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COMMUNICATION

Definitive screening designs for multistep kinetic models in flow

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Currently, rate-based understanding of organic reactions employed in the manufacture of active pharmaceutical ingredients (APIs) is often not obtained. In many cases, the generation of kinetic models is still seen as a specialised and time intensive activity, which can only be justified at certain instances in development. In this Communication, we report the application of a definitive screening design (DSD) in combination with reaction profiling for the efficient collection of kinetic data. The experimental data (10 profiles, 40 experimental data points) were collected within a short time frame (<1 week) within a continuous flow reactor. The data were fitted to a multistep kinetic model consisting of 3 fitted rate constants and 3 fitted activation energies. The approach is demonstrated on a Friedel-Crafts type reaction used in the synthesis of an important API. Our approach enables early identification of the sensitivity of product quality to parameter changes and the early use of process models to identify optimal process-equipment combinations in silico, significantly reducing development time and scale-up risks.

Over the past 10 to 15 years continuous processing has started to transform the discovery and manufacture of active pharmaceutical ingredients (APIs).[1] This paradigm shift is reflected by a new focus in the pharmaceutical industry on process intensification, sustainability, product quality, safety, energy usage and cost.[2] However, given the relative infancy of continuous processing within the pharmaceutical sector in comparison to batch processing, there is no well-established process development strategy which is used throughout the industry for the development of flow processes.[3] The bulk and commodity chemicals sector predominately uses continuous processing for the manufacture of low value, high volume products, and the corresponding production plants are generally designed and engineered as dedicated continuous processes.[4] In contrast, pharmaceutical manufacture uses more complex synthesis steps for the preparation of high value, low volume products. The approach used in the bulk and commodity chemical sectors for reaction scale-up is to obtain the process rates at the small-scale then the understanding and predictive models generated are used to determine the optimal operating conditions and equipment configuration to be used for manufacture.[5] Process rate models are generated to describe the rate determining chemical kinetics and heat and mass transfer. Scale-up by using such models significantly reduces the risk when compared to directly transferring laboratory conditions to a plant scale with the implicit assumption that the same performance will be observed.[6]

In the context of pharmaceutical development, experimentation stops at the degree of detail allowed by time and financial constraints.[7] A rate-based approach for scale-up is seldom used by the pharmaceutical manufacturing sector, with one-variable-at-a-time (OVAT) and design of experiments (DoE) approaches favoured for the optimization of many processes.[8] The goal of statistical experimental design is to evaluate the system behaviour in a structured manner, thus minimising the total number of experiments and therefore reducing effort and increasing developer confidence. The output is a polynomial model which describes the influence of input parameters on a response and is predictive only within the experimental envelope explored. Statistical optimisation approaches, such as design of experiments (DoE)[8] and numerical self-optimizing systems,[9] are used to understand the sensitivity of response *y* (e.g., conversion, yield, purity) to variation of input parameter *x* (e.g., temperature, concentration), and then to optimise the operating conditions within the experimental envelope covered. These techniques optimize the chemistry for the specific equipment and scale used, but do not reveal an explanation as to why a response is dependent on a particular input parameter.[10] Thus, the model does not necessarily accurately predict reaction performance in different reactor

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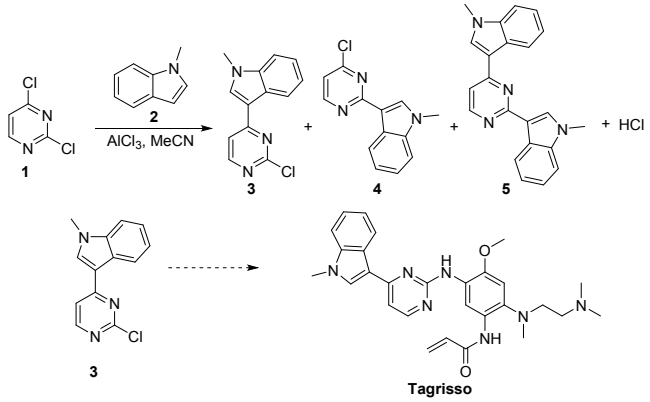
types, scales nor can it indicate potentially interesting conditions to explore outside the study space.

