

**Continuous Manufacturing with Carbon Supported
Nanoparticle Catalysts for the Self-Optimisation of
Heterogeneous Reduction Reactions**

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I confirm that the work submitted is my own, except where work which has formed part of jointly authored publications has been included. My contribution and the other authors to this work has been explicitly indicated below. I confirm that appropriate credit has been given within the thesis where reference has been made to the work of others.

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Abstract

Heterogeneous catalysis is used widely in industry, both in batch systems and in continuous flow, via the use of packed bed reactors. The advantages of converting traditional batch processes to continuous flow are well defined in the literature. These include improved heat and mass transfer, easier scale up and better process control, leading to less waste and improved safety of the systems. Optimisation of these flow processes leads to further efficiency in exploring new reactions, as with higher yield often comes higher purity, reduced waste, and a greener synthesis. Despite the vast number of processes that make use of heterogeneous catalysis in the pharmaceutical industry, the adoption of continuous flow for these systems is limited.

The combination of automation and optimisation algorithms with continuous flow through closed-loop feedback control has been shown to be highly beneficial for chemical reaction optimisation in recent decades. However, this has mainly been limited to homogeneous systems. With a drive towards converting traditionally homogeneously catalysed reactions to heterogeneous ones, to improve the sustainability of the process, more work is required to develop and integrate solid catalysts into self-optimising platforms.

The work reported in this thesis aims to highlight the current challenges in the implementation of heterogeneous continuous systems and improve existing technologies. This includes the development of an online continuous flow packed bed reactor platform, the improvement of processes via self-optimising algorithms in the formulation of APIs, the application of self-optimisation in the development of a telescoped system, the demonstration of a novel catalyst deactivation optimisation protocol, and the formulation of new spherical carbon supported catalysts for heterogeneously catalysed three-phase reactions.

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List of Abbreviations

2-MeTHF – 2-Methyltetrahydrofuran

AC – Activated carbon

ACS GCI – American Chemical Society Green Chemistry Institute

AI – Artificial intelligence

AIDS – Acquired immunodeficiency syndrome

API – Active pharmaceutical ingredient

BET – Brunauer-Emmet-Teller

BO – Bayesian optimisation

BOAEI – Bayesian optimisation with adapted expected improvement acquisition function

BPR – Back pressure regulator

CCF – Face centred composite

CNTs – Carbon nanotubes

CSTR – Continuous stirred tank reactor

DoE – Design of experiments

EDS – Energy dispersive x-ray spectroscopy

EGFR-TKI – Epidermal growth factor receptor tyrosine kinase inhibitor

FDA – Food and Drug Administration

FTIR – Fourier-transform infrared spectroscopy

GC – Gas chromatography

GNFs – Graphitised nanofibers

GSK – GlaxoSmithKline

GUI – Graphical user interface

HIV – Human immunodeficiency virus

HPLC – High performance liquid chromatography

ICP-MS – Inductively coupled plasma mass spectrometry

IM – Intermediate mixture

IPPC - EU Integrated Pollution Prevention and Control

JM – Johnson Matthey

LHC – Latin hypercube

MFC – Mass flow controller

MLR – Multiple linear regression

MS – Mass spectrometry

Nitropip – 1-(4-nitrophenyl)piperazine

NMR – Nuclear magnetic resonance

NMSIM – Nelder-Mead simplex

NP – Nanoparticle

OSAT – One step at a time

OVAT – One variable at a time

PAT – Process analytical technology

PBR – Packed bed reactor

PBSAC – Polymer-based spherical activated carbon

PdNPs – Palladium nanoparticles

PFIB-SEM-EDS – Plasma focussed ion beam-SEM-EDS

PMI – Process mass intensity

PVD – Physical vapour deposition

R1 – Reactor one

R2 – Reactor two

REACH - Registration, Evaluation, Authorisation and Restriction of Chemicals

RME – Reaction mass efficiency

RMSE – Root mean squared error

SAC – Spherical activated carbon

SEM – Scanning electron microscopy

SMSIM – Super-modified simplex

SNOBFIT - Stable noisy optimization by branch and fit

STEM – Scanning transmission electron microscopy

STR – Stirred tank reactor

STY – Space-time yield

TEM – Transmission electron microscopy

TOF – Turnover frequency

TON – Turnover number

TPP - Triphenylphosphine

TSEMO – Thompson sampling efficient multi-objective optimisation

UHPLC-MS - Ultra-high performance liquid chromatography-mass spectrometry

UV-Vis – Ultraviolet-visible spectroscopy

VWD – Variable wavelength detector

WHO – World Health Organization

XPS – X-ray photoelectron spectroscopy

Chapter 1 : Introduction

1.1 Continuous flow chemistry

Continuous flow chemistry has been present in industry for more than 100 years, however, this has been mostly limited to large petrochemical processes. The adoption of continuous flow in the pharmaceutical and agrochemical industries has only been reported in more recent decades, with increasing interest towards continuous processes due to their advantages over batch chemistry. For primarily historical reasons, pharmaceutical industrial chemical processes are largely batch dominated as they are highly versatile. Batch reactors can tolerate a wide range of chemical transformations and can also handle heterogeneous systems well, unlike flow systems which are prone to blockages with solid formation.¹ While these systems can produce most of the desired products, they can in several cases be improved upon by using flow chemistry.² In 2011, the American Chemical Society Green Chemistry Institute (ACS GCI) labelled continuous processing a key green engineering research area that should be implemented in the pharmaceutical industry for active pharmaceutical ingredient (API) production.³

Flow chemistry provides safety and environmental benefits over batch as it creates a more controlled reaction space that produces less waste. Industrial scale batch processes can involve the use of large volumes of solvent and hazardous materials in stirred tank reactors (STR), which can be an explosion risk. This has often caused some classes of reactions to either be abandoned or significantly adapted due to safety concerns. In contrast in continuous flow, there is precise control over the reaction conditions as only relatively small amounts of reactants are being handled at any one time, meaning a faster rate of heat dissipation, avoiding runaway reactions. This allows more hazardous chemistries to be investigated with reduced safety concerns, as only small amounts of materials are subject to the reaction conditions, removing the possibility for the build-up of large amounts of hazardous intermediates in the reactor. This feature also aids in improving heat and mass transfer in the reaction and enhanced mixing of the reagents, reducing the chance of side product formation.^{4,5} Unlike batch reactors, in continuous flow exploring higher temperatures and pressures above the boiling points of solvents is possible, as exotherms can be closely monitored and controlled.⁶

Flow chemistry is also advantageous when considering process intensification.⁷ Process intensification refers to the reduction in size of the chemical plant while producing the same scale of products. In continuous flow this can happen in three main ways: scale up – the process is run in larger reactors; numbering up – the process can be run on many small scale reactors in parallel; and scale out – the process is run for a longer period of time.^{8,9} Continuous systems are generally small footprint units that can be made modular and interchangeable, allowing for scale out through an increase in the flow rates and reactor length (which provides the same residence time). As higher temperatures and pressures can be accessed in continuous flow, this often leads to an improved rate of reaction, meaning reactions can be performed on much smaller timescales, making scale out possible. Numbering-up allows small footprint units to be used in parallel, meaning that no new reactor designs are required for an optimised process to be produced at scale. This means that changes to the mixing of reagents is not an issue, which can be a significant concern when scaling up batch processes.¹⁰ Styring *et al.* show the benefits of numbering-up in the transition from a single channel to a 120 multichannel packed bed reactor (PBR) for a nickel catalysed Kumada coupling reaction, increasing the throughput from 1.1 to 137 g day⁻¹ on a relatively small footprint reactor system.¹¹ Flow chemistry also has the capability to combine multiple reaction steps more easily, creating multistep processes that can be monitored at each stage via inline or online process analytical technology (PAT).¹² This creates the possibility for end-to-end continuous manufacturing that requires minimal work-up operations between reaction steps, leading to significant environmental and economic benefits.¹³⁻¹⁵

Continuous flow chemistry can be categorised into four main systems as described by Masuda *et al.*, each with their own reactor types demonstrated in Figure 1.¹³ The reaction can proceed with all the reactants in one phase with no catalyst (Type A) or with multiple phases, where one of the reactants is immobilised in the reactor (Type B). The immobilised substrate is usually in excess but will be consumed over time, requiring the reactor/column to be replaced periodically. A catalyst can also be introduced to the system in the form of a homogeneous (Type C) or a heterogeneous catalyst (Type D).^{9,16} Catalysts are beneficial to chemical reactions as they can reduce waste and often require less forcing conditions, due to a lower activation energy. Type D, with a solid catalyst, is the most desirable continuous flow system, especially from a

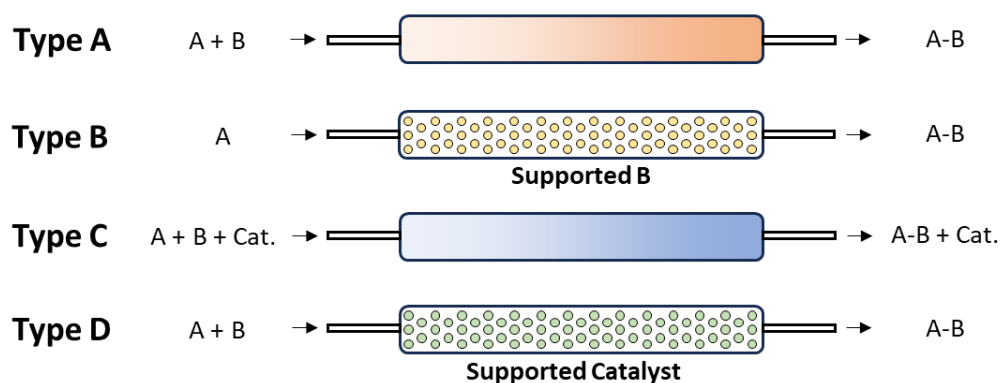


Figure 1. Types of continuous flow systems available for the synthesis of A-B from substrates A and B with and without catalysts.¹³

sustainability standpoint, as it requires no additional separation steps, meaning the catalyst is almost completely recoverable. The use of a fixed bed reactors in continuous flow avoids the need to separate the catalyst from the products and can provide a 'higher throughput per volume per unit time' compared to batch reactors.^{5,17}

1.1.1 Heterogeneous catalysis in continuous flow

Catalysis is highly important in industry as it provides an alternative reaction pathway with a lower activation energy, meaning significantly less energy input is required for high conversions to be achieved.¹⁸ In 2016 it was reported that 80% of all industrial chemicals were made through at least one catalysis step, generating more than \$10 trillion in goods and services annually across the globe.¹⁹ Effective catalysts are ones that are not only active for a process and achieve high yields but can also provide selectivity for the desired product, making the process less wasteful and more efficient. Homogeneous catalysis is a catalytic reaction where both the reactants and the catalyst are in the same phase. This reaction type is easy to perform, the catalysts are often highly active, and they suffer less from deactivation in continuous flow. However, they require at least one separation step after the reaction has occurred which is often expensive and time consuming, with the catalyst often not fully recoverable.¹⁸ Heterogeneous systems involve a catalyst that is in a different phase to the reagents, and this is usually in the form of a solid catalyst. Heterogeneous catalysis benefits from an ease in separation, as the catalysts are in a different phase to the reactants so can easily be filtered out. Most catalysts used in the production of APIs are made of precious

metals, which are highly active but expensive and nonabundant, making it essential that they are recovered and reused many times.

It is important to consider the type of catalyst that is needed for the desired process as this directly affects the activity and selectivity of the process through their chemical and physical properties.^{13,19} The active catalyst is usually dispersed over or within a solid support, creating a large catalytically active surface area. The support provides a more stable environment for the catalyst particles, reducing the chance of catalyst deactivation, particularly via metal leaching or agglomeration.²⁰ The solid catalysts can be fixed in a column or flowed through the system as a slurry, however, slurries require large channels or small particle sizes to avoid reactor blockages. Slurries also must be filtered at the end of the reaction and require another separation step unlike fixed beds. Continuous stirred tank reactors (CSTRs) have been shown to be effective for reactions in flow with multiphase systems, where liquid or gaseous reagents are flowed into the STR and filters on the inlet and outlet help to contain the catalyst inside the reactor, allowing complete inline phase separation.^{21,22} They can be connected in a cascade of CSTRs to alter the allowed residence time. However, careful consideration of the system is required to ensure there is sufficient mixing, and that filters do not become blocked over time causing over pressurisation. Fixed bed reactions also benefit from the ease of separation of the catalysts and four main fixed bed support types are dominant in the literature (Figure 2):¹³

- Catalytic capillary – A narrow tube with catalysts immobilised on the reactor wall with a small space for the reactants to flow through.
- Packed bed – A column which is packed with pellet or bead forms of the catalyst support which the reactants can flow past.
- Honeycomb – A porous material that contains parallel channels with immobilised catalyst particles attached, which the reactants can flow past.
- Monolith – A microporous structured catalyst material, containing a fine microstructure, which can either be packed into a column or formed in the column through a chemical reaction. The reactants can then be flowed over the catalyst through the column.

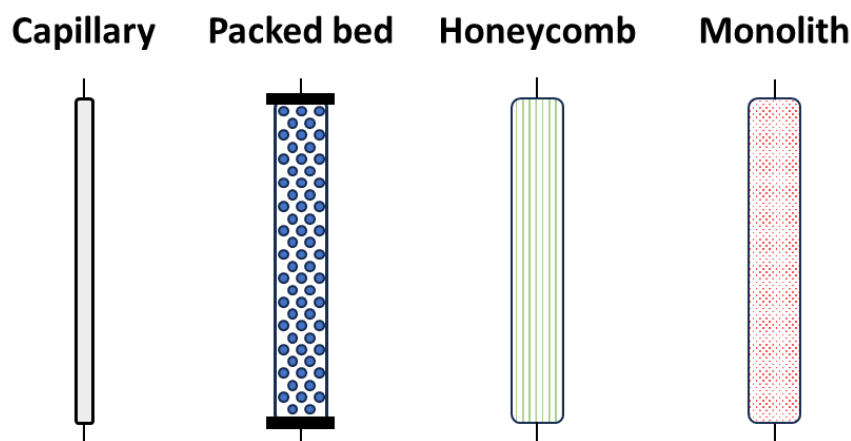


Figure 2. Four categories of heterogeneous flow systems.

Capillary reactors are typically used on the lab-scale and involve the walls of the reactor being coated in the catalyst material. These work well in small micro-reactors due to the increase in mass transfer from enhanced mixing in small diameter tubing and provide a rapid reaction screening platform that minimises the use of reactant and catalyst materials.^{23,24} Honeycomb fixed beds such as coated static mixers have seen increasing interest in the past few years as a support for catalysts, as they further improve the mixing of the phases and are easily scalable. They provide a large active surface area with a thin layer of catalysts applied to the support, and can be produced by 3D printers making them widely accessible to a range of industrial and academic groups.²⁵ Many academic papers have reported the development of functionalised catalytic monoliths for flow applications, noting their reproducible synthesis providing the same packing to the catalyst bed each time, increasing the repeatability of reactions.²⁶ A summary of the advantages and disadvantages for each reactor type is shown in Table 1. PBRs are one of the mostly widely used ways of incorporating heterogeneous catalysts into continuous flow systems due to their ease of accessibility and the diverse catalyst substrates that can be packed into them.

