A Self-Optimising Automated Flow Reactor System for Impurity Scouting in Organic Synthesis

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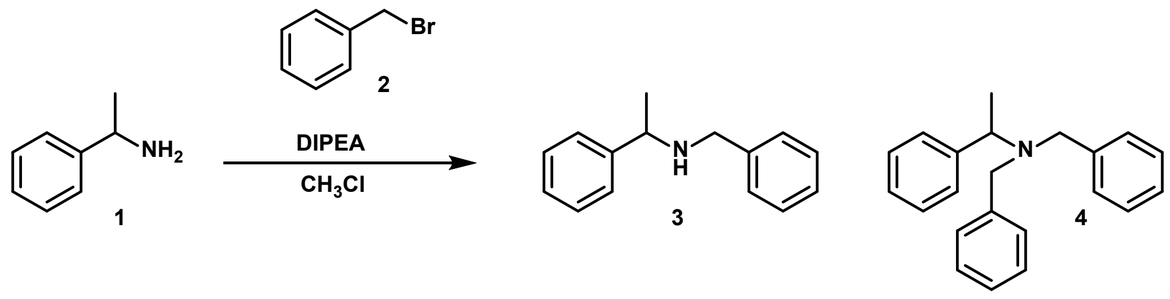
1. Project Background

- The costs associated with drug development continues to rise, with an average R&D spending of $1.1 billion to deliver new drugs into market (1).
- Impurity characterisation and quantification are an important part of pre-clinical trials to ensure drug safety and quality (2).
- Impurities are often present in small quantities, thus making the process challenging and time-consuming (3).
- Flow chemistry provides a unique opportunity to create an autonomous platform for impurity scouting and reaction optimisation.

2. Automated Flow Reactor Platform



Scheme 1. 1) Starting material α-methylbenzylamine **2)** benzyl bromide **3)** mono-benzylated product **4)** di-benzylated by-product

Model reaction shown in **Scheme 1** was implemented into an automated flow reactor platform (**Figure 1**) with compound **3** labelled as product and compound **4** as impurity 1.

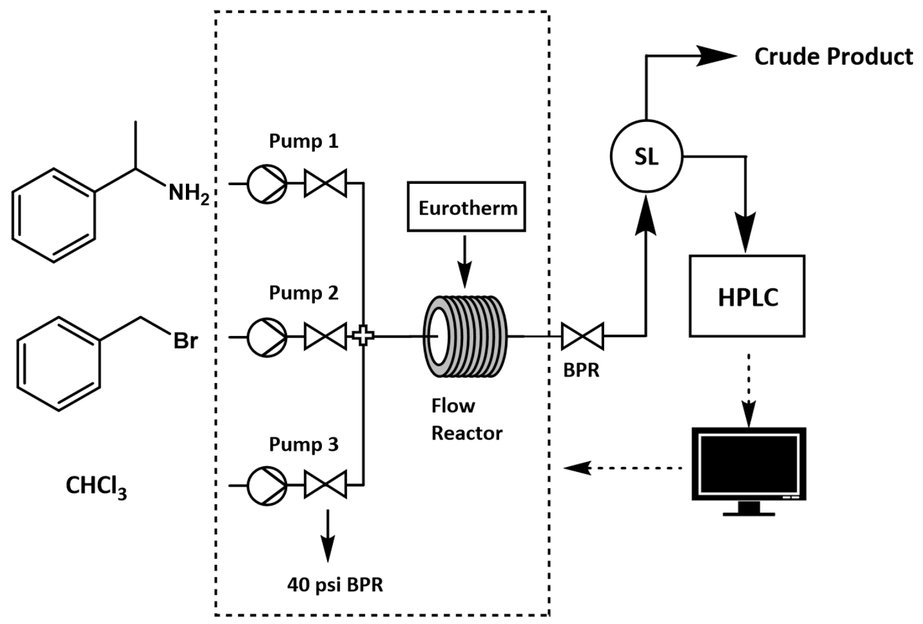


Figure 1. Automated flow reactor platform comprised of: Three HPLC pumps, back-pressure regulators (BPR), metal flow reactor , sampling loop, and HPLC.

