Reaction Optimization

DOI: 10.1002/anie.201100412

Self-Optimizing Continuous Reactions in Supercritical Carbon Dioxide**

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Currently there is considerable interest in the automation of continuous reactors, where the key aim is to create self-optimizing processes. In effect, the reactor and its process control instrumentation become an autonomous unit into which the reactants are pumped, and from which products emerge with optimized yield without requiring any intervention from the operator. The development strategy utilizes reactors, on-line analytical techniques, and control algorithms that are all relatively well known. What is novel is the integration of the three, so that they operate as a single autonomous unit.

For example, Krishnadasan et al.[1] have used an automated microreactor to synthesize CdSe quantum dots. The flow rates of the pumps and the temperature of the reactor were monitored and could be controlled by computer. The same computer also received data from an on-line fluorimeter, the results from which were used to determine the quality of the nanoparticles produced under those reaction conditions. Thus it was possible to construct an automated feedback loop by the sequential application of the stable noisy optimization by branch and fit (SNOBFIT) algorithm to generate the new conditions required to produce nanoparticles continuously that emit with optimal intensity at certain emission wavelengths.

More recently, McMullen et al.[2] used a similar automated and integrated approach for the optimization of a Heck reaction conducted in a microreactor. On-line high-performance liquid chromatography (HPLC) was employed to determine the yield of the product and the Nelder–Mead Simplex (NMSIM) algorithm[3] to generate new conditions to complete the feedback loop.[2] In separate studies, the same group used three different algorithms for the two-parameter optimization of a Knoevenagel condensation reaction and the NMSIM algorithm[3] for the four-parameter optimization of the oxidation of benzyl alcohol to benzaldehyde.[4]

All three of these studies have been carried out in microreactors,[1,2,4] and the application of this approach has been restricted to the very small scale. Furthermore, in each of these cases, the focus has also been limited to a single target product. Only in the Heck reaction did the authors transfer the optimized reaction parameters to a larger reactor. However, their subsequent work to match conditions at two different reactor scales was achieved manually.

In parallel to Krishnadasan et al.,[1] we have been developing a self-optimizing reactor for reactions in supercritical CO_2 ($scCO_2$). We have previously reported the development of an automated reactor for heterogeneous acid catalyzed etherification reactions in $scCO_2$ capable of continuously changing key reaction parameters and monitoring the effect on the reaction outcome by on-line gas–liquid chromatography (GLC).[5] We have since applied this technique to a range of different reactions, such as hydrogenations,[6,7] aldol condensations,[8] and methylations.[9–11]

However, this reactor, like many other automated reactors,[12] uses a univarient approach where only a single variable at a time is adjusted during an experiment. This approach is inherently inefficient, because it does not account for interactions between parameters; rather, a large amount of superfluous data must be collected for every possible parameter combination, to ensure that all the potential reaction environments are covered. Ultimately, a large percentage of the data collected will be redundant.[13,14]

Herein we describe a highly efficient approach to self-optimization of etherification reactions conducted in $scCO_2$ that combines the use of an automated reactor with feedback generated by a Simplex search algorithm. In particular, we demonstrate that it is possible to 1) optimize on the yield of the target product; 2) optimize for multiple products from the same reaction mixture; 3) operate on a larger scale than previous literature reports (ca. 0.1–0.7 kg day^{-1}); and 4) access a wider range of reaction conditions than in the studies discussed above.[1,2,4]

Our reactor (Figure 1) indeed operates like the autonomous unit described above, namely reactant in and product out. HPLC pumps pressurize the reactants and CO_2 which pass through the reactor and the product(s) flow out of the back pressure regulator (BPR). The temperature (controlled by proportional-integral-derivative (PID) heating controllers) is monitored by thermocouples, pressure (controlled by a

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[**] We thank the EPSRC, grant no. EP/D501229/1 (the DICE project), the EU SYNFLOW project, AstraZeneca, and Croda Europe Ltd. for funding. We also thank David Litchfield, James Warren, Peter Fields, Richard Wilson, and Mark Guyler for technical support. We are grateful to Prof. Walter Leitner for suggesting the Simplex algorithm for self-optimization.