1.2 Packed bed reactors

Heterogeneous catalysts have been used in the petrochemical and fine chemical industry to produce products on a ton day⁻¹ scale in continuous flow since the 1930s.²⁷ These systems are most often performed in PBRs for three-phase reactions and are used

Table 1. Summary of the advantages and disadvantages of different fixed bed reactor types.^{13,25,28}

Reactor Type	Advantages	Disadvantages
Capillary	✓ High surface area ✓ Enhanced mass transfer and mixing ✓ Reduction in catalyst use from thin coatings applied	✗ Catalysts can be difficult to immobilise on reactor material – poor compatibility ✗ Usually limited to lab scale ✗ Costly to replace deactivated catalyst
Packed Bed	✓ Easy recycling and regeneration ✓ Most catalysts commercially available ✓ Easy scale up	✗ High pressure drop ✗ Larger particle size requirements leading to lower active surface area ✗ Flow maldistribution, channelling
Honeycomb	✓ Low pressure drop ✓ Scalability ✓ Enhanced mixing and mass transfer	✗ Limited commercial availability ✗ Expensive ✗ Mechanical instability - fragile structure
Monolith	✓ High surface area ✓ Low pressure drop ✓ Efficient mass transfer	✗ Limited commercial availability ✗ Scalability not well reported ✗ Blockages in flow channels common

for common processes such as catalytic hydrocracking, hydrogenations, the oxidation of formic acid in water and hydrodesulfurization.²⁹ Typically when performing three-phase reactions in batch, large headspaces of gaseous reactants are required, which often suffer from poor mass transfer of the gaseous reactants into the liquid phase due to small interfacial areas. Usually three-phase PBRs are operated as a trickle bed, where both the gas and liquid phases are flowed down through the column, providing a near uniform distribution of both phases over the catalyst bed, increasing mass transfer and improving the reaction kinetics.²⁸ Comparatively smaller amount of reagents are subject to high temperatures and pressures at any one time when used in continuous flow operation, improving the safety of these systems meaning harsher reaction conditions can be explored, which is beneficial for increasing mass transfer at higher pressures. Another advantage of transferring gas-liquid-solid reactions to PBRs is that the beds can easily be replaced/interchanged with minimal structural changes to the system, minimising plant downtime in replacing spent catalyst, increasing the productivity of the processes. However, the translation of heterogeneous catalysts to continuous flow for many pharmaceutical companies is slow, and the use of traditional STRs still dominates.³⁰ Although there are many benefits to moving towards continuous flow, there are many issues that need to be addressed when translating reactions to PBRs, including pressure drops, difficulties with the reproducibility of reactions, and issues with ensuring complete contact of all the catalyst particles with the reagents. The

product demand is much smaller for pharmaceutical processes, with only 500 – 5000 kg of API required per year, compared to the 1000s of tons required in petrochemical processes.^{31,32} This change in demand means that existing petrochemical scale PBR platforms and the size, structure, and morphology of their commercial catalysts/supports are not often suitable for pharmaceutical processes, creating a demand for new reactors, and novel catalysts for use at this scale. The commercial availability of appropriate active catalysts for pharmaceutical scale reactors can be a major bottle neck to transferring processes to PBRs.²⁷ Liquid holdup within the reactor can also be an issue as the packing of the catalyst particles can never be entirely uniform, meaning small amounts of the reactants can become stuck between the pellets, resulting in a portion of the active sites on that catalyst being blocked. These obstacles reduce the amount of available active catalyst in the reactor and consequently decreases the conversion to the product. It can also lead to increased side product formation, as molecules that spend prolonged amounts of time in the reactor may undergo other reaction pathways, e.g. reactions where the product and the starting material react with each other to form unwanted byproducts.³³

1.2.1 Mass transfer

Mass transfer between phases is an important factor to consider in multiphase systems as the reagents must be available in the correct phase for a reaction to be successful. Mass transfer is facilitated by diffusion between phase interfaces due to a concentration or pressure difference, and this can often be the limiting factor for the rate of reaction in multiphase systems. An example concentration profile for the mass transfer between gas, liquid, and solid phases is shown in Figure 3.^{34,35} The mass transfer process happens through the following steps:

1. The gas phase must first transfer from the bulk gas phase to the gas film.
2. The gas then diffuses into the liquid film before transferring to the bulk liquid.
3. The reactants then travel to the liquid film near the solid particle.
4. The reactants can then transfer to the catalyst surface where they diffuse into pores and to the catalyst active sites.
5. The reactants undergo a reaction to form the products at the active site.

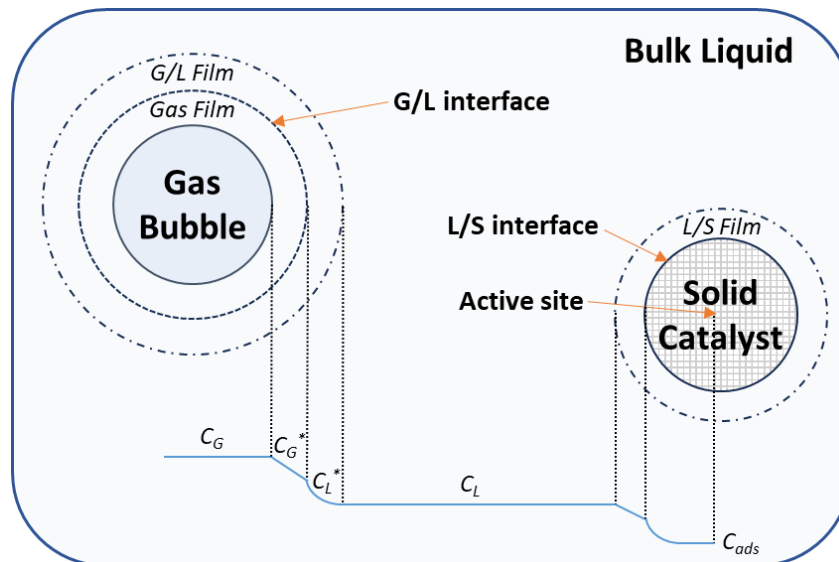


Figure 3. Mass transfer concentration profiles for gas (C_G), liquid (C_L), and solid (C_S) phases.³⁴

6. The products can then transfer out into the bulk liquid phase by the reverse of the previous steps (and into the gas phase if the products are gaseous).³⁶

The reaction conditions and the reactor type play a large role in affecting the rate of mass transfer, and therefore the rate of reaction. Increasing the mixing of the reaction materials helps to bring reactant molecules in contact which enhances mass transfer. Reaction variables such as pressure, temperature and gas and liquid flow rates also affect the rate of mass transfer in a reaction.³⁵ An increase in pressure leads to an increase in mass transfer of the gas to the liquid phase as described by Henry's Law.³⁷ Increases in temperature often lead to poorer gas solubility, however, it provides thermal energy to the system which can help improve the kinetics of the reaction. The flow rates of the liquid and gas change the residence time in the reactor, affecting the contact time of the phases with the solid catalyst surface and mixing within the PBR.³⁸ Catalyst particle size can also affect the rate of mass transfer, and any increase to the catalyst surface area will increase the interfacial area between phases, increasing mass transfer.

1.2.2 Pressure drop

A pressure drop across a PBR is created by the frictional interactions between the catalyst particles and the fluid flowing through the reactor. The shape and roughness of the catalyst used in the PBR has a direct effect on how large the pressure drop is.³⁹

Smaller particle sizes, such as powder catalysts that are typically used in STRs, generally increase the active surface area of the catalyst, but lead to large pressure drops and often blockages in PBRs. Large pressure drops across the reactor mean that the flow rate and gas pressure required to maintain the desired operating conditions are unsustainable. This affects the energy requirements of the system and therefore the operating costs and size of the reactor needed.⁴⁰ It can also have a direct effect on the selectivity of the reaction as different areas of the bed would be subject to different reaction conditions. A pressure drop of no greater than 20% from the inlet pressure of the system was determined to be an acceptable limit by Hickman *et al.* It is important to consider these parameters in not only the design of the reactor but also the flow rates of the precursors, the physical properties of the gas and liquid phases (e.g. viscosity and density), and the design of the catalyst support.⁴¹

1.2.3 Catalyst supports

Many types of catalyst support have been developed for heterogeneous catalysis, and the physical characteristics (such as, pore size, pore volume, and surface area) of the support also affect their performance in a reaction, Figure 4.¹³ In STRs, powdered catalysts show the greatest activity and work extremely well in a range of multiphase processes. However, these types of support sizes are not transferrable for reactions in PBRs, due to the large pressure drops they create and their plugging of reactor systems, creating blockages which can lead to over pressurisations. Conversely, an increase in particle size often leads to a decrease in active surface area, due to a smaller surface area to volume ratio. The size of the catalyst support also has a significant effect on the pressure drop in the reactor, as well as the mixing. Catalysts that were developed and are used in PBRs on the petrochemical plant scale are also not appropriate for use in PBRs in the pharmaceutical industry due to the difference in product and reactor scales required. Therefore, there is a requirement for the development of new active catalysts that can be used at both the lab and pilot scale.⁴²

Al₂O₃ has been used successfully by many groups as a support for Pd¹⁷, Pt⁴ and Au⁴³⁻⁴⁵ nanoparticle (NP) catalysts in heterogeneous hydrogenation reactions. One example includes the work done by Leveque *et al.* in the hydrogenation of α -methyl

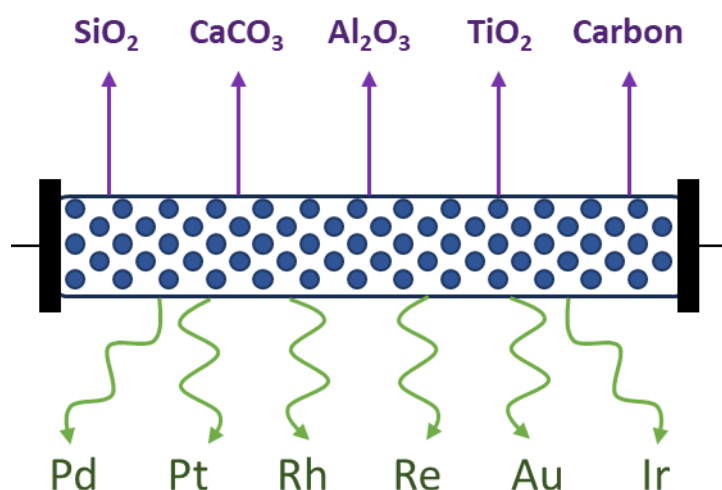


Figure 4. Examples of common support types (purple) and active catalysts (green) that are commercially available and used in heterogeneously catalysed transformations.

styrene to cumene using a stainless steel solid foam, which was wash-coated with Pd/Al₂O₃.³⁶ The pressure drop, liquid holdup and the mass transfer in a concurrent flow configuration were investigated resulting in high mass transfer coefficients (0.2 - 0.9 s⁻¹) and low Reynold numbers. TiO₂ and SiO₂ are also commonly used in continuous flow heterogeneous catalysis for chemical transformations such as hydrogenations of alkenes,⁴⁶ nitroarenes,⁴⁷ aldehydes,⁴⁸ and alkynes.⁴⁹ These supports provide strong-metal support interaction,⁵⁰ mechanical stability,⁵¹ and have highly tuneable porous surfaces which helps to offer a large area for the dispersion of NP catalysts. However, these supports have significant drawbacks, including, lower thermal stability, a higher solubility in acids and a lower electrical conductivity.²⁰ Carbon based materials can overcome these drawbacks and have been shown to display comparatively higher surface areas than other supports such as silica and alumina making them attractive for heterogeneous reactions in PBRs.⁵² An ideal support has uniform polydispersity to minimise the chance of liquid holdup and to allow for reproducible packing in the catalyst bed. The particle to tube diameter ratio has also been shown to have significant impacts on reactions carried out in PBR systems, with Hickman *et al.* stating that this ratio is important for maintaining reasonable pressure drops and liquid flows in the reactor.⁴¹ Reactors used in pharmaceutical scale processes have reported a diameter ratio of 10-15 as an acceptable range, and this should be maintained throughout scale up.^{31,53}

1.3 Reactions in PBR systems

PBRs have been reported for many multiphase chemical transformations including oxidations, carbonylation, acid base catalysis, enzymatic reactions, and hydrogenations.²⁷ The use of both gaseous oxygen and air have been reported in the continuous flow oxidations of primary and secondary alcohols to produce carbonyls.⁵⁴ Oxidations are an important reaction class for the production of useful chemical building blocks from raw materials for the production of APIs.⁵⁵ Due to the enhanced safety benefits of continuous flow, oxygen can be safely handled with decreased explosion risks, therefore making them an ideal candidate for the translation to continuous manufacturing. Mannel *et al.* reported the use of micro-PBRs to screen a host of heterogeneous catalysts for the aerobic oxidation of primary alcohols, developing a new PdBiTe based catalyst immobilised on a carbon support that showed great functional group tolerance and stability.⁵⁶

In 2016, it was reported that 10 – 20% of the reactions conducted to produce chemicals in industry were three-phase catalytic hydrogenations with hydrogen gas as the reducing reagent.¹⁸ GlaxoSmithKline (GSK) stated in 2020 that 77% of their fundamental gas/liquid transformations were heterogeneous hydrogenations, with half of those carried out in PBR systems, showing the prevalence of this reaction class in industry.⁵³ There are many novel and commercial PBR systems reported in the literature to perform interesting reduction reactions with hydrogen gas.⁵⁷ It is important to consider these systems when designing new automated reactor platforms, such as the one that will be discussed in this report, in order to make the work transferable for different types of multiphase reactions and applicable to both academia and industry.