- All modules were connected and remotely controlled by LabVIEW.
- Yield optimisation were achieved by varying temperature, residence time, and equivalents of **1**:**2.**

3. Self-Optimisation Procedure

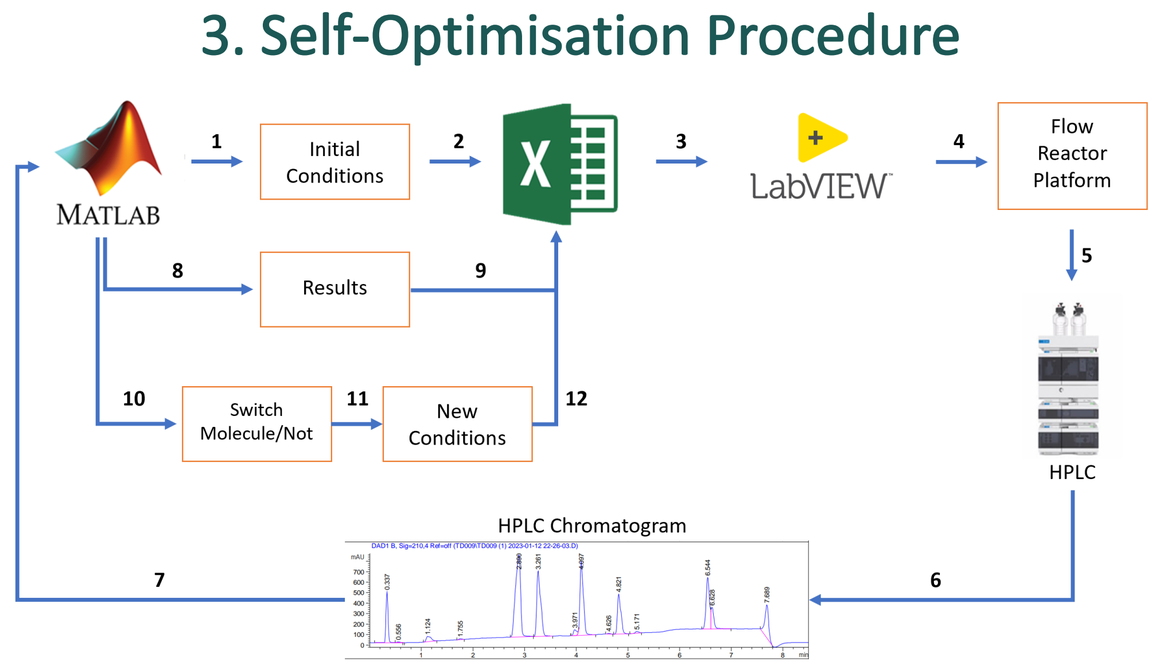


Figure 2. The closed-loop self-optimisation procedure facilitated by interaction between hardware and software.

- The optimisation procedure was initialised with seven initial conditions generated by Latin Hypercube Sampling.
- Bayesian optimiser with an Adapted Expected Improvement acquisition function was used to generate reaction conditions for yield optimisation.
- Surrogate models were updated as new observations are made.
- MATLAB was utilised to script the optimisation algorithm, generate new experimental conditions, and perform automated data analysis.

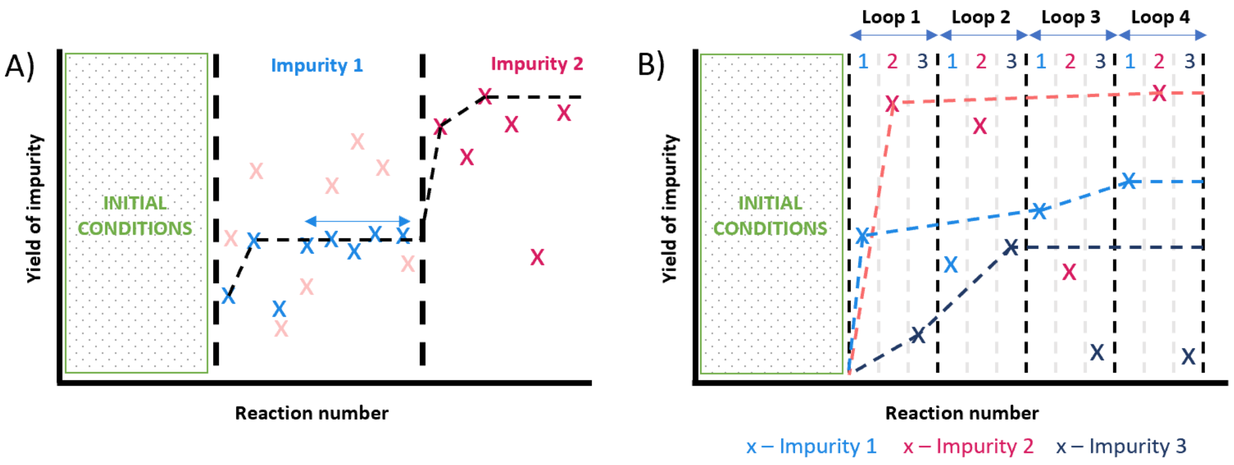


Figure 3. Compound-switching methods **A)** pre-defined cut-off number and ±5% average and **B)** loop

- Objective function of compound:internal standard ratio was maximised that is proportional to yield.
- Three compound-switching methods were developed to allow the yield of multiple compounds to be maximised in one experiment.

