Walters, S. L. Morgan, S. N. Deming, L. R. Parker, *Sequential simplex optimization : a technique for improving quality and productivity in research, development, and manufacturing*, CRC Press, Boca Raton, **1993**.
- [17] D. E. Long, *Analytica Chimica Acta*, 46, **1969**, 193.
- [18] K. W. C. Burton, G. Nickless, *Chemometrics and Intelligent Laboratory Systems*, 1, **1987**, 135.
- [19] W. Spendley, G. R. Hext, F. R. Himsforth, *Technometrics*, 4, **1962**, 441.
- [20] C. J. Welch, X. Y. Gong, J. Cuff, S. Dolman, J. Nyrop, F. Lin, H. Rogers, *Organic Process Research & Development*, 13, **2009**, 1022.
- [21] B. C. Shi, B. H. Davis, *Journal of Catalysis*, 157, **1995**, 359.
- [22] Knözinge.H, *Angewandte Chemie-International Edition*, 7, **1968**, 791.
- [23] E. Morgan, K. W. Burton, G. Nickless, *Chemometrics and Intelligent Laboratory Systems*, 7, **1990**, 209.
- [24] E. Morgan, K. W. Burton, G. Nickless, *Chemometrics and Intelligent Laboratory Systems*, 8, **1990**, 97.