Work by Rahman *et al.* in 2020 demonstrated a Pd/C continuous PBR system that used hydrogen gas and water as a solvent to hydrogenate pharmaceutically important

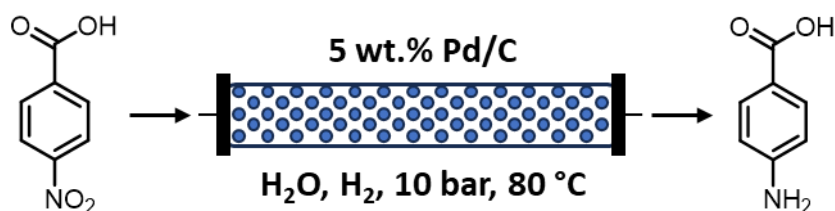


Figure 5. 5 wt.% Pd/C PBR system reported by Rahman *et al.* to perform the heterogeneous hydrogenation of para-nitrobenzoic acid in continuous flow.⁵⁸

nitrobenzoic acids to their corresponding anilines (Figure 5).⁵⁸ The aim of this work was to produce a smaller lab-scale PBR system that could be directly scaled up to a pilot scale reactor with the ability to produce 10 kg week⁻¹ of the desired products. A commercial 5 wt.% Pd/C catalyst was provided by Arran Chemical Co., and the group compared the systems capability for the reduction of *para*-nitrobenzoic acid in batch and continuous flow. The group showed that fewer intermediates were produced when using continuous flow, stating that this was due to the aqueous phase being saturated in enough hydrogen to convert the intermediates to the amine product, due to enhanced mass transfer. Lower flow rates (increasing residence times) were also found to produce a higher purity of the desired product, as the intermediates would spend longer in the reactor allowing them enough time to be converted to the product. The group assessed the stability of the catalyst over a six hour reaction period and found that there were minimal decreases in catalyst activity, showing the applicability of this continuous flow process to the extended operating periods required for industrial scale up. This showed the beneficial transfer and scale up of a heterogeneous process in continuous flow, compared to batch systems, achieving higher selectivities and throughput for the desired product.

Petho *et al.* reported the use of a commercial H-Ion flow reactor platform to develop a Pd/alumina based heterogeneous hydrogenation for a key reaction step in the formation of Afizagabar, a possible drug candidate to treat post-stroke central nervous system effects.⁵⁹ The group screened seven possible catalyst candidates experiencing issues such as blockages in the reactor and degradation of the catalyst supports under flow conditions. A 5 wt.% Pd/alumina catalyst with a 200 µm particle size was shown to be highly active and stable for the process, producing an 87% yield of the desired product with no deactivation experienced over the reaction time. This step was then integrated into a four-step telescoped system in continuous flow for the complete synthesis of the final drug molecule, with the outlook for scale up of the system. This article showed the successful integration of multiphase chemistry into a telescoped scaled-up synthesis of an important drug molecule, reducing manufacturing costs and lead times compared to the original batch system reported.

Lau and coworkers reported the continuous flow preparation of the antimalarial drug candidate OZ439 via a heterogeneous hydrogenation.⁶⁰ The group used the

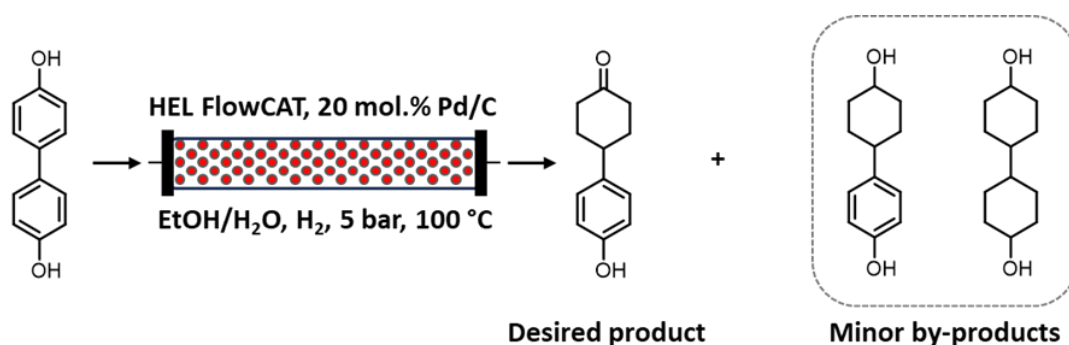


Figure 6. The selective partial hydrogenation of biphenol to the desired product 4-(4-hydroxyphenyl)cyclohexan-1-one in the H.E.L. FlowCAT reported by Lau *et al.*⁶⁰

commercial H.E.L. FlowCAT to initially screen a range of catalysts (Rh, Pt and Pd based) for their activity and selectivity in the partial reduction of biphenol to the desired product 4-(4-hydroxyphenyl)cyclohexan-1-one. The 20 mol.% Pd/C catalyst was identified as an appropriate candidate for the hydrogenation, as other metals and lower catalyst loadings resulted in the formation of unwanted side products (shown in Figure 6). The article noted that the process could produce the product with a throughput of 0.4 g hr^{-1} scale, which showed significant improvements on the batch protocol. However, this is lower throughput than desired for an industrial scale manufacturing process, so significant scale up efforts would be required to improve its productivity.

Another novel continuous flow platform was developed by Duan *et al.* to determine accurate reaction kinetics for the reduction of nitrobenzene and α -methyl styrene.⁶¹ A tube-in-tube reactor was used to increase hydrogen transport into the liquid phase, consisting of a porous inner permeable gas membrane tube that contained the liquid flow stream, inside of a larger non permeable outer tubing that the gaseous H_2 could flow through. This made the downstream PBR system bi-phasic (no longer a three-phase system) as the liquid in the inner tubing could be fully saturated with hydrogen in only 12 s through the gas permeable membrane, allowing for easy reaction sampling. Kinetic data for both reactions was collected by transient flow rate ramping of the reactant pumps, noting that accurate kinetic data could be obtained with an ideal flow rate ramp of lower than $0.03 \text{ mL min}^{-1} \text{ min}^{-1}$. This article illustrates how continuous flow and automation can be used to rapidly screen reactions to generate kinetic models, which aid in the optimisation and understanding of reaction conditions.

These examples demonstrate useful progress in integrating heterogeneous multiphase systems into both custom-built and commercial continuous flow PBR

platforms. They show how continuous flow can have benefits in improving yields and selectivities over their original batch based processes, and how end-to-end telescoped systems can aid in reducing manufacturing costs, waste, and lead times for important drug molecules. The integration of automation can also aid continuous flow systems, demonstrated here for the rapid kinetic analysis of reactions.

1.4 Automation and self-optimisation in continuous flow

The automation of continuous flow systems ensures that there is precise control over the reactor equipment and reduces the risk of human error, leading to an improved quality of data. This often means the systems are safer, and the availability of many commercial automated chemical platforms provides easy access for the integration of automated flow chemistry in to process development.^{15,62,63} These systems require little prior knowledge about flow chemistry, making them versatile and user friendly. However, in academic settings, they are often not financially viable for many groups, leading to a significant barrier in the education and adoption of these techniques.⁶⁴ For heterogeneous catalysis in flow, systems such as the ThalesNano H-Cube and the H.E.L. FlowCAT have been used successfully to perform automated hydrogenations both in industry and in academia, with easy to use software, minimising human interaction with the reactor platform.^{65,66} The coupling of automation and PAT can improve the optimisation of these processes, swiftly finding optimum conditions on shorter timescales. Unoptimised reactions can cause problems in processes downstream, as they are inefficient and may require further purification steps to remove any unwanted byproducts from the reaction mixture.⁶⁷ Therefore, before scaling up, it is imperative that reactions are optimised to produce pure products, whilst maintaining a high productivity for the process.

1.4.1 One variable at a time

Traditionally, reaction optimisation has been performed by following a chemist's intuition or by changing one variable at a time (OVAT). For example, a variable such as temperature could be investigated, and a response from the reaction would be

monitored e.g. yield. When an optimum temperature is found, this variable would be kept constant whilst another variable is altered in an attempt to find the overall optimum conditions for the reaction. However, this method usually results in the actual optimum for the reaction being missed, as it does not consider the interactions between reaction variables.⁶⁸ The OVAT method is visually shown in Figure 7 for the investigation of a two variable system. Variable 1 is first investigated across six reaction conditions, at a fixed value of variable 2 (y_i), indicated by the solid black circles on the horizontal line. Once an optimal condition is found for variable 1 (x_i) variable 2 is then investigated while variable 1 is fixed at x_i . This finds optimal conditions indicated with the dotted circle in the diagram using this approach. The true optimum is shown by the red star in the design space and is missed by the OVAT approach, as it cannot account for interactions between the two variables. This often results in many unnecessary experiments being conducted, wasting reaction material and operator time.

This approach to reaction optimisation is reported heavily by process chemists in the pharmaceutical industry.⁶⁹ A recent literature example of this optimisation approach in the pharmaceutical industry was reported by Chen *et al.* in the investigation for the hydrogenation of nitroarenes with a ligand/Raney Nickel catalyst, shown in Figure 8.⁷⁰ The group first explored the ligand choice for the catalyst at a set of predetermined reaction conditions, before selecting the most appropriate ligand for this process as triphenylphosphine (TPP) due to its high selectivity for the desired product. Using the selected TPP/Raney Ni catalyst, the effect of solvent was investigated, with

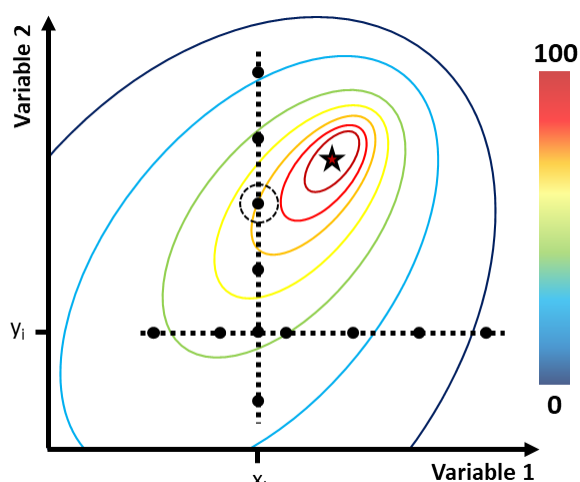


Figure 7. The OVAT approach with the optimum shown as a red star, blue is the worst experimental conditions and red is the best. Each experimental point is given by a black circle, with the optimum conditions found in the OVAT approach highlighted with a dashed circle.

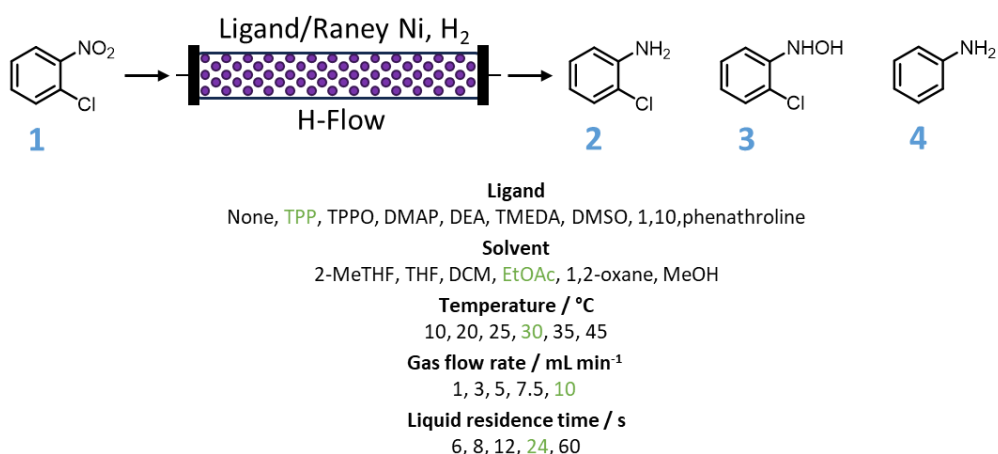


Figure 8. OVAT optimisation of the ligand/Raney Ni catalysed hydrogenation of 1-chloro, 2-nitrobenzene, with the optimum conditions highlighted in green. Where, TPPO = triphenylphosphine oxide, DMAP = 4-dimethylaminopyridine, TMEDA = N,N,N',N'-tetramethylethylenediamine, DMSO = dimethyl sulfoxide, and DEA = diethylamine.⁷⁰

EtOAc found to produce high yields of the desired product, a 98% yield and >99% selectivity. The effects of temperature on the reaction were then investigated with EtOAc and the TPP/Raney Ni, finding that a temperature of 30 °C was sufficient in producing both yields and selectivities of >99%. Finally, the effect of the molar ratio of hydrogen to the substrate and residence time were both investigated individually finding the overall 'optimal' conditions of the system. Both discrete and continuous variables were investigated by the group with a minimum number of 29 experiments reported in the paper using a OVAT approach. However, there is likely interactions between the variables listed, which are left undetermined using this method. This approach for the optimisation of processes is still preferred by many chemists and is reported for the optimisation of reactions to produce APIs, with the adoption of new approaches for experimental design still overlooked in many industrial settings. To ensure that the real optimum of a system is found, an optimisation that fully explores the reaction space would be more beneficial.

1.4.2 Design of experiments

Design of experiments (DoE) is a statistical optimisation technique that is commonly used to explore a chemical reaction space. Multiple variables are changed simultaneously which enables the chemist to observe the relationships and interactions between variables, and can often minimise the number of experiments needed to find

the optima for a reaction.⁷¹ DoEs can be used for three main objectives: to screen reactions, to optimise reactions, and to test the robustness of a reaction.⁷² The boundaries of the chemical design space are predetermined and set by the user (from information on initial testing of the reaction either reported in the literature or by preliminary experiments). A computational program, such as MODDE or JMP, can be used to help determine the experimental conditions that should be investigated for the desired objective.⁶³ These software packages can also be used to analyse and fit models to the data once reactions are carried out, and are great tools for exploring interactions between variables or visualising the response surfaces. A single DoE works from a pre-set list of experiments confined by boundaries, but iterative or sequential batch based DoE approaches such as the one shown in Figure 9 can be used for the optimisation of reaction conditions, where previous DoE experiments can be used to influence the next set of experimental conditions required to find the optima of the system. The 2^k factorial design explores the 2D surface, with centre points providing information on the repeatability of the reaction. The initial DoE is used to scan a large area of the experimental design space, before a second smaller DoE is used to explore the highest yielding area of the design space. An example of a space filling design, face centred composite (CCF) arrangement of the experiments, for a 3D (three variable) system is shown in Figure 10. This arrangement allows three variables to be investigated simultaneously for multi-dimensional problems, where the centre point/experiment of the cube is repeated three times in order to check for repeatability.⁷³ CCF designs are useful in design spaces that exhibit curvature, and the responses are often fitted with

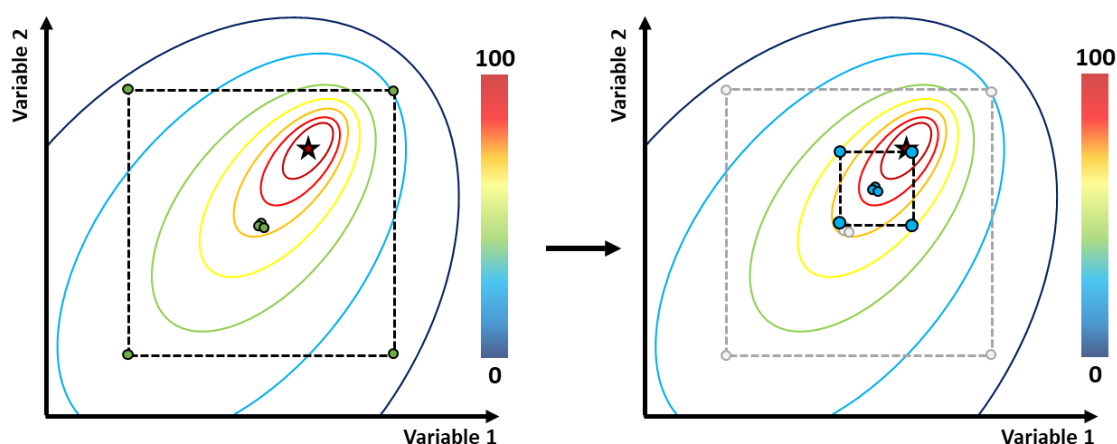


Figure 9. Sequential DoEs for a two variable system showing an initial screen of the design space with three repeat centre points (left), and a second smaller design space screen with three repeat centre points (right).