4. Optimisation Results

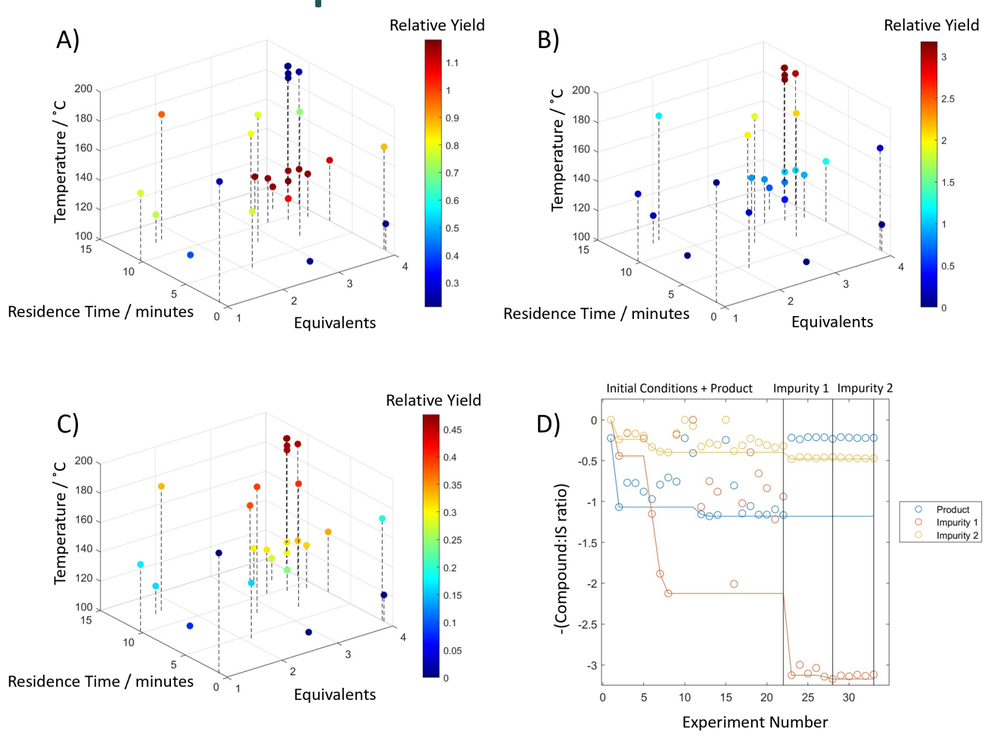


Figure 4. Optimisation results for **A)** product **B)** impurity 1 **C)** impurity 2 and **D)** minimum response curve using ±5% average method. Relative yield was calculated from ratio of compound to internal standard.

Design Space:

- Temperature: 100 – 190˚C
- Residence Time: 1 – 12.5 mins
- Equivalents: 1 – 4

Optimal Reaction Conditions:

Compound Optimised	Equivalents	Residence Time (mins)	Temperature (˚C)
Product	4	12.5	112
Impurity 1	4	12.5	182
Impurity 2	4	12.5	190

- The self-optimising algorithm was able to maximise the yield for multiple compounds in one optimisation experiment.
- Once initialised, the self-optimisation procedure was run autonomously without human intervention.
- The algorithm was able to distinguish different optimal points despite the small differences in temperature for impurity 1 and impurity 2.
- Results were reproducible indicating that precise control of flow rates and temperature was achieved.

5. Conclusion and Future Work

- An **autonomous self-optimising flow reactor system** for impurity scouting and yield optimisation was **developed and established**.
- The system comprised of **three key elements**: an automated flow platform, on-line analytical tool (HPLC) and a self-optimising Bayesian algorithm.
- Four different **optimisation experiments** were successfully **run autonomously**.
- **Future work** may involve utilising the platform for other pharmaceutically-relevant reactions, such as Suzuki-Miyaura coupling.

6. References and Acknowledgements

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