Supporting information for this article (including color figures) is available on the WWW under http://dx.doi.org/10.1002/anie.201100412.

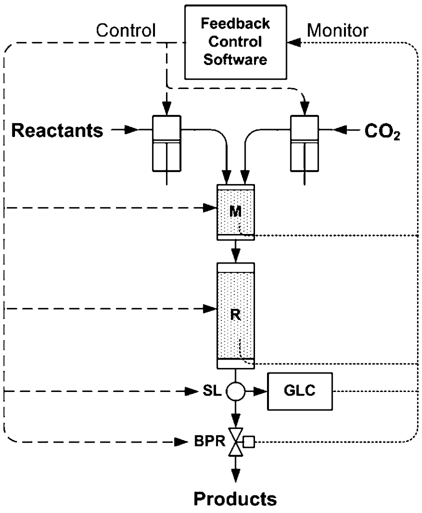
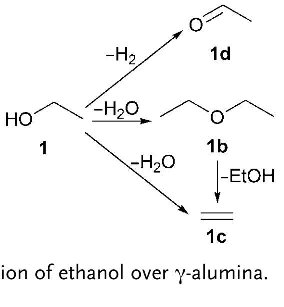


Figure 1. An automated supercritical reactor equipped with software for a controlled feedback loop. The left-hand side indicates the control paths and the right-hand side the reactor monitoring. The reactor comprises a CO_2 HPLC pump and a liquid HPLC pump which feed into a static mixer (M; length 157 mm, 9 mm internal diameter, sand-packed). The material then passes into a tubular fixed bed reactor (R; same dimensions as M, packed with catalyst). The static mixer and reactor were heated by heating cartridges inserted into aluminum heating blocks. The downstream composition of the reactor output was determined by on-line GLC analysis using a high-pressure sample loop (SL). Pressure control was achieved with a back-pressure regulator (BPR) at the outlet of the system. The internal reactor temperature was measured by a thermocouple inserted into the centre of the reactor tube, and pressure by transducers in the BPR.

BPR) by pressure transducers and the product composition by on-line GLC. All these data are used as inputs to the control algorithm, which is based on the super modified simplex (SMSIM) algorithm.[15,16] The algorithm then outputs control signals to vary the temperature, pressure, and the flow rate of the CO_2 pump to maximize the yield of the desired product.

In the experiments described herein, the flow rate of the organic pump was kept constant (0.2 mL min^{-1}) so as to define the flow rate of the reactants and thus the rate at which product is delivered. The feedback control software will be the subject of a future publication.

The first reaction to be optimized was the dehydration of ethanol (**1**) over γ-alumina (Scheme 1). This reaction was chosen because it is well-understood in the literature[17–20] and also formed the basis of the proof-of-concept experiments in the development of our original automated reactor.[5] Furthermore, this reaction was particularly useful for testing the optimization procedure because it produces multiple products, including the desired product diethyl ether (**1b**), ethene (**1c**), and acetaldehyde (**1d**).[18]



Scheme 1. Dehydration of ethanol over γ-alumina.

The SMSIM algorithm requires $n+1$ sets of conditions to optimize n parameters. Thus, as our experiment aimed to optimize three parameters, the algorithm required four predefined starting points. Table 1 lists the parameters and the corresponding yield for these four starting points. The reactor then carried out the optimization, eventually reaching the optimal parameters and yield as shown in the last entry of Table 1.

Table 1: Initial parameters (runs 1–4) and optimal conditions for the three-parameter optimization of **1b** yield from the dehydration of **1**.

Run	Yield of **1b** [%]	CO_2 flow [mL min^{-1}]	T [°C]	P [bar]
1	1.8	0.88	200	150
2	1.6	1.10	200	150
3	0.0	0.99	228	150
4	2.8	0.99	209	158
optimal	75.4	0.88	314	189

Figure 2 and Figure 3 show different representations of the same optimization pathway, which improved the yield of **1b** from 2% to 75%, with a selectivity of 86%. The algorithm stops the optimization process at only 87% conversion of **1** because changing the parameters further to increase the conversion (for example by increasing the temperature) also reduces the selectivity to **1b** and increases the formation of by-products.