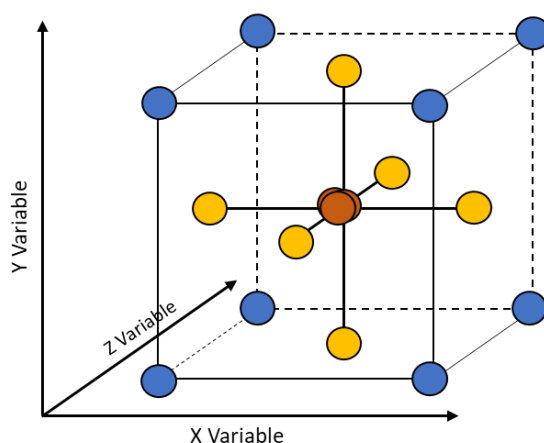


Figure 10. Three-dimensional CCF DoE.

polynomial models that contain factor, interaction, and square terms, each with their own corresponding coefficient. The general equation for a polynomial model fitted to the CCF design is given by equation 1, where b are the coefficients determined by the model, and x , y , and z are the variables on each axis given by the CCF design in Figure 10.

$$a = b_0 + b_1x + b_2y + b_3z + b_4x^2 + b_5y^2 + b_6z^2 + b_7xy + b_8xz + b_9yz + b_{10}xyz \quad (1)$$

DoEs have been reported in the literature for many uses including the development of new catalytic materials and chemical reaction screening or optimisation.⁷⁴ Guercio *et al.* at GSK used DoE in the optimisation of a heterogeneously catalysed reduction reaction for the multistep synthesis of the novel drug GW597599, a neurokinin receptor antagonist for the treatment of central nervous system disorders.⁷⁵ The group performed an initial catalyst screen before carrying out a fractional factorial DoE optimising for hydrogen pressure, temperature, and catalyst charge, with only four experiments carried out in total. This showed a significant reduction in experiments could be used with a DoE to rapidly screen a desired design space to find optimal process conditions, leading to a reduction in the time required to optimise a process and raw material use.

There are many examples where users compare OVAT and DoE approaches for the optimisation of reactions, demonstrating the benefits of DoEs for experimental design. One such example is that reported by Bowden *et al.* in the optimisation of a copper mediated radiofluorination reaction to develop radiotracers for medical imaging.⁷⁶ The group compared a DoE optimisation approach to an OVAT approach

previously reported for the same reaction, which used a minimum of 74 experiments to optimise an eight variable system. Initially a fractional factorial DoE was used to identify which of six reaction variables had the greatest influence on the reaction yield, which allowed the temperature and the reaction solvent volume to be discounted due to their non-significance. Modelling of the data also allowed key interactions to be identified between several variables, showing that an inert argon atmosphere was only required when high catalyst loading was used. These eliminations allowed a three variable DoE optimisation study to be performed on only the catalyst, starting material and base loading, reducing the number of dimensions and therefore the number of experiments required. Modelling of this data showed a strong negative interactions term between the pyridine and substrate loading, where higher pyridine loading was required at lower substrate loadings. The use of DoE resulted in a reduced number of experiments required to find optimal conditions to produce the desired radiotracer (36 experiments), rapidly identifying non-significant variables. Modelling of the reaction results enabled the identification of interaction and squared terms for the design space, allowing for better process understanding.

Although DoEs can be useful for the investigation of experimental design spaces, they also come with some disadvantages. Software packages are user friendly and take away the need for modelling knowledge and expertise, however, these packages can be expensive pricing out many research groups, making the adoption of DoE techniques more difficult. The number of experiments required can be large for high dimensional problems that are used to investigate the effect of many variables, meaning that DoE may not be the most efficient technique for process optimisation. DoE principles are also not regularly taught in undergraduate chemistry degrees, meaning graduating chemists often do not possess the expertise required to introduce DoE to their process optimisations. The integration of digital chemistry and process chemistry principles at this level would lead to a much wider adoption of these approaches, leading to its expanse and integration into many chemical sectors.⁷² DoEs are performed from a pre-defined list of experiments, and models are built after all experiments have been performed. In contrast, optimisation techniques that use active learning makes use of all the experiments that have been performed previously and can in many cases be more efficient in finding the optimum reaction conditions.

1.4.3 Self-optimisation

The proposal to use optimisation algorithms, which date back to the 1970s, for reaction optimisation was first reported in 2007 by Krishnadasan *et al.* to self-optimize the synthesis of quantum dots.⁷⁷ Since then, optimisation algorithms have been applied to a host of pharmaceutically important reaction classes including oxidations, hydrogenations, and Suzuki-Miyaura cross-couplings, among many others. Self-optimisation is an approach that involves the employment of algorithms and autonomously controlled reactor platforms that rely on automated feedback loops to optimise reactions for a specific reaction output through iterative cycles.¹⁵ The reaction is first run at a set of reaction conditions, analysed inline/online at steady state, and the analytical response is fed back to an algorithm. Based on the response, the algorithm will then suggest and run a new set of experimental conditions, with the aim of identifying the optimal reaction conditions for a specific objective, e.g. yield, space-time yield (STY), or the cost of materials. The data created from previous experiments is used to influence and train the algorithm and reactions are performed until the optimum conditions are reached or a certain termination criterion is met (Figure 11). Examples of these include reaching a maximum number of iterations (which can be useful when reaction material is limited) or deciding to terminate when there have been no significant improvements to the objective after a defined number of iterations. These termination criteria aim to reduce the number of extra experiments that are performed once the optimum has been reached, to reduce unnecessary waste. Optimisation algorithms can be coupled with continuous flow platforms and inline/online PAT for example, nuclear magnetic resonance (NMR),⁷⁸ gas chromatography (GC),⁷⁹ mass

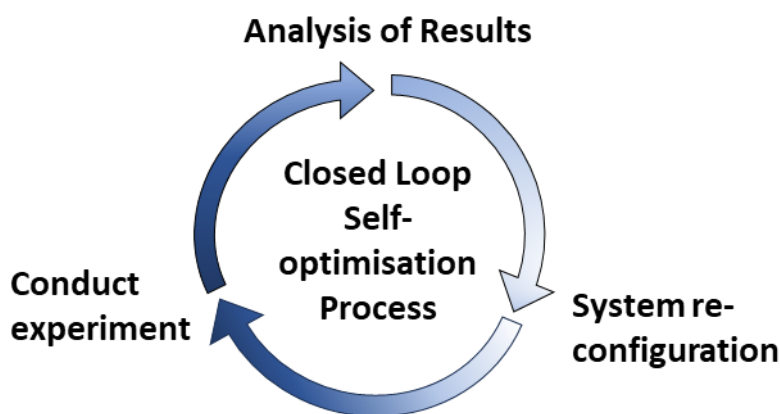


Figure 11. Iterative closed-loop self-optimisation process.

spectrometry (MS),⁸⁰ high performance liquid chromatography (HPLC),⁸¹ Fourier-transform infrared spectroscopy (FTIR),⁸² and/or ultraviolet–visible spectroscopy (UV-Vis),⁷⁷ providing a closed-loop autonomous system that is controlled via a single computer platform. The type of PAT used in each optimisation is chosen to facilitate the analysis of most/all components for the specific reaction, but it also must meet other requirements for the optimisation. Instruments such as HPLC and GC result in the separation of materials and are easy to use but often have long method times (minutes), increasing solvent and reaction waste and resulting in extended optimisation times. Techniques such as FTIR and UV-Vis provide rapid real-time data analysis (in seconds) but require more complex chemometric modelling. Therefore it is important to choose the best analytical techniques to suit the reaction of interest.^{83,84} Self-optimisation as a tool can efficiently explore multidimensional reaction space, reducing the number of required experiments to find optimum conditions for the desired objective. This has significant benefits in reducing the material consumed and therefore making the approach greener and cheaper. Automated self-optimisations also have the benefit of often being able to be performed in the typical downtime of the chemist, for example overnight, exploiting previously unused reaction time, making this approach more efficient and reducing the time taken to find optimal conditions.¹⁵

Optimisation algorithms can be used to optimise reactions in both batch, typically via the use of high throughput experimentation techniques, and in continuous flow.⁷² Most reported cases in the literature are performed on simple reactions in homogeneous systems. Performing these optimisation approaches on multiphase systems is much more challenging and often requires specialist equipment to ensure the separation and accurate analysis of only one or multiple phases.⁸⁵ There are many optimisation algorithms available to choose from and selecting the right one to explore the reaction space is important, as some algorithms require *a priori* chemical and mechanistic knowledge which is not always available for heterogeneous systems.⁸⁶ The understanding of heterogeneous catalytic reactions is low when compared to homogeneous catalysis. The reaction mechanisms of homogeneous systems are easier to identify as there are a wider range of direct techniques that can be used, such as monitoring the catalyst and reactant molecules during the reaction (e.g. NMR, single crystal X-ray diffraction). Heterogeneous systems are more difficult to monitor and are

identified by indirect methods, which observe the products and not the catalyst itself.^{87,88} Typically, self-optimising algorithms can be split into two categories, local and global, which are designed for specific optimisation problems.

1.4.3.1 Local optimisation algorithms

Local optimisation algorithms are useful when there is a single optimum in the reaction space as this algorithm can work efficiently to find a nearby optimum. However, when the reaction surface becomes more complex, with multiple optima present, a local optimisation algorithm may fail to find the global optimum of the system. The reaction space may have multiple areas (shown in Figure 12) where the surface converges, causing the algorithm to become trapped in a local optimum. In these cases, a global optimisation algorithm may be more appropriate.^{63,89}

The basic simplex algorithm was first introduced in 1962 by Spendley *et al.*, and is a ‘black-box’ derivative-free algorithm that requires no information prior to starting its exploration of the surface.⁹⁰ The simplex algorithm moves through the reaction space by creating a convex polyhedron with $n + 1$ vertices (where n represents the number of variables that are being explored) within the variable bounds set by the user (visually shown in Figure 13).⁹¹ The algorithm then takes the vertex/data point that has the poorest results and moves on to exploring the area of the design space in the direction that reflects from this vertex through the centre of the opposite vertices.^{15,68} This workflow is continued iteratively, until the optimum conditions are found in the design

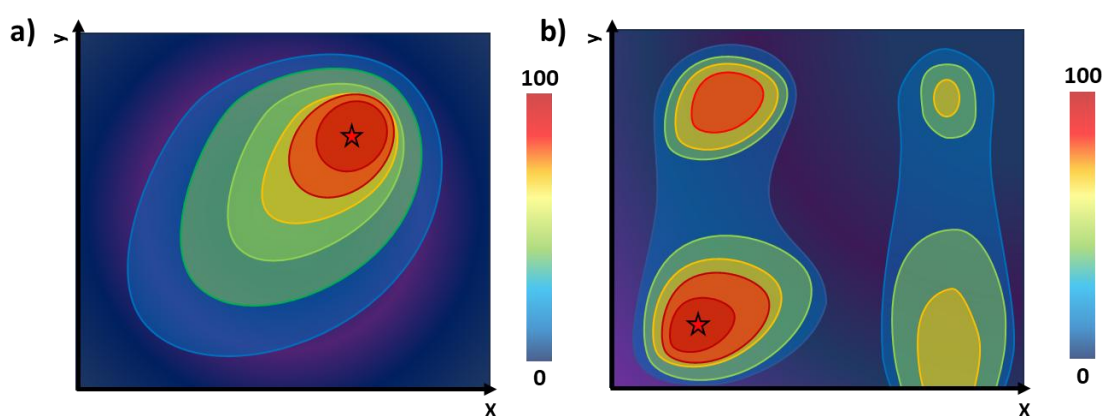


Figure 12. Graphs that represent two response surfaces, a) a surface which contains only one optima, and b) a surface which contains multiple local optima.

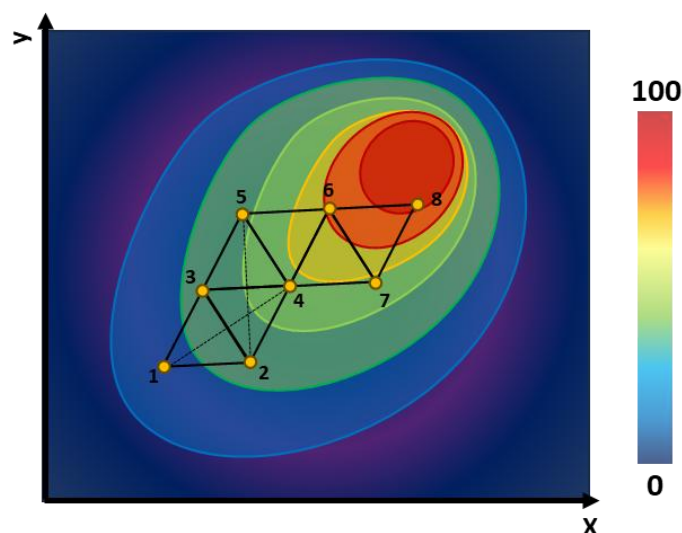


Figure 13. Visualisation of a basic simplex optimisation for a two dimensional system.

space. It can be difficult to approximate the correct initial simplex size without previous knowledge of the reaction space, and the algorithms performance is closely related to the starting point of the simplex. Too small of a simplex size results in an inefficient optimisation, with an excess of experiments being performed. Too large of a simplex size could lead to the optimum conditions being missed due to too large of a polyhedron.