The measurement of the reaction kinetics can be decoupled from transport processes and heat transfer by using small scale flow systems.[11] Small length scales make isothermal temperature control possible for exothermic and endothermic reactions. Microreactor systems have been reported for rapid experimental data collection for the generation of kinetic models,[12] however most examples focus on the measurement of a single rate-determining step.[13] A limited number of examples examine multistep sequences; these studies usually isolate individual reaction steps to deconvolute the reaction kinetics, thus requiring more experimental effort.[14] One example not requiring the isolation of individual steps was reported by Jensen and co-worker. They fitted two *a priori* rate expressions to a Paal–Knorr pyrrole reaction after using an exponential flow ramp with online infrared spectroscopy to collect experimental data.[15] More recently, Lapkin and co-workers reported an automated continuous flow platform for the prediction of kinetic parameters for a C-H activation mechanism by using a model-based Design of Experiments.[16] In another recent example by our group, transient data were collected which explored a wide input parameter space. The data were used to identify parameters to discriminate between several model structures and to identify parameters for four *a priori* rate expressions without isolating individual rate-determining steps.[17]

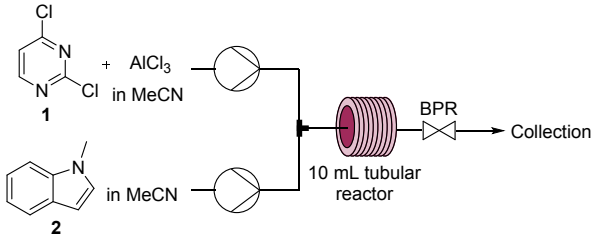
In this Communication, a definitive screening design (DSD) is shown to provide an efficient approach to explore the experimental design space for the generation of a multistep kinetic model. Subsequently, the generated model can be applied in silico to simulate alternative scenarios and optimise equipment configurations and process conditions so as to achieve significant reductions in scale up risks and costs. Jones and Nachtscheim proposed the definitive screening design, a three-level non-linear approach to explore parameter space.[18,19] Three-level definitive screening designs are particularly relevant for investigating chemical reaction systems which almost always display non-linear behaviour. For instance, temperature dependence of reaction rate typically obeys the non-linear Arrhenius relationship. The design is orthogonal and all main effects and quadratic effects are estimable. Although there is some correlation of quadratic effects to interaction effects. The number of experiments, N_{exp}, is twice the number of factors, m, plus an additional centre point experiment for measurement of experimental error (2m+1), therefore it is the most efficient design for modelling linear and quadratic effects. Our hypothesis is that a DSD combined with reaction profiling would be an effective experimental design methodology to collect data to underpin the generation of kinetic models.

There is an absence of quantitative data for systems under Friedel–Crafts type conditions within the literature, with most remaining qualitative.[20,21] The approach outlined in this Communication is illustrated using an $AlCl_3$-promoted reaction of 2,4-dichloropyrimidine (2,4-DCP) **1** with 1-methylindole (Me-Ind) **2** in acetonitrile (MeCN) to give a mixture of desired product 4-substituted **3**, and 2-substituted **4** and *bis*-adduct **5** as side products (Scheme 1). The desired product **3** is an early intermediate in the manufacture of Tagrisso (AZD9291, osimertinib), a selective epidermal growth factor receptor (EGFR) inhibitor for non-small cell lung cancer (NSCLC).[22,23] Isomer **4** is the impurity which causes the most problems downstream due to it sharing similar physical properties with the desired product **3**. We were interested in identifying conditions that would give close to quantitative conversion of starting material **1** and maximise the yield of **3** whilst minimising the formation of isomer **4**.[24]



Scheme 1. $AlCl_3$-promoted reaction of 2,4-dichloropyrimidine (2,4-DCP) **1** and 1-methylindole (Me-Ind) **2** towards Tagrisso (AZD9291, Osimertinib).

A Vapourtec E-series flow reactor system was configured according to Fig. 1 in order to study the influence of four input parameters on reaction rate and selectivity: (i) 2,4-DCP **1** concentration, (ii) Me-Ind **2** molar equivalents, (iii) $AlCl_3$ molar equivalents and (iv) temperature. The parameter design space explored in this four-factor DSD study is shown in Scheme 2.