This result establishes that the automated reactor combined with the SMSIM algorithm can successfully optimize a simple multi-component system. Therefore, a more complex

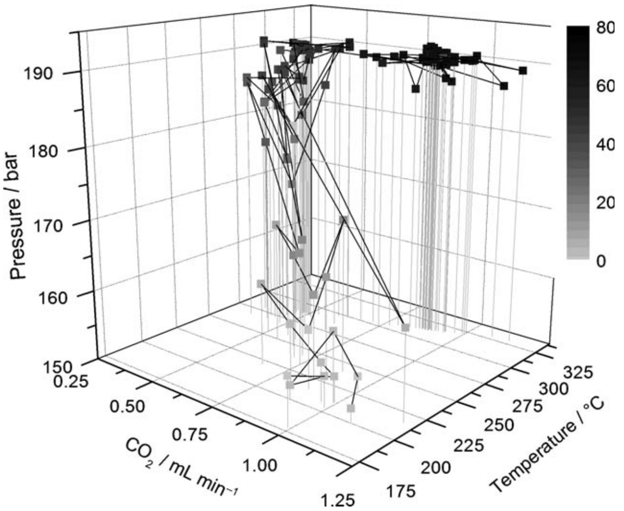


Figure 2. The optimization pathway for **1b** from the acid-catalyzed dehydration of **1** with three parameters: CO_2 flow, temperature, and pressure. The optimization search route was determined by the SMSIM algorithm. The shading of each point indicates the percentage composition of **1b** in the product stream, which increased from 2% to 75% during the optimization process.

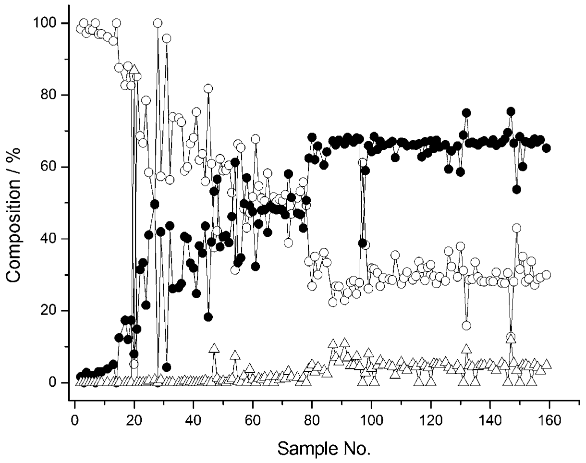
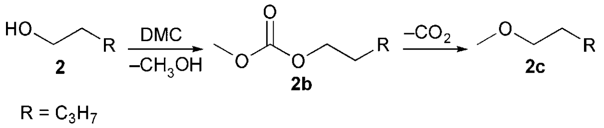


Figure 3. Composition of the output stream determined by GLC analysis for a run during the optimization for **1b**. ○ starting material **1**, ● desired product **1b**, △ by-products.

multiple component reaction optimization was attempted. The reaction of an aliphatic alcohol with dimethyl carbonate (DMC) which was chosen for study because: 1) DMC can replace toxic methylating reagents, such as methyl halides,[21–27] and 2) we have recently reported the continuous synthesis of methyl ethers from aliphatic alcohols using DMC with $scCO_2$ and γ-alumina as a catalyst.[10,11] However, whilst we reported that a high yield of methyl ethers could be achieved, we found that the reaction could also give rise to several different products.

Initially, our aim was to optimize for the carboxymethylation reaction of DMC with 1-pentanol (**2**) to produce methyl pentyl carbonate (**2b**) using a 1:1 molar mixture of **2** and DMC (Scheme 2). The starting conditions used were those that had been found to give significant yields of **2b** previously.[10] Table 2 lists the starting conditions and the optimized yield of **2b**, while Figure 4 shows the optimization pathway. The optimization produced only a moderate improvement compared to the starting conditions, which has been attributed to the fact that **2b** is an intermediate product. However, it can be seen that the algorithm carried out a broad exploration of reaction space such that this optimization pathway was certainly more efficient and more cost-effective than would be achieved by manual operation.