The basic simplex algorithm has been modified to try and alleviate this issue.⁹² One of the most commonly used is the Nelder-Mead Simplex (NMSIM) which allows for other possible transformations of the simplex via predefined coefficients, including the ability to change its size and shape (the allowed geometrical transformations shown in Figure 14).^{91,93} This allows for a more efficient exploration of the design space and makes the simplex algorithm adaptable to local landscapes, contracting when nearer to local optima, and expanding to traverse the design space quicker, helping to identify the optima in fewer iterations.⁹⁴ One such demonstration of the NMSIM algorithm was

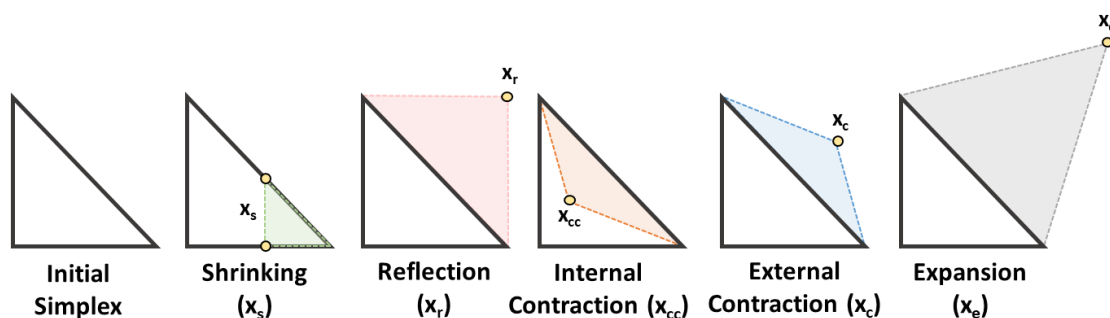


Figure 14. The possible transformations involved in a Nelder-Mead simplex optimisation.¹¹⁰

reported by Cortes-Borda *et al.* in a Heck-Matsuda reaction for a four variable optimisation.⁹⁵ Three individual optimisations were performed with individual single objectives – to maximise the yield of the reaction, to maximise the reaction productivity, and to minimise the production costs of the reaction. A yield of 92% in 25 experiments, a productivity of 427.2 mg hr⁻¹ in 13 experiments, and a minimum cost of production of 8.5 € g⁻¹ in 25 experiments were found with the NMSIM algorithm. The group showed the application of the algorithm to optimise a variety of industrially useful objectives for a multivariable problem.

Further modifications to the simplex algorithm have been applied to increase its adaptability to different problems. One such modification is the super modified simplex (SMSIM) developed by Routh *et al.*, where the defined coefficients for expansion and contraction transformations can be altered by the algorithm autonomously during the optimisation.^{68,91} This makes the algorithm more versatile as it has further adaptability to different design space landscapes. The expansion transformation is visually shown in Figure 15. The initial simplex is created and is shown as points 1, 2, and 3. The typical reflection point 5 is carried out, reflected from the worst experimental point 1, and a result is predicted for experimental point 4. The optimum expansion distance is then calculated from a second order polynomial taken through points 1, 4, and 5, given by the dotted red line in the figure. When an expansion leads to no improvement in the objective function, the model can predict an appropriate contraction distance along the same red line.⁹⁶ This modified version of the simplex can explore the design space more

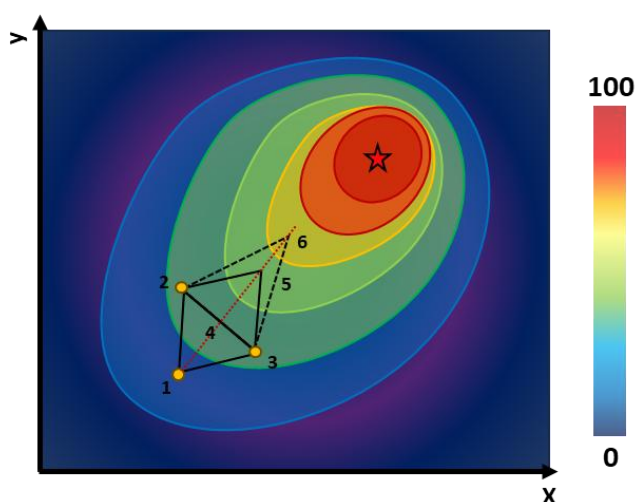


Figure 15. Visualisation of the SMSIM algorithm for a two dimensional reaction surface.

efficiently due to the adaptability of these coefficients, allowing many more sizes of transformations to be possible.

One example of the application of SMSIM to a heterogeneous system is by Fabry *et al.* in the optimisation of the hydrogenation of benzaldehyde and similar substrates using a ThalesNano H-cube. This publication was particularly significant as it showed the first reported instance of a fully autonomous self-optimisation for a three-phase heterogeneous system.⁸⁶ The group used the SMSIM algorithm to explore the 3D design space with three different variables: temperature, flow rate of the substrate, and hydrogen pressure. The H-Cube and inline FTIR analysis were connected to the computer to create a continuous control feedback loop which allowed the algorithm to analyse responses and conduct the next experiment autonomously. The use of FTIR was shown to be beneficial in the self-optimising platform, with the authors noting its convenience and faster analysis times when compared to other online/inline PAT techniques. Four initial starting conditions for the SMSIM were defined and a total of 17 experiments were performed in the optimisation of the hydrogenation of benzaldehyde, with the optimum conditions found after only 14, at high temperatures, high substrate flow rate and high hydrogen pressures. Further optimisation studies were performed on the hydrogenation of ethylphenyl glyoxylate, finding optimum conditions in ten experiments and identifying key relationships between hydrogen pressure and the substrate flow rate; increased hydrogen pressure was required to achieve high yields at higher liquid flow rates.

Inline PAT techniques allow the reaction conditions to be related to the catalyst's activity in the reaction and local optimisation algorithms have been shown in many cases to deliver optimum conditions on relatively short timescales. However, the experimental noise of some chemical systems can cause local optimisations to terminate prematurely and not find the true optima of the design space. When this is the case, global optimisation algorithms may be more appropriate.

1.4.3.2 Global optimisation algorithms

In more complex systems that have more than one optima, or when little is known about the reaction before optimisation, a global optimisation algorithm can be

more useful in balancing the exploration and exploitation of the reaction space, to identify the global optimum in a reasonable number of experiments.

The stable noisy optimisation by branch and fit (SNOBFIT) algorithm was developed by Huyer and Neumaier as a derivative-free global optimisation tool that can be used to optimise for single objectives.⁹⁷ The algorithm works by suggesting new reaction conditions in batches, based on previous experimental responses to explore the design space and optimise for a specific objective function. It generates local polynomial surrogate models in the most attractive areas of chemical space, but also explores distant regions of the reaction space to ensure that the algorithm is not converging around a suboptimal local optima.^{7,15} This is beneficial as the algorithm is often more likely to find the global optimum of the system, however, this can result in an increased number of iterations. This optimisation algorithm's first reported use for chemical reaction optimisation was in the formation of CdSe nanoparticles in a homogeneous microfluidic platform by Krishnadasan *et al.*⁷⁷ However, there are much fewer examples demonstrating the use of the SNOBFIT optimisation algorithm in heterogeneous systems. One example reported by Bedard *et al.* described a modular plug and play automated reactor system that could be used to optimise a variety of chemistries in one adaptable platform.⁹⁸ A heterogeneously catalysed Suzuki-Miyaura cross-coupling was optimised using a packed bed continuous flow system with a SilicaCat DPP-Pd catalyst, shown in Figure 16. The system performed 30 experiments in eight hours to achieve the optimum conditions with closed-loop feedback control provided by online HPLC analysis. The five variable optimisation found conditions to achieve a product yield of 96% with a throughput of 630 mg hr⁻¹. A substrate scope in the reactor platform was also performed under the optimised conditions for nine more molecules, all attaining >84% conversion and throughputs of >832 mg hr⁻¹. This

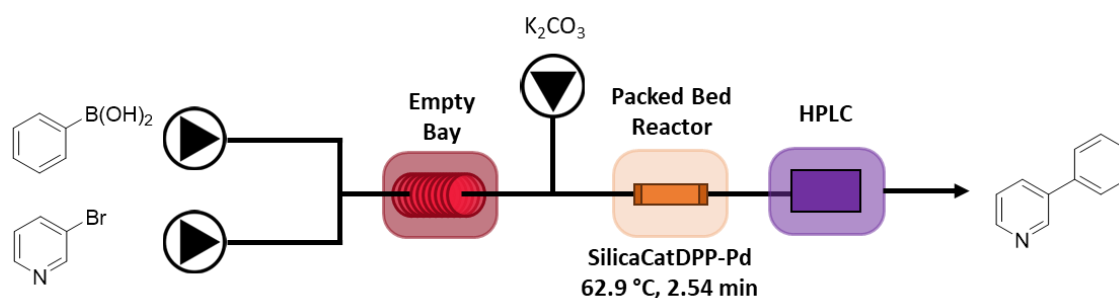


Figure 16. Suzuki-Miyaura cross-coupling performed by Bedard *et al.* in modular plug and play optimisation platform.⁹⁸

substrate scope study showed the versatility of the system and its ability to produce synthetically useful amounts of desired molecules in a short period of time after only one optimisation with the SNOBFIT algorithm.

Bayesian optimisation (BO) algorithms have seen increasing attention in the literature as an efficient ‘black box’ global optimisation tool for expensive to evaluate functions (Figure 17).⁹⁹ The algorithm is first initialised with an initial data set to create a probabilistic surrogate model. The algorithm then predicts the response for the design space for a specific objective (defined by the objective function) and conducts experiments to reduce the uncertainty in the surrogate model.¹⁰⁰ It does this by exploring or exploiting areas that have a high value in the acquisition function (for maximisation objectives). This is done iteratively, where, most often, a predefined hyperparameter controls the trade-off between exploitation and exploration of the design space, with the aim to find optimum reaction conditions for the given objective function (Figure 18).¹⁰¹

BO has been shown to be useful in the optimisation of chemical reactions, such as that reported by Slattery *et al.* in a novel reactor platform ‘RoboChem’ for the self-optimisation of photocatalytic reactions.¹⁰² The open source ‘Dragonfly’ Bayesian optimiser¹⁰³ was used for a single objective self-optimisation to maximise the yield of a photocatalytic hydrogen atom transfer alkylation, by optimising the concentration, THF loading, photocatalyst loading, light intensity, and residence time. 19 experiments in

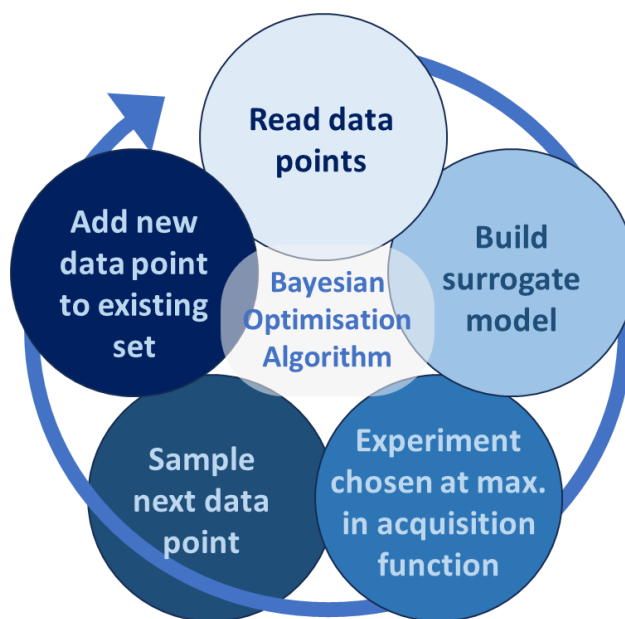


Figure 17. Diagram showing the workflow of a Bayesian optimisation algorithm.

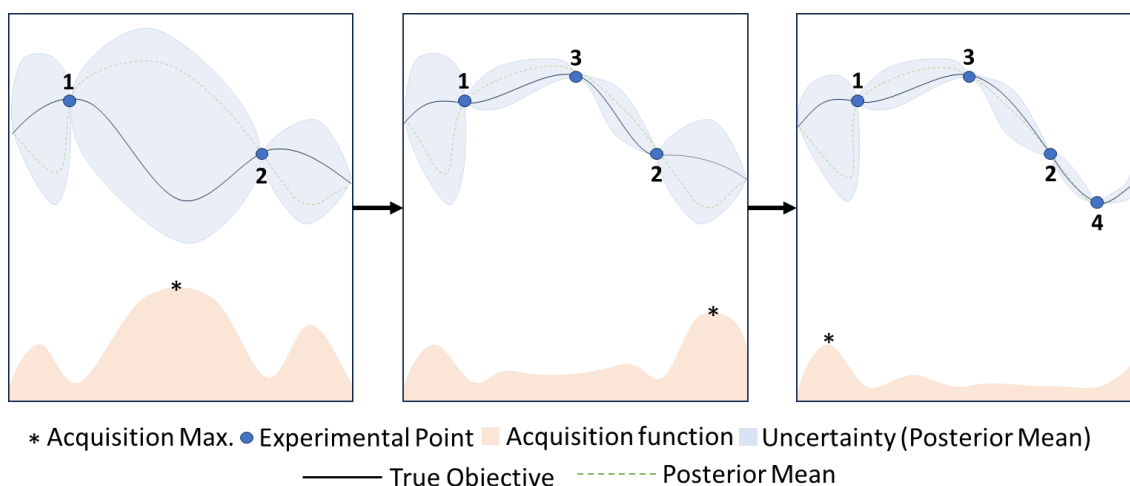


Figure 18. Successive iterations of a Bayesian optimisation approach to maximise an objective. Each new data point is conducted in the area at the maximum of the acquisition function, which will either favour exploitation or exploration, based on a defined hyperparameter, and reduce the uncertainty in the model.

total were performed, with optimum conditions found for the five variable system after only 17, with an isolated yield of 97% for the alkylated product.

The combination of both local and global optimisation algorithms has recently been explored. Liang *et al.* developed a novel optimisation protocol that involved initially employing a NMSIM algorithm to explore local optima in the design space, before switching to a Bayesian optimisation algorithm to ensure that the global optimum of the system is not missed.¹⁰⁴ The BO algorithm was initialised with the initial simplex data to provide preliminary information about the response surface and aids the local optimiser in ensuring the accuracy of the optimisation. This new methodology was demonstrated in a three-phase gas-liquid-solid hydrogenation of nitrobenzene, 3,4-dichloronitrobenzene, and 5-nitroquinoline showing that the new protocol could outperform both the OVAT approach and pure BO procedure. Optimum yields were found in all three case studies in fewer experiments, with significantly higher yields found in the 5-nitroisoquinoline example.

Most reports in the literature show the exploration of continuous variables such as temperature or residence time. The introduction of discrete variables (for example, catalyst type, catalyst loading, base, or solvent) are much less widely described and are most often explored using high throughput screening platforms, before the continuous variables are optimised in continuous flow.⁷² Discrete variables require significant changes to reactor designs to accommodate their evaluation, including the need for

specialist equipment and adaptations to the optimisation algorithms. However in recent years there have been several publications that highlight the development of new systems and algorithms that can investigate these parameters.^{105,106} The examples highlight the benefits of optimising both continuous and discrete variables simultaneously, highlighting the significant interactions present between them, yielding new, previously undiscovered optima. The exploration of discrete heterogeneous catalysts is underreported but these variables could exhibit substantial interactions with other variables, leading to drastically different yields and selectivities for reactions.

Global optimisation algorithms have been shown to efficiently explore multidimensional design spaces and find optimum conditions in a minimum number of experiments. All the optimisations discussed so far have explored single objective problems. It is often useful to explore the effect of reaction conditions on more than one objective, as a process must satisfy multiple criteria to be taken forward for scale up.