Scheme 2. Small-scale continuous-flow reactor system. Vapourtec E-series flow reactor system comprising of two peristaltic pumps for pumping the two feed solutions into a T-piece for mixing prior to a heated reactor coil (PFA coil, 10 mL internal volume, 0.1 mm internal diameter). The internal reactor temperature was measured by using a thermocouple inserted into the centre of the reactor. Pressure control was achieved with a back-pressure regulator (BPR) at the outlet of the system. Aliquots of neat reaction were diluted with acetonitrile before analysis by ultra-performance liquid chromatography (UPLC).

A numerical algorithm maximizes the determinant of the information matrix to construct the DSD. Further details of the design construction can be found in reference 18a. The parameter level ranges were selected to strain the system, thus to establish a broad experimental envelope for the kinetic model which would be used for reaction optimisation (Table 1).

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Experiments were conducted to generate a series of concentration-time profiles for the definitive screening design experiments listed in Table 1, giving a total of 9 profiles (+1 profile for a centre point repeat). Four residence time points were collected per profile providing 40 experiments in total. The centre point repeat was used to evaluate experimental error.

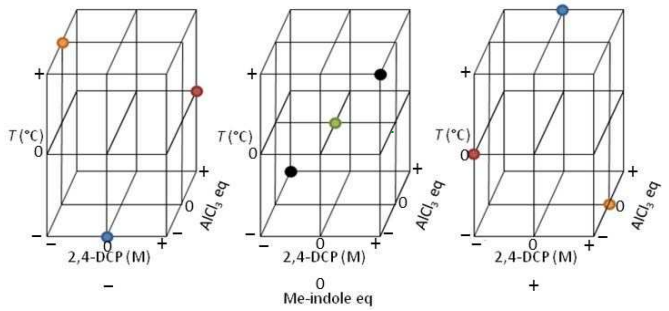


Figure 1. Three-level definitive screening design for four factors. Each circle represents an experiment listed in Table 1.

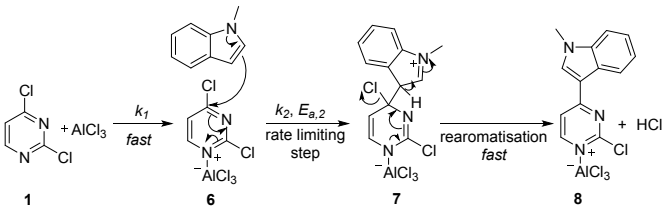
Table 1. Definitive screening design matrix.[a]

Exp.[b]	Levels[c]	*T* (°C)	2,4-DCP **1** (M)	Me-Ind **2** mol eq	$AlCl_3$ mol eq
1[d]	0000	100	0.40	1.11	1.1
2	+0++	120	0.40	1.41	1.5
3	−0−−	80	0.40	0.81	0.7
4	+−0−	120	0.33	1.11	0.7
5	−+0+	80	0.47	1.11	1.5
6	−−+0	80	0.33	1.41	1.1
7	++−0	120	0.47	0.81	1.1
8	0++−	100	0.47	1.41	0.7
9	0−−+	100	0.33	0.81	1.5

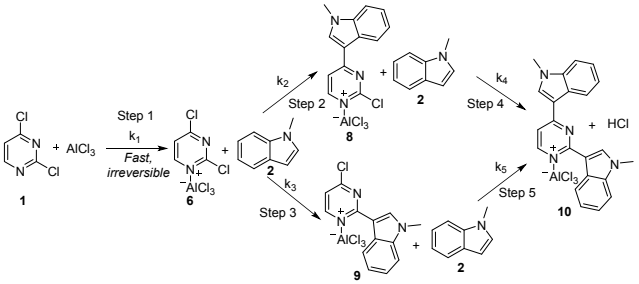
[a] Input parameter levels and conditions. [b] The experimental order was randomized and four residence time points were collected for each set of experimental conditions. [c] Levels: − = low point value, 0 = mid-point value, + = high point value. [d] The centre point experiment was conducted twice.