Scheme 2. Reaction of dimethyl carbonate (DMC) with **2** to give **2b** and **2c**.[10,11]

Table 2: Initial parameters (runs 1–4) and optimal conditions for the three-parameter optimization of **2b** yield from the reaction of **2** with DMC.

Run	Yield of **2b** [%]	CO_2 flow [mL min^{-1}]	T [°C]	P [bar]
1	20.2	0.80	150	90
2	18.9	1.01	150	90
3	19.2	0.91	177	90
4	22.7	0.91	159	108
optimal	36.9	0.78	165	146

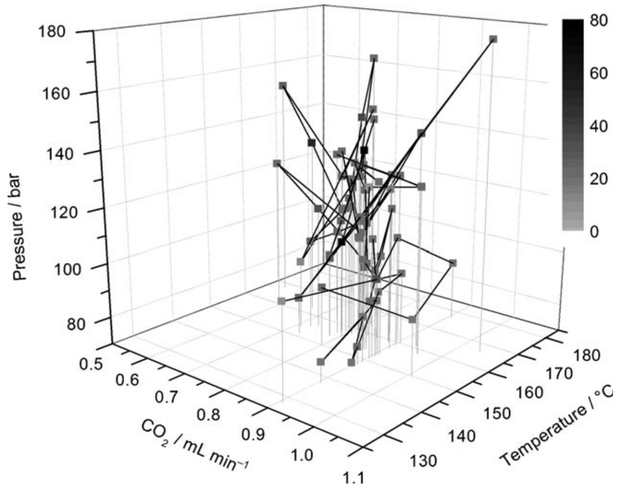


Figure 4. Three-parameter optimization pathway for **2b** from the reaction of **2** with dimethyl carbonate (DMC). Optimization search route determined by the SMSIM algorithm. The shading of each point represents the percentage composition of **2b** in the product stream, which increased from 20% to 30% during the optimization routine.

The optimization of the reaction to maximize the yield of 1-methoxypentane (**2c**) was then attempted (Table 3, Figure 5). It is clear that this optimization was more successful than the **2b** case and the maximum yield achieved was 70%. The algorithm also explored a significantly different volume of parameter space in this latter case than it did when the target was **2b**.

Table 3: Initial parameters (runs 1–4) and optimal conditions for the three-parameter optimization of **2c** yield from the reaction of **2** with DMC.

Run	Yield of **1b** [%]	CO_2 flow [mL min^{-1}]	T [°C]	P [bar]
1	47.3	0.80	200	100
2	12.7	1.01	200	100
3	49.6	0.91	222	100
4	49.6	0.91	207	116
optimal	69.7	0.91	267	116

The optimizations in Figure 4 and 5 each took about 35 h to complete, which is far less than the time required to cover the same volume of parameter space with our previous automated reactor. For example, if the reaction parameter space was split into 10 values of CO_2 flow rate and 10 values of reactor pressure, and a standard temperature ramp (100 °C to 300 °C, 20 h duration) was conducted to cover all combinations, it would therefore require 100 temperature ramps, taking more than 83 days and providing an accuracy of about ± 0.1 mL min^{-1} and ± 6 bar. However the rate of optimization