1.4.3.3 Multi-objective algorithms

Multi-objective optimisation algorithms have been developed to optimise for more than one response objective simultaneously. This allows other important aspects of the reaction to be considered during the optimisation, for example environmental and economic factors, as well as reaction yield. When a reaction is optimised for multiple conflicting objectives, as one objective is improved another is worsened – a non-dominated solution, the optimum conditions of each objective lie in different areas of the design space meaning there is no one single optimum for the reaction. Usually this would require multiple single objective optimisations to find the individual optima for each objective.¹⁰⁶ Multi-objective optimisations find trade-offs between the objectives that form a Pareto front of non-dominated solutions that shows their relationship, and can be plotted as a trade-off curve (as shown in Figure 19).¹⁰⁷ The most common way in which this is done is through hypervolume improvement, where the algorithm will suggest conditions that lead to improvements in the hypervolume of the system, finding a good distribution of points along the Pareto front.¹⁵ The user can then make an informed decision about the reaction conditions that is a compromise of the

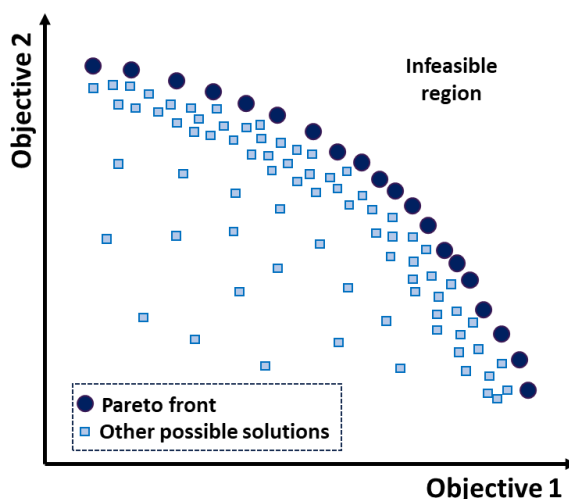


Figure 19. The Pareto front created by a multi-objective optimisation algorithm, which shows the trade-off between two objectives, where $\circ$ = Pareto front, and $\square$ = possible solutions.¹⁵

response variables based on their desired outcome of the experiment. ‘Green processes’ use solvents and catalysts that have environmentally friendly life cycles which include their design, manufacture, and disposal. One way in which multi-objective algorithms can be useful is in making ‘greener’ processes, by minimising the use of solvents, such as toluene, or the use of precious metal catalysts, which are nonabundant, expensive and can be difficult to recover.

Recent work published by Qi *et al.* shows the use of BO and a multi-objective optimisation algorithm (qNEHVI) in the self-optimisation of a multiphase heterogeneous isomerisation reaction to produce hexafluoroacetone, an important fine chemical used in medicine.¹⁰⁸ The group developed a micro-PBR system, filled with an AlCl_3 Lewis acid catalyst, and a self-optimisation was performed where the reaction temperature and gas hourly space velocity were optimised to maximise the conversion and minimise the energy cost of the reaction kg^{-1} of the product. A Pareto front was found, with 25 total experiments performed in the two variable optimisation, where any increase in conversion would lead to detrimental increases in energy costs. The trade-off between these variables was initially shallow, where a conversion of 98.6% could be achieved with a small increase in the energy cost of the reaction conditions. However, above this conversion value, a significant increase in energy costs was experienced due to the use of high temperatures in the reaction. The group could then decide, based on this trade-off that 98.6% was an acceptable yield with an energy cost of $0.0121 \text{ kWh kg}^{-1}$. The group demonstrated the use of a multi-objective optimisation on a two-phase

system; however, this was only limited to two reaction variables. Increasing the number of reaction variables will lead to further complexity and require an increase in the number of experiments for the optimisation.

Autonomous, self-optimising flow reactor systems allow large regions of reaction space to be searched on shorter timescales and lead to a reduction in material use, making multi-objective optimisations attractive in these platforms. However, the increase in variables and objectives leads to an increase in experiments required. This application is not always feasible in heterogeneous systems due to catalyst deactivation, and there are limited examples of their use in the literature.¹⁰⁹

1.5 Project aims

Heterogeneous catalysis forms a large part of commercial chemical synthesis and is set to increase with the push to convert traditional processes to become more sustainable and satisfy the 12 principles of green chemistry. This review highlights the benefits of using continuous flow chemistry for heterogeneous systems, but also outlines the challenges faced in converting existing systems to PBRs (e.g. deactivation and the lack of appropriate catalyst supports). The use of self-optimisation can afford optimised processes on short timescales, with minimum human contact, and accelerates reaction development towards scale up. Flow reactors provide an ideal opportunity for the implementation of automation, PAT, and self-optimisation, and has been demonstrated on many homogeneous systems in the last few decades. However, the application and reported examples of these systems applied to heterogeneous three-phase chemistries for the production of APIs is limited.

Chapter 2 shows the development of an automated closed-loop self-optimising PBR platform that will be used in all subsequent chapters. The system is characterised initially with a simple nitrobenzene reduction, leading to a full self-optimisation of the process with two single objective optimisation algorithms. The self-optimisation protocol is then applied to a second reaction, showing that a minimal number of preliminary experiments are required before a self-optimisation can be conducted.

Chapter 3 focuses on applying the developed platform to a more complex API reaction step. The process is first investigated in batch on a small scale, to choose an appropriate catalyst and investigate reaction conditions. The reaction is then translated into the continuous flow PBR platform and optimised using a BO algorithm. The catalyst loading in the reaction is investigated and the results are compared to previously optimised conditions found using an OVAT approach.

Chapter 4 investigates the integration of heterogenous systems into multistep processes and compares single step and multistep optimisation protocols for their effect on the optimisations efficiency. The work employs multipoint sampling and a tube-in-tube gas-liquid separator to allow complete telescoping and analysis of the two reaction steps.

Chapter 5 addresses an example where catalyst deactivation is experienced. Deactivation means that self-optimisation of the reaction is not possible, so an alternative novel methodology is explored using a simplex algorithm. Simulations are used in order to investigate parameters *in silico* before being applied to a real system.

Chapter 6 addresses the need for new active stable catalysts for heterogenous catalysis in continuous flow in both lab and pilot-scale PBRs. Different NP deposition methods on to spherical activated carbon beads are investigated and compared to commercial pelletised supported NP catalysts. A novel recirculating platform is developed for catalyst screening on a small scale, and the most successful catalyst candidate is evaluated for its use in the scaled up PBR platform developed in Chapter 2.

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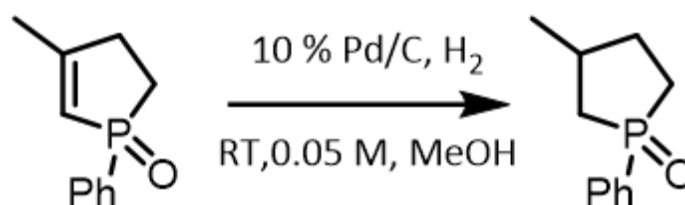
Chapter 2 : The Development and Characterisation of an Automated Self-optimising Packed Bed Reactor Platform

2.1 Introduction

PBRs are one of the most widely used reactor types for integrating heterogeneous catalysts into continuous flow platforms and have been documented for their use in a range of chemical industries since the 1930's (i.e. petrochemicals and fine chemicals).¹ This well-established reactor is most often used for chemical processing applications such as, absorption, separation, and catalytic reactions for multiphase processes. There has been an increasing interest in their use in the pharmaceutical sector for heterogeneous and enzymatic based catalytic reactions. This is because the catalyst can be recovered and reused easily from the reaction mixture, unlike homogeneous catalysts, reducing operational costs and the number of reaction steps/separations required to purify the product. Heterogeneous hydrogenations account for 10-20% of reactions performed in the pharmaceutical industry,¹ with GSK alone reporting that 77% of their fundamental gas-liquid transformations are heterogeneous hydrogenations.²

2.1.1 Commercial PBR

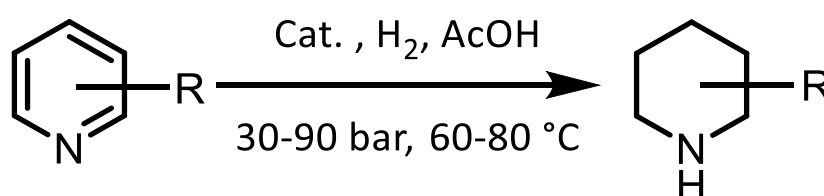
Commercial automated PBR flow platforms can perform heterogeneous hydrogenations with great efficiency on short timescales in a relatively small footprint unit.³ The H-Cube, developed by ThalesNano, is a cartridge-based continuous high pressure (100 bar) hydrogenation system and produces hydrogen gas via the electrolysis of distilled water, which can be directly flowed into a PBR.^{4,5} The system works by creating hydrogen *in situ* with water and uses pumps to flow the liquid and gaseous reagents through the column to perform reactions under the desired conditions specified by the user. It can also be adapted to use hydrogen cylinders, as water electrolysis has a limited gas flow rate restricting the throughput capabilities in the platform. Pre-packed columns can be purchased with a variety of different transition metal supported catalysts, meaning the handling of pyrophoric and/or dangerous



Scheme 1. The reaction performed with the H-Cube Midi to form the phosphine pre-catalyst for a Wittig reaction reported by O'Brien *et al.*⁷

transition metals catalysts is minimised. Empty cartridges can also be purchased, allowing the user the option to test their own catalysts in the system.⁶

The use of this commercial system was demonstrated by O'Brien *et al.* to perform a 10 wt.% Pd/C heterogeneously catalysed hydrogenation to produce a phosphine oxide pre-catalyst for the Wittig reaction, shown in Scheme 1.⁷ The Wittig reaction is used to form carbon-carbon double bonds and is an important chemical reaction step in the synthesis of numerous APIs. Many catalysts have been reported and successfully used in the Wittig cycle; however, O'Brien *et al.* created a phosphine based catalyst that could convert aryl, alkyl, and heteroaryl aldehydes into alkenes with varying yields. The H-Cube was also used by the Kappe group to perform heterogeneously catalysed hydrogenations of substituted pyridines in continuous flow.⁸ They compared the reactions in both batch and flow showing that the system could be fully automated, noting the process was more efficient and safer in flow than when the same reactions were performed in batch. A range of catalysts (Pd/C, Pt/C and Rh/C) were tested in the hydrogenation of functionalised pyridines showing nearly full conversion (>99%) could be achieved in all the molecules that were investigated (shown in Scheme 2). As they changed the reaction conditions, the selectivity of the reactions was affected, meaning the system could be fine-tuned to favour one particular diastereomer.



Scheme 2. A general scheme showing the conditions for the reduction of functionalised pyridines where R is a variety of different functional groups and cat. represents a range of catalysts tested (Pd/Al₂O₃, Pd/C at various loadings) reported by the Kappe group.⁸

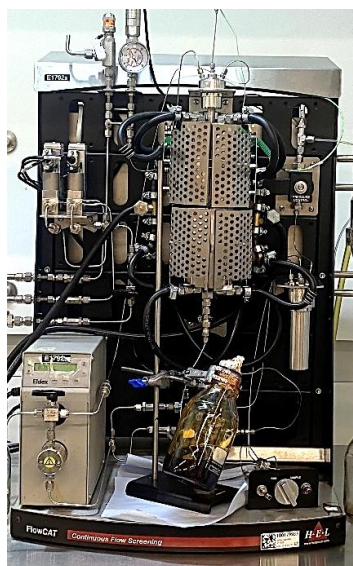
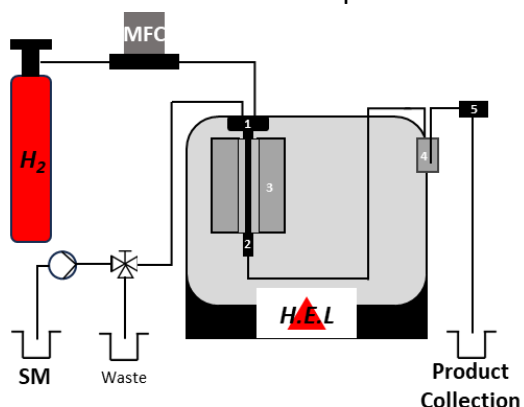


Figure 20. H.E.L. FlowCAT benchtop PBR that can be used for automated hydrogenations.

Another commercial automated PBR platform was created by the H.E.L. company that can perform high pressure (up to 200 bar) reactions with gas cylinders as the hydrogen source (shown in Figure 20).⁹ The FlowCAT is an automated benchtop system that pumps liquid and gas feeds through a packed column that can be purchased in many sizes to accommodate the desired reactor dimensions (6, 12, 18, or 24 mm outer diameter). The Ley research group has demonstrated its use and capability to scale up heterogeneously catalysed reactions. A notable example is in the process intensification of the partial and full hydrogenation of ethyl nicotinate performed in the system (Figure 21).¹⁰ Pyridines are industrially important as they are the precursor to more interesting functionalised piperidines, which can be used to make biologically active products. The full hydrogenation of ethyl nicotinate was achieved at 100 bar hydrogen pressure, 160 °C, and a gas flow rate of 0.6 L min⁻¹ with complete selectivity for the fully



1. G/L mixing zone 2. Trickle bed 3. Heating/cooling jacket 4. G/L separator 5. BPR

Figure 21. Schematic of the H.E.L. FlowCAT system and its components.

Table 2. The operating conditions of the H.E.L. FlowCAT and ThalesNano H-Cube Pro reactor platforms.^{4,9}

Conditions	HEL FlowCAT	ThalesNano H-Cube Pro
Temperature	0-550 °C	10-150 °C
Pressure	200 bar	100 bar
Flow Rate	Variable depending on pump	0.3-3.0 mL min ⁻¹
H ₂ Production	Gas cylinder	Electrolysis of water
Reactor Dimensions	6, 12, 18, 24 mm OD, 15 cm length	30 or 70 mm length

hydrogenated product. The group managed to achieve a high-throughput of close to 2 kg day⁻¹ with a PBR of 5 wt.% Rh/Al₂O₃ (4 g) catalyst, showing the systems capability to produce products on a scale which is suitable for the application in a pharmaceutical manufacturing setting.

These reactor platforms demonstrate the applicability of the PBR to chemical research,¹¹ and their individual operating conditions are shown in Table 2. The H.E.L. FlowCAT offers a platform that can use higher temperatures and pressures and is not limited by the rate of hydrogen production. The conditions outlined in the table are for the standard FlowCAT, but this platform can be adapted to reach lower temperatures, use other gases, and have a variety of reactor lengths depending on the process it is being used for. This makes the platform more modular and not only useful for hydrogenations but many other chemical transformations. The H-Cube Pro is a more compact unit which operates under safer conditions as it generates hydrogen *in situ*, but is limited as the equipment, such as the pump and BPR, are encased in the system and cannot be adapted as easily as the FlowCAT.