The complete dataset was used to fit a range of kinetic motifs (DynoChem software, Scale-up Systems). The motifs differed in the order with respect to compounds **1, 2, 6, 8, 9** and $AlCl_3$ and all 9 profiles were simultaneously fitted with the Levenburg-Marquardt algorithm to successive postulated kinetic motifs. Subsequently, the model fits were assessed through a series of statistics to identify the optimal kinetic model (Table S2). The reaction displaying second order kinetics, first order with respect to the Me-Ind **2** and first order in the complex **6**, with the rate-determining step as bimolecular nucleophilic attack of Me-Ind **2** on to the complex, displayed the best fit to the experimental data, see Schemes 3 and 4. The best fitting model structure is in-line with expectations based on the literature data available.[25] Molecular dynamic simulations had indicated that 2,4-DCP **1** in the presence of $AlCl_3$ forms complex **6**, with coordination of $AlCl_3$ to the N-1 position. Coordination at the N-3 position is unfavourable, because within the N-3 complex there is strong repulsion from unavoidable interaction between Cl atoms on $AlCl_3$, therefore this species is less likely to form.[26] The chlorine atom at C-4 becomes more labile due to the electron withdrawing effect involving both the nitrogen atoms through mesomeric effects and hence is more reactive to a nucleophile.

Step 1 was fixed and assumed to be fast and irreversible. $AlCl_3$ was pre-mixed with dichloropyrimidine **1**, so this could have allowed for pre-complexation to form complex **6**. Step 2, to complex **8**, is dominant and its activation energy was higher than for the isomer **9** formation, with E_{a2} and E_{a3} at 88.2 kJ mol^{-1} and 73.2 kJ mol^{-1} respectively. All the uncertainties were less than 6% for the monosubstitution pathways (Table 2). The *bis* complex **10** was formed in larger quantities using more aggressive reaction conditions (higher temperature and higher molar equivalents of Me-Ind **2**). The data indicates that **10** is formed via step 5. Desired complex **8** appears to have a low reactivity (step 4). More aggressive, or longer experiments are required to confirm if this pathway was not occurring or just very slow. The formation of the *bis* complex **10** via step 5 has a significantly higher activation energy, 128.4 kJ mol^{-1}, compared to the pathways to product **8** and isomer **9**. The kinetic model gave a reasonable fit to all the experimental data, corresponding to a R^2 of 0.861 (Figure 2). Previously, we reported a method to measure the dispersion effect on the measured rate constants.[14] The same procedure was used to assess the impact of dispersion on the second order rate constants for the $AlCl_3$-promoted system, and the error in the observed rate constants due to dispersion showed an error of 4% or lower.



Scheme 3. Proposed $AlCl_3$-promoted reaction mechanism.



Scheme 4. $AlCl_3$-promoted reaction network.

Table 2. Kinetic parameter estimates and standard errors (SE) based on 95% confidence level. Rate constants, *k*, and given at T_{ref} = 100 °C. R^2 = 0.861 σ = 0.212.

	$k \pm$ SE (10^{-3} M^{-1} s^{-1})	$E_a \pm$ SE (kJ mol^{-1})
Step 1	2000 M^{-1} s^{-1} (fixed)	
Step 2	6.20 ± 0.39 M^{-1} s^{-1}	88.2 ± 4.0 kJ mol^{-1}
Step 3	1.60 ± 0.09 M^{-1} s^{-1}	73.2 ± 4.2 kJ mol^{-1}
Step 4	Converged to zero	Converged to zero
Step 5	0.61 ± 0.07 M^{-1} s^{-1}	128.4 ± 9.4 kJ mol^{-1}