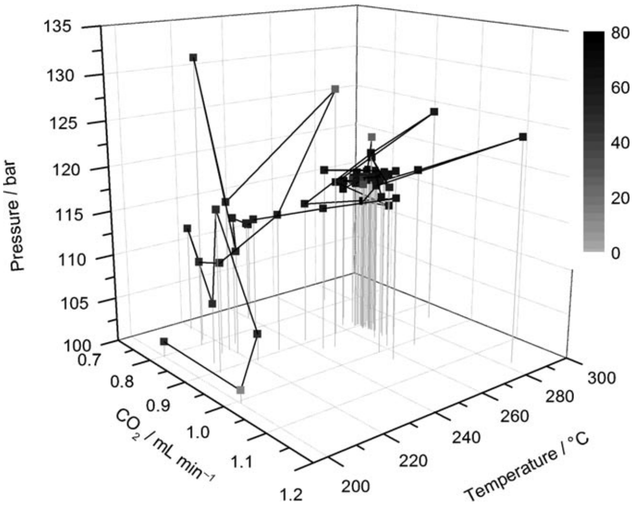


Figure 5. Three-parameter optimization trajectory for **2c** from the reaction of **2** with DMC. The optimization search routine was determined by the same algorithm as in Figure 4. The shade of each point represents the percentage composition of **2b** in the product stream, which increased from 48% to 70% during the optimization process.

with the new feedback reactor is primarily determined by the thermal characteristics of the reactor itself and the time required for analysis. Therefore, the procedure could be further accelerated by engineering development of the reactors and faster analytical techniques.

In conclusion, we have demonstrated the first self-optimizing $scCO_2$ reactor on a scale that is considerably larger than those used in previous studies with self-optimizing reactors in conventional solvents.[1,2,4] This work represents a significant step forward in the use of optimization algorithms. Self-optimization is particularly important for $scCO_2$ reactors because the highly compressible nature of the solvent introduces an extra dimension into parameter space compared to more conventional solvents. We have also shown that conditions can be optimized for more than one product from the same reaction mixture.

Our approach has been based on the use of the SMSIM algorithm, but the method is in no way restricted to a particular algorithm. In fact, our prototype operated using the modified Simplex routine.[28–30] The experiments have been optimized for the maximum yield of a product. However, there is no reason why the reactor could not be optimized for different criteria; other objective functions could include maximizing or minimizing the ratio of two products, or minimizing the production of a troublesome by-product. Indeed, in the context of sustainable chemistry, it might even be possible to minimize the E factor, namely the number of kilograms of waste per kilogram of product.[31–33]

Experimental Section

Experiments were conducted in the reactor shown in Figure 1. In each experiment the flow rate of the organic substrates was set to a constant 0.2 mL min^{-1} and the values for other parameters were set at the first condition. The reactor was allowed to stabilize for at least 15 min before the GLC analysis commenced. Once GLC analysis was complete the algorithm would calculate the values for the next condition and send control signals to the equipment. The coordinates for the initial four conditions were calculated to produce a regular tetrahedron with the distance between each experiment being 25% of the total range between the first experiment and the maximum boundary condition for that parameter. All command and monitoring signals were communicated via RS-232 connections and all the software was written in Matlab, apart from the commercial software for controlling the Shimadzu GLC (GCSolution).

Optimization for **1b**: Ranges allowed CO_2 flow rate 0.35–1.77 mL min^{-1}, reactor temperature 100–330 °C and reactor pressure 70–190 bar, GLC analysis time was 5 min.

Optimization for **2b** and **2c**: Ranges allowed CO_2 flow rate 0.15–1.62 mL min^{-1}, reactor temperature 100–275 °C (300 °C for **2c**) and reactor pressure 70–180 bar, GLC analysis time was 17.5 min.

Received: January 17, 2011

Keywords: alkylation · heterogeneous catalysis · reaction optimization · supercritical fluids · sustainable chemistry