These commercial systems were used to aid the development of an automated reactor platform and provided a base for the conditions that would be required in order to make the work applicable to industry and other research groups. Automated continuous flow reactors can be coupled with optimisation algorithms and controlled via a computer to explore chemical reaction space. However, commercial platforms are usually controlled via the company's own software that is often inaccessible to the user for the integration of their own optimisation platforms.

2.1.2 Examples of bespoke PBR self-optimisations

Many other research groups have developed their own bespoke automated PBR platforms in order to overcome these challenges. Qi *et al.* developed a micro-PBR platform for a multi-objective optimisation to produce hexafluoroacetone with an AlCl_3 Lewis acid catalyst.¹² The system was automated, but there was no integration of online analysis, and all samples were analysed offline via GC-MS. They performed a two variable optimisation (changing temperature and the gas hourly space velocity – ratio of gas flow rate to the amount of catalyst) and simultaneously optimised both the yield of the reaction, and the energy cost kg^{-1} of product of the experimental conditions. Using a BO algorithm based on the q-noisy expected hypervolume improvement acquisition function, a trade-off was seen between the two objectives forming a Pareto front, and a ‘best compromise’ optimal point was determined after 14 experiments (including LHC initial conditions).

Liang *et al.* also reported a Bayesian based optimisation to optimise complex three-phase continuous reactions with a micro-PBR, for four reaction variables (temperature, liquid flow rate, hydrogen pressure, and gas flow rate).¹³ The group showed the use of a new optimisation approach, combining an initial NMSIM, followed by a BO to find the global optimum conditions of a process. The simplex is initialised and allowed to perform a number of experiments equal to three times the number of variables being optimised. If the objectives requirements are satisfied, the optimisation would be stopped, otherwise a Bayesian algorithm would be initialised with the simplex

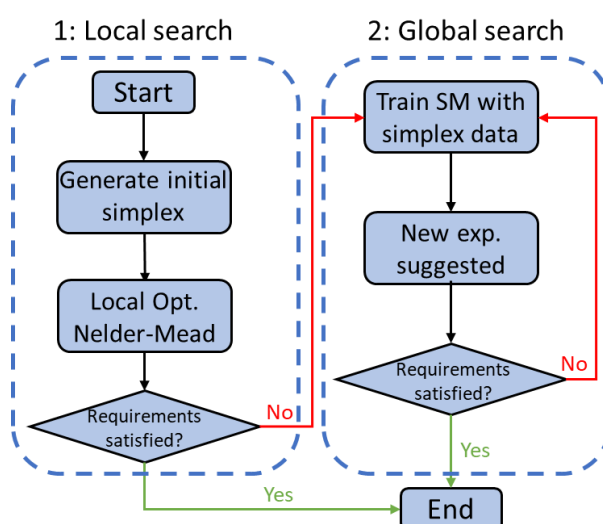


Figure 22. Flow diagram for new proposed combined optimisation protocol reported by Liang *et al.*¹³

data and allowed to optimise the process further (Figure 22). This reactor did not have any online analysis, and all reactions were, again, sampled offline to a GC.

It is often difficult to incorporate online analytics into multiphase systems, as most analytical equipment cannot tolerate and analyse both liquid and gas phases simultaneously. For example, gas bubbles cause significant problems to online and inline PAT, such as UV-Vis, HPLC, and NMR, resulting in the poor analysis of liquid reactants. Therefore, more research is required into creating fully automated gas-liquid separators that can separate the phases to allow for accurate analysis of the reaction, making the implementation of PAT into these systems simpler. By transforming platforms into fully autonomous and closed-loop systems, the user could save significant time sampling the reaction, increasing the efficiency of the overall process. Therefore, it is imperative in this work that online analysis is integrated into the system to make a fully autonomous, self-optimising platform.

2.2 Aims

In this chapter the construction of a bespoke automated PBR platform will be described. Important safety features will be outlined as well as specific equipment choices. The system will be coupled with online analysis to provide a control feedback loop to facilitate the integration of a bespoke optimisation platform developed previously in MATLAB. This will allow the self-optimisation of heterogeneous hydrogenation reactions to be performed for important API reaction steps.

2.3 Results

2.3.1 Automated reactor construction

A fully automated PBR platform was developed for use in the self-optimisation of heterogeneous reduction reactions (Figure 23 and Figure 24). Automated precise control of the liquid flow rates, gas flow rates, temperature, and pressure were required to achieve this, in order to understand how these variables affected the outcomes of chemical reactions. HPLC dual piston pumps were used to allow the liquid reagents to

be pumped at high pressures, and back pressure regulators (BPRs) were placed on their outlets to ensure accurate flow rates were achieved. A mass flow controller (MFC), calibrated for hydrogen gas, was used to precisely control gas flow rates into the system. To protect the MFC from liquid back flow, which is problematic for the electronic systems in MFCs, a check valve was placed on the outlet of the gas stream, allowing only one way flow. Pressure relief valves were placed at either end of the catalyst bed and adjusted to be 10 bar above the operating pressure of the system. This was to ensure that if the system contained a blockage (for example at the filter on the outlet of the reactor) it would not over pressurise. Pressure gauges were placed at the top and bottom of the catalyst bed to measure any pressure changes in the system. The catalyst was contained and packed in a stainless steel column (1/4" or 1/2" OD depending on the catalyst used) and more details of catalyst packing can be found in section 2.5.2.3. The column was encased in an aluminium heating block which contained holes for heating cartridges and a thermocouple. Heating cartridges were connected to a Eurotherm temperature controller, which was used to control the temperature of the catalyst bed. A thermocouple was fitted with Swagelok and connected to a cross piece at the bottom of the reactor. This temperature could be measured manually or connected to the Eurotherm temperature controller for monitoring of the temperature at the outlet the reactor. A 200 μm filter was placed after the outlet of the reactor, to ensure that the downstream equipment would not be blocked or affected by solid

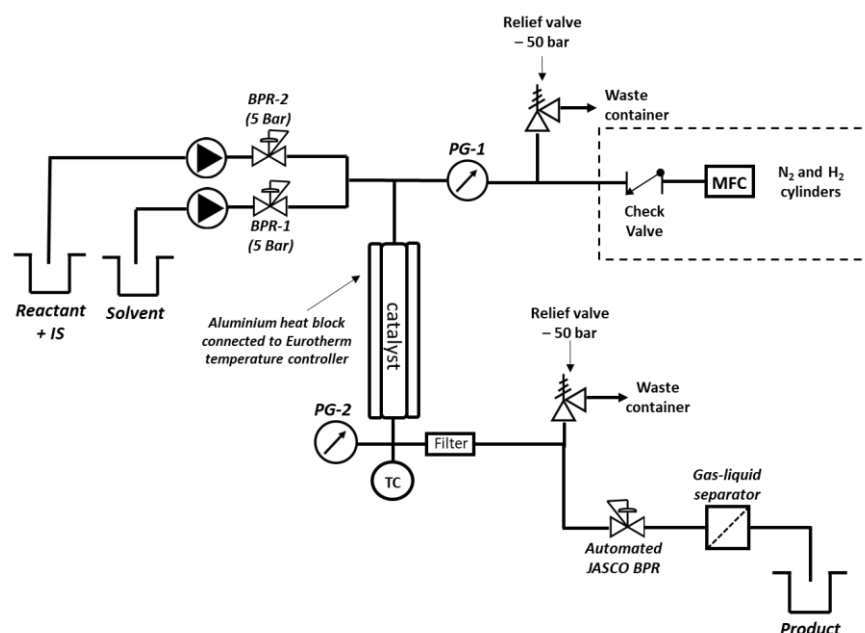


Figure 23. P&ID of the initial automated PBR platform.

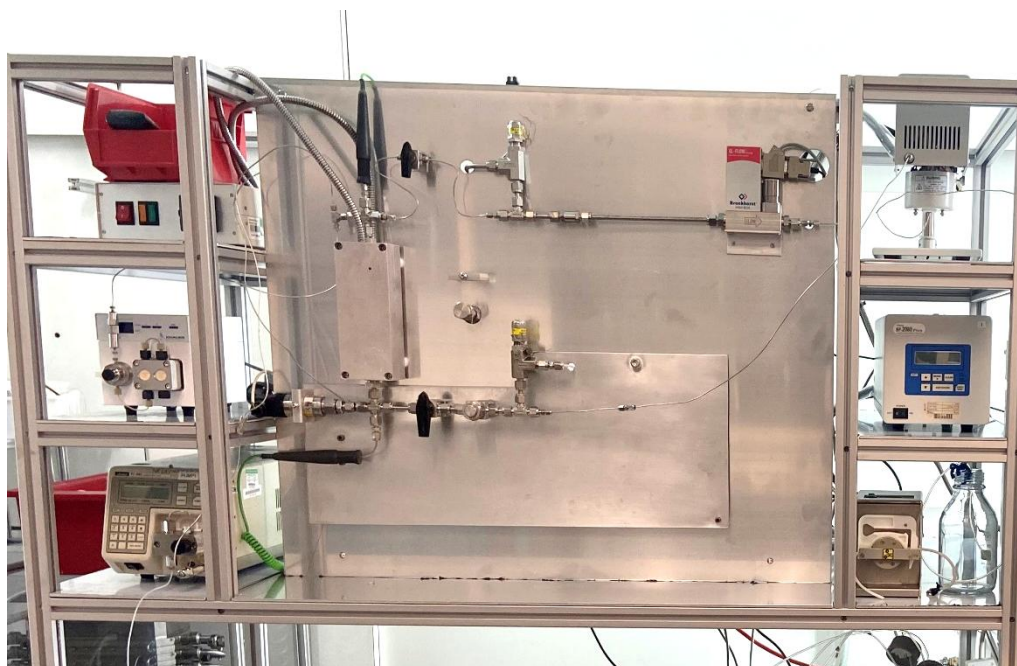
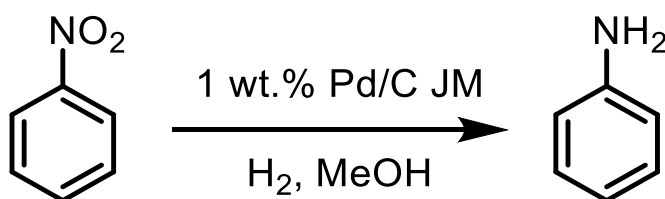


Figure 24. Image of the PBR platform designed for performing heterogeneous reduction reactions.

particles (for example, if the catalyst support were crushed under high pressures). An automated needle valve based BPR was placed at the end of the reactor to control the pressure of the entire system. Initially, a cyclone gas-liquid separator was used to separate the two phases after the BPR, and samples from the reaction could be collected at the bottom for analysis offline. With the initial system construction complete, the equipment was connected to a computer via a bespoke automated control graphical user interface (GUI) written in MATLAB. This could be used to control the liquid pumps, MFC, Eurotherm, and BPR.

2.3.2 Reactor characterisation – nitrobenzene reduction

Initial characterisation tests in the system were performed to check the functionality of the platform using a model nitrobenzene reduction reaction (Scheme 3)



Scheme 3. The reduction of nitrobenzene to aniline with commercial pelleted 1 wt.% Pd/C catalysts from JM.

with commercial Johnson Matthey (JM) 1 wt.% Pd/C catalyst pellets that are described in more detail in Chapter 6. These tests would also provide knowledge on the length of time required to reach steady state conditions for future optimisations. It was essential that the reactions were reproducible and that there was no significant deactivation of the catalysts for this reaction.

2.3.2.1 Catalyst stability

A catalyst stability test was conducted for three hours in the automated PBR platform described above, following the typical procedure as outlined in section 2.5.2.2. Reaction conditions were applied to the reactor to ensure a good yield for the reaction and sampled at the end of the reactor for offline analysis via GC (a typical GC chromatogram is shown in section 2.5.2.4); the results are shown in Figure 25. The reaction profile shows an initial period of high activity of the catalyst before steady state of the catalyst is reached, and this reaction profile was seen on every subsequent reaction that was performed in the catalyst bed. Before the reaction is performed, the catalyst is activated with hydrogen and the reaction solvent, meaning there is a large amount of hydrogen adsorbed to the catalyst surface before the reaction is started. Therefore, when the liquid reagent is pumped through the system, there is an initial high concentration of the product made, due to this excess of hydrogen on the catalyst

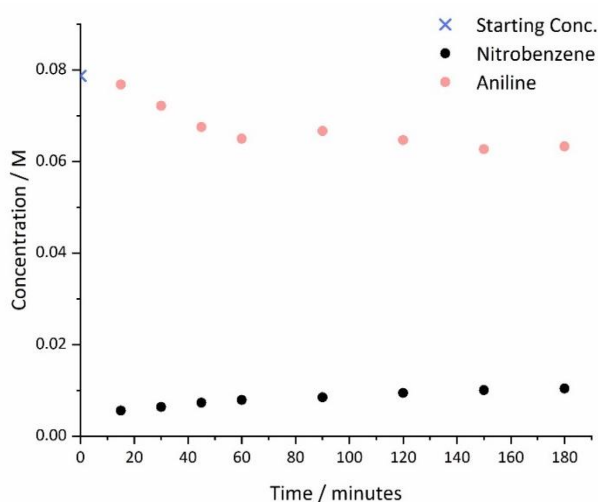


Figure 25. Concentration profile for a catalyst stability test over three hours. Fixed conditions: catalyst – 1 g, temperature – 35 °C, pressure – 20 bar, liquid flow rate – 0.5 mL min⁻¹, H₂ flow rate – 50 mL min⁻¹, and concentration – 0.08 M.

surface causing a higher initial rate of reaction. It can be seen in the figure that it takes one hour for this to reach steady state, when a constant rate of adsorption and desorption from the catalyst surface can be seen. For future reactions, the catalyst will be conditioned for at least one hour before any reaction data is collected, to ensure that the data collected is accurate and reflects the steady state activity of the catalyst, and not this initial high activity period. The resulting solution was also analysed by ICP-MS to investigate metal leaching, and no traceable amounts of Pd were detected during the stability test under these process conditions. All other catalyst stability tests for future reactions were also subject to analysis via ICP-MS to check for deactivation via metal leaching.

2.3.2.2 Changing reaction conditions

After the catalyst had been evaluated, it was then important to prove that different conditions could be applied to the catalyst, and the same yield would be seen when the reactor was returned to the original conditions. This was important to evaluate the repeatability and accuracy of the reaction conditions within the system. The temperature of the reactor was increased from 35 to 50 °C, before reverting back to the original temperature, while keeping all other conditions constant (and the same as the previous stability tests).