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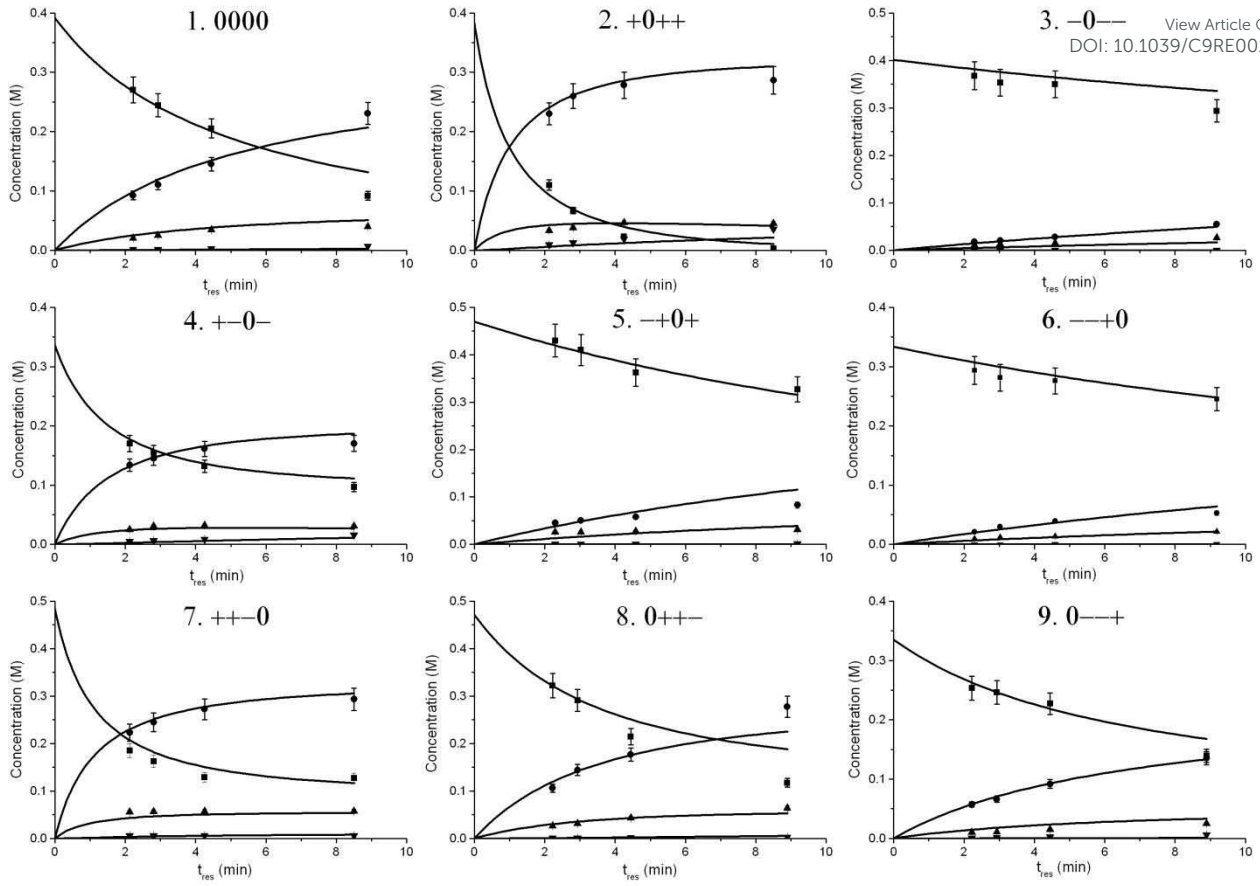

Figure 2. Concentration-time profiles from simultaneous parameter fitting, points = experiments ■ 2,4-DCP **1**, ● Product **3**, ● Isomer **4**, ▼ *bis*-**5**, lines = model predicted using Table 2 kinetic parameter estimates. See Table S1 for raw experimental data.

In order for a process developer to have confidence in a model, they require it to: (a) represent the data observed over a wide range of conditions; and (b) not contravene prior art and experience, unless data are extensive and very convincing. In the case presented here, most data closely matched the second order rate model and the proposed model was generated from a set of motifs that are consistent with prior art. Thus, the confidence in the model is sufficient for utilization in process design. Closer inspection shows that (i) the model deviates more at the longer residence times, and (ii) the decrease in 2,4-DCP **1** was almost linear down to the longest residence time in some cases. These observations may suggest possible alternative motifs such as those involving the regeneration of $AlCl_3$ or the effect of acidity.