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[1] S. Krishnadasan, R. J. C. Brown, A. J. Demello, J. C. Demello, *Lab Chip* **2007**, *7*, 1434–1441.
[2] J. P. McMullen, M. T. Stone, S. L. Buchwald, K. E. Jensen, *Angew. Chem.* **2010**, *122*, 7230–7234; *Angew. Chem. Int. Ed.* **2010**, *49*, 7076–7080.
[3] J. A. Nelder, R. Mead, *The Computer Journal* **1965**, *7*, 308–313.
[4] J. P. McMullen, K. F. Jensen, *Org. Process Res. Dev.* **2010**, *14*, 1169–1176.
[5] B. Walsh, J. R. Hyde, P. Licence, M. Poliakoff, *Green Chem.* **2005**, *7*, 456–463.
[6] R. A. Bourne, J. G. Stevens, J. Ke, M. Poliakoff, *Chem. Commun.* **2007**, 4632–4634.
[7] J. G. Stevens, R. A. Bourne, M. V. Twigg, M. Poliakoff, *Angew. Chem.* **2010**, *122*, 9040–9043; *Angew. Chem. Int. Ed.* **2010**, *49*, 8856–8859.
[8] J. G. Stevens, R. A. Bourne, M. Poliakoff, *Green Chem.* **2009**, *11*, 409–416.
[9] P. Licence, W. K. Gray, M. Sokolova, M. Poliakoff, *J. Am. Chem. Soc.* **2005**, *127*, 293–298.
[10] P. N. Gooden, R. A. Bourne, A. J. Parrott, H. S. Bevinakatti, D. J. Irvine, M. Poliakoff, *Org. Process Res. Dev.* **2010**, *14*, 411–416.
[11] A. J. Parrott, R. A. Bourne, P. N. Gooden, H. S. Bevinakatti, M. Poliakoff, D. J. Irvine, *Org. Process Res. Dev.* **2010**, *14*, 1420–1426.
[12] J. P. McMullen, K. F. Jensen, *Annu. Rev. Anal. Chem.* **2010**, *3*, 19–42.
[13] F. H. Walters, L. R. Parker, S. L. Morgan, S. N. Deming, *Sequential Simplex Optimization*, CRC, Boca Raton, **1991**.
[14] D. E. Long, *Anal. Chim. Acta* **1969**, *46*, 193–206.
[15] M. W. Routh, P. A. Swartz, M. B. Denton, *Anal. Chem.* **1977**, *49*, 1422–1428.
[16] E. Morgan, K. W. Burton, G. Nickless, *Chemom. Intell. Lab. Syst.* **1990**, *8*, 97–107.
[17] K. Sohlberg, S. J. Pennycook, S. T. Pantelides, *Chem. Eng. Commun.* **2000**, *181*, 107–135.
[18] H. Knözinger, *Angew. Chem.* **1968**, *80*, 778–792; *Angew. Chem. Int. Ed. Engl.* **1968**, *7*, 791–805.
[19] B. C. Shi, B. H. Davis, *J. Catal.* **1995**, *157*, 359–367.
[20] C. W. Seo, K. D. Jung, K. Y. Lee, K. S. Yoo, *Ind. Eng. Chem. Res.* **2008**, *47*, 6573–6578.

[21] P. Tundo, M. Selva, *Acc. Chem. Res.* **2002**, *35*, 706–716.
[22] P. Tundo, S. Memoli, D. Herault, K. Hill, *Green Chem.* **2004**, *6*, 609–612.
[23] P. Tundo, F. Arico, A. E. Rosamilia, S. Memoli, *Green Chem.* **2008**, *10*, 1182–1189.
[24] A. A. G. Shaikh, S. Sivaram, *Chem. Rev.* **1996**, *96*, 951–976.
[25] Y. Fu, T. Baba, Y. Ono, *Appl. Catal. A* **1998**, *166*, 419–424.
[26] Y. Ono, *Pure Appl. Chem.* **1996**, *68*, 367–375.
[27] Y. Ono, *Appl. Catal. A* **1997**, *155*, 133–166.
[28] A. J. Parrott, Ph.D. thesis, The University of Nottingham, **2011**.
[29] A. J. Parrott, R. A. Bourne, D. J. Irvine, M. Poliakoff in *12th European Meeting On Supercritical Fluids*, I.S.A.S.F., Graz, Austria, **2010**.
[30] A. J. Parrott, R. A. Bourne, D. J. Irvine, M. Poliakoff in *1st PACN Green Chemistry Congress*, RSC, Addis Ababa, Ethiopia, **2010**.
[31] R. A. Sheldon, *Green Chem.* **2007**, *9*, 1273–1283.
[32] R. A. Sheldon, *Ind. Environ. Chem.* **1992**, 99–119.
[33] R. A. Sheldon, *Chem. Ind.* **1992**, 903–906.