Nonetheless, the overall dataset appears to be well fitted and the parameter uncertainty is relatively small (Table 3). Thus, the design space was visualised through computational simulation, see Fig. 4. The simulations demonstrated that the highest isomer **4** levels are predicted at 90 °C, with more elevated temperatures resulting in a reduction in isomer **4** levels since it is then readily converted to the *bis*-indole product **5**. Thus, the best compromise for the formation of **3** in good yields, and very little of **4**, was identified as by using forcing conditions to cause the overreaction of species 4 to dimer **5**. Dimer **5** was preferred in place of isomer **4** because it causes fewer problems downstream in terms of reactivity and purification. Based on the kinetic model obtained, we should be able to obtain a realistic prediction of reaction outputs at any reaction time. However, we selected to simulate the optimisation within the experimental space explored to increase the likelihood of success. The use of a relatively short residence time (<10 min) also allows for a higher throughput of material. Our goal was a multi-objective target: (1) provide >98% starting material consumption, (2) maximise desired yield of product **3** and (2) minimise the yield of isomer **4**. Simulation of the kinetic model determined the optimal operating conditions to be: 110 °C, 1.6 molar equivalents of 1-methylindole **2**, a small excess of $AlCl_3$ (1.1 mol eq) with a 9 min residence time gives model predicted 99% conversion, desired product yield of 82% and 7% of **4.** A validation experiment at these conditions resulted in 80% UPLC yield and 69% isolated yield after purification by column chromatography, which was comparable to the yield obtained under optimised batch conditions.[24]

Table 3. Assessment of confidence in the selected kinetic motif and model.

Number of experiments	36 (+4 for error bars)
Number of data points	144
Number of fitted reactions	4
Number of parameters fitted	6

Relative error in parameter fitting	≤ 6%
Degrees of freedom	138
R^2	0.861

Conclusions

A continuous flow reactor was used to collect experimental data in a combined DSD and reaction profiling approach. The experimental data generated was fitted to different model structures. The fitted kinetic model consisted of 3 reactions, 6 fitting parameters, with less than 6% uncertainty. A definitive screening design provides an efficient approach for exploring non-linear behaviour within the design space. With 40 experiments conducted, there is extra experimental effort comes from the combined DSD and reaction profiling approach when compared to a standard experimental design approach. However, this extra experimental effort is minimal compared to subsequently undertaking a study a separate study for the measurement of reaction kinetics. The approach allows for rate-based understanding to be obtained earlier than usual in the development, with the ability to evaluate and validate different kinetic models, thus improving developer confidence for scale-up. The generated kinetic model was used in silico to identify the optimal operating conditions which was successfully validated.

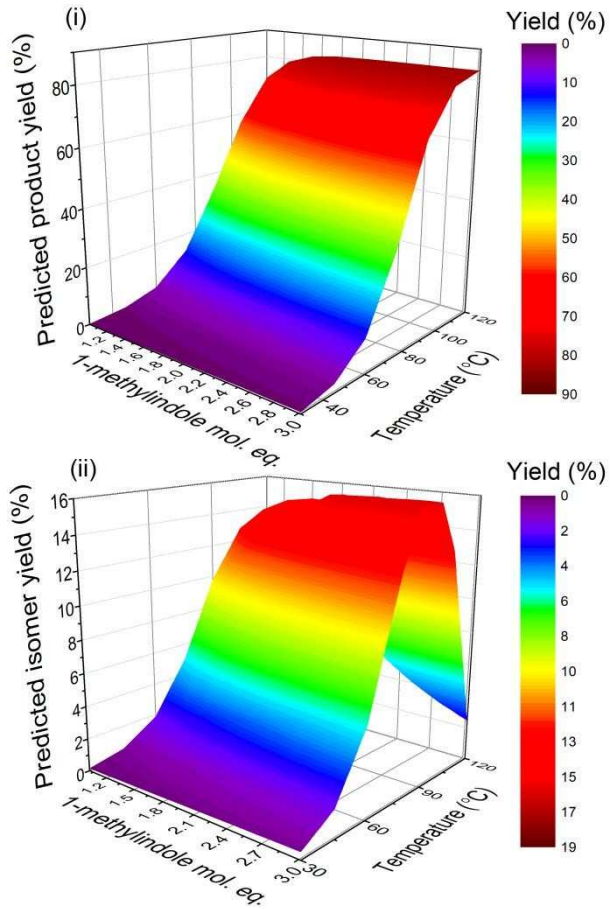

Figure 4. Kinetic model predicted using Table 2 kinetic parameter estimates: (i) desired product **3** yield; and (ii) isomer **4** yield. Constant $C_{1,0}$ = 0.40 M, $AlCl_3$ = 1.1 mol eq. and t_{res} = 9 min.

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Keywords flow chemistry • continuous processing • kinetics • definitive screening design • experimental design

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