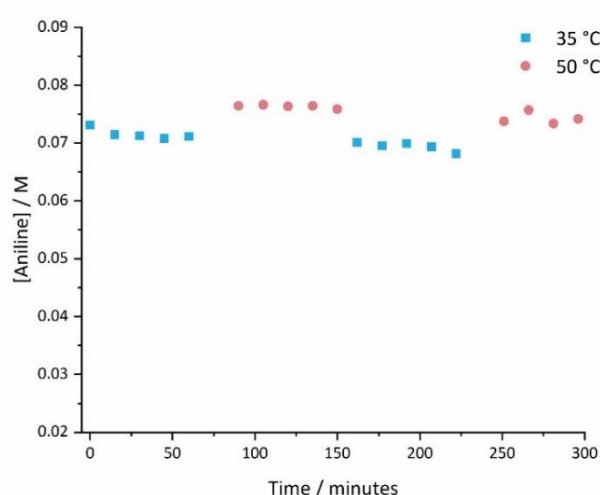


Figure 26. Concentration profile when the reaction conditions were changed during a reaction. Fixed conditions: catalyst – 1 g, pressure – 20 bar, liquid flow rate – 0.5 mL min⁻¹, H₂ flow rate – 50 mL min⁻¹, and concentration – 0.08 M.

The results are shown in Figure 26. There was an increase in the reaction yield when the temperature was increased to 50 °C, which decreased when the temperature was lowered back to 35 °C. This proved that the reaction conditions could be changed during a continuous reaction with the same catalyst bed and return to the same yield as previously seen. This confirmed again that there was no deactivation of the catalyst at these two reaction conditions over this timescale, but also that the reactions were reproducible.

2.3.2.3 OVAT testing

The effect of changing OVAT was then investigated, initially by stepping the temperature of the catalyst bed from 25 to 85 °C while keeping all other reaction variables constant. The same reaction conditions as stated above were used, but the catalyst loading in the column was reduced to 0.5 g, as nearly full conversion was seen for 1 g of catalyst when the reactor was operated at 50 °C. The results are summarised in Figure 27, showing an increase in the concentration of aniline with an increase in temperature applied to the reactor. An average yield for each temperature was calculated and shows a linear increase in the yield of the reaction with temperature, demonstrating an increase in the rate of reaction.

A flow rate ramp from 0.5 to 3 mL min⁻¹ was then conducted in a fresh bed of catalyst while keeping all other conditions constant (50 °C) to investigate the effect of

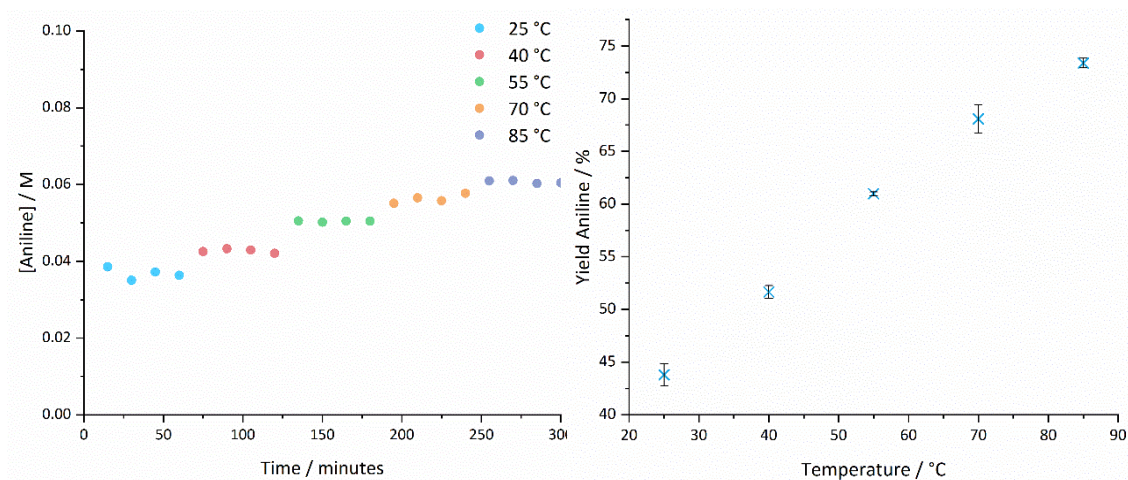


Figure 27. Left - Concentration data for a temperature ramp, right - summary of average yields at each temperature, with error bars calculated from the standard deviation at each temperature.

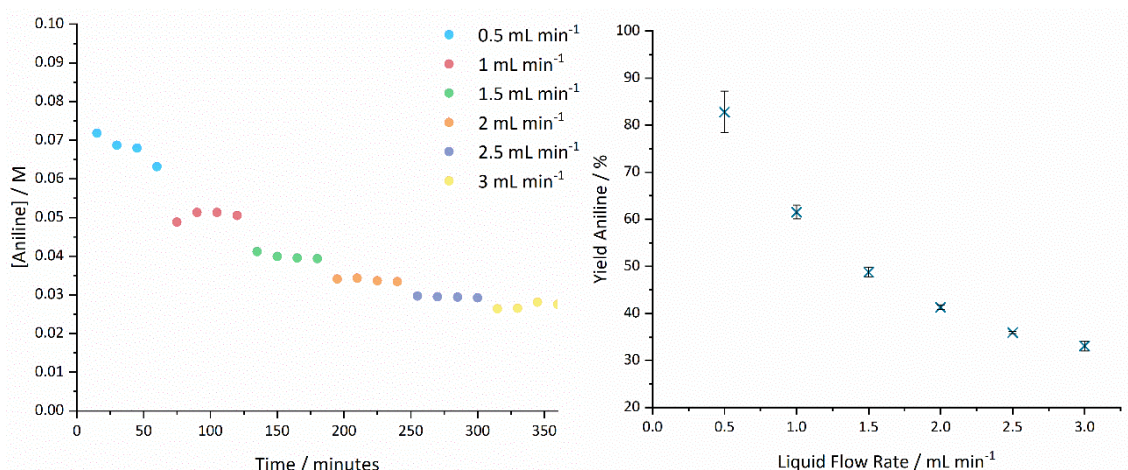


Figure 28. Left - Concentration data for liquid flow rate ramp, right - summary of average yields at each liquid flow rate, with error bars calculated from the standard deviation at each flow rate.

flow rate on the yield of the reaction. At each flow rate the reaction was sampled every 15 minutes for one hour. The results are summarised in Figure 28. It can be seen from the figure that the reaction takes much longer to reach steady state at the lower flow rates as the amount of material that passes over the bed for a given time period is much lower than that at higher flow rates. Therefore, as expected, it takes longer for the adsorption/desorption rate on to the catalyst surface at the new flow rate to reach steady state. It was concluded that going forward, all optimisation reactions would be required to wait eight residence times before the reaction was sampled, to allow the reaction to reach steady state, and ensure that all samples reflected an accurate yield at any specific condition.

2.3.2.4 Design of experiments

Four 2² factorial DoEs were performed in order to investigate the effect of changing multiple variables at once on the yield of the reaction. Changing the temperature and liquid flow rate at four discrete pressures was investigated, due to the difficulties in changing the pressure of the reactor system autonomously and re-establishing the steady state flow of both gaseous and liquid reactants over the catalyst (with the chosen BPR). The following variables were investigated:

- Temperature – 40 – 85 °C.
- Liquid flow rate – 0.5 – 3 mL min⁻¹.

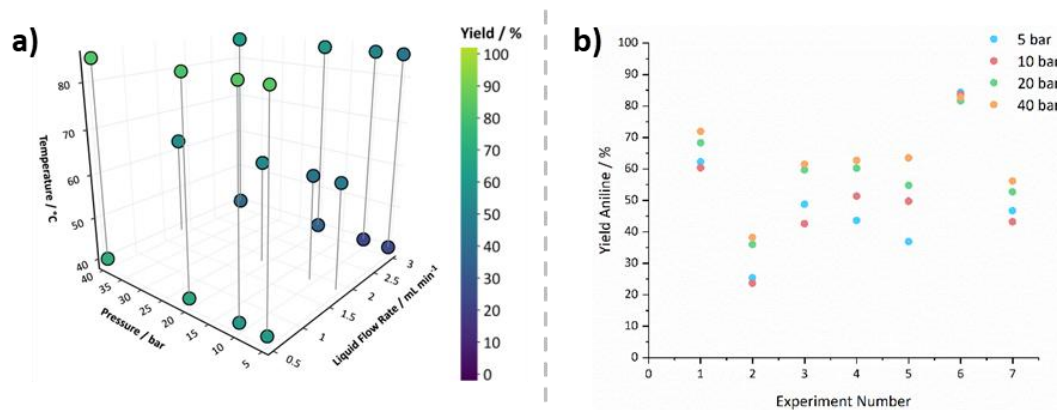


Figure 29. a) DoE results showing area of the design space that was explored and each yield shown in the colour scale. b) Graph showing how the yield varies with each experiment at the four pressures tested. Fixed conditions: catalyst – 0.5 g, H₂ flow rate – 50 mL min⁻¹, and concentration – 0.08 M.

- Pressure – 5, 10, 20, and 40 bar.

A summary of the experimental conditions and yields for each reaction are shown in appendix section 2.6.1. The results for the DoE, shown in Figure 29, demonstrate a clear trend in all the variables, that higher temperatures, lower liquid flow rates, and higher pressures lead to a greater yield of the reaction. This is as expected as pressure has a direct effect on the mass transfer of hydrogen into the liquid phase. Increasing the pressure increases the rate of mass transfer, therefore more is available in the correct phase for the catalytic reaction. The results also showed that at milder conditions, the pressure of the reactor has a greater impact on the yield of a reaction, compared to experiments performed at harsher reaction conditions (lower liquid flow rates and higher temperatures). For example, this can be seen in experiment six (0.5 mL min⁻¹, 85 °C) where high yields can be achieved at all pressures tested, showing there is some interactions between the variables investigated. For the subsequent nitrobenzene optimisations, a pressure of 40 bar was chosen, as this gave the greatest yields at a range of different reaction conditions. The individual trends in liquid flow rate and temperature found in the DoE are the same as was seen in the individual OVAT experiments with optimum conditions found at high temperatures and low liquid flow rates.

2.3.2.5 Catalyst stability overnight

Due to the explosive and dangerous nature of hydrogen gas, an automated optimisation could not be left to run overnight without supervision. Therefore, it was important to establish whether the catalyst would be stable when left overnight and if it could be used over multiple days after a shutdown procedure was performed. The shut down procedure (more details in experimental section 2.5.2.2) involved flushing the system with hydrogen gas and solvent, to remove any starting material, side products, or products from the column to limit catalyst deactivation by fouling or poisoning overnight. The liquid pump would then be stopped, and the reactor would be flushed with only hydrogen to remove all liquid from the column. The pressure of the reactor would then be decreased to three bar to avoid a large excess of hydrogen remaining in the reactor overnight. The column would then be isolated by valves at the top and bottom of the reactor, and the rest of the system could be depressurised. This allowed the catalysts to stay active under an atmosphere of hydrogen overnight, to limit deactivation of the catalyst, but to also leave the reactor in a safe state between reactions.

A test for deactivation of the catalyst was performed where the conditions were kept constant and the activity of the catalyst was monitored via offline sampling. Figure 30 shows that the concentration of aniline decreased slightly over the two day experiment but stayed mostly stable with no large activity drop between days. This

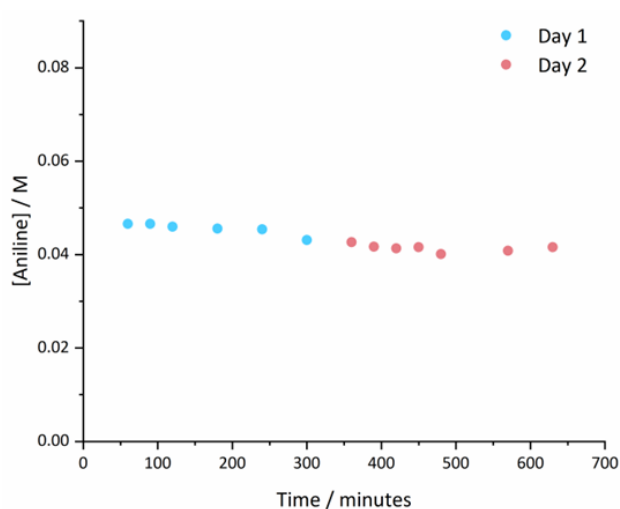


Figure 30. Concentration profile for catalyst activity testing over two days. Fixed conditions: catalyst – 0.5 g, concentration – 0.08 M, H₂ flow rate – 50 mL min⁻¹, liquid flow rate – 1 mL min⁻¹, pressure – 40 bar, and temperature – 50 °C.

meant that this procedure could be used to perform optimisations over multiple days for this reaction. For every optimisation performed this test would also need to be carried out to ensure that the same stability results could be achieved.

2.3.3 Manual SNOBFIT optimisation - nitrobenzene

An initial manual optimisation was performed with a SNOBFIT algorithm, developed in-house, on the PBR system described in previous sections. The equipment was manually controlled, and reaction conditions were set to those suggested by the algorithm. SNOBFIT was selected as the algorithm of choice for this initial optimisation as it would allow the design space to be explored more. It was configured to generate experiments in batches of four (batch sequential), where three experiments would aim to exploit areas of high interest (exploitation), and one experiment would explore vacant areas of the design space (exploration). This would mean that it would be less efficient in finding the global optimum of the system but would explore more areas of the design space for an initial optimisation (decision flow diagram shown in section 2.5.4). As experiments were suggested in batches of four, the time taken waiting for analysis of the reactions would be decreased. As experiments were performed in sequential batches, the analysis of the reactions could be performed while waiting for the next experiment to reach steady state. The optimisation objective was to maximise the yield of the reaction and variable bounds were defined as:

- Temperature – 40 – 85 °C.
- [Nitrobenzene] – 0.02 – 0.08 M.

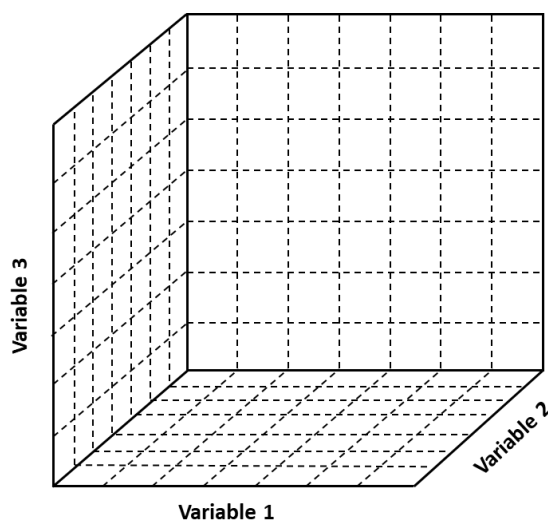


Figure 31. Three variable design space showing the $2n+1$ seven by seven grid explored by the LHC.

- Liquid flow rate – 0.5 – 3 mL min⁻¹

Seven initial conditions were chosen by a Latin hypercube (LHC) space-filling design, to initialise the algorithm. The number of initial samples is calculated to be $2n+1$, where n is the number of variables being optimised. This design was chosen as it ensures a good spread of samples across the experimental space. The LHC design splits the space into a grid sized N -by- N , where N is the number of samples, and distributes the experiments as such that no two experiments are in the same column or row as each other. An example of a three variable LHC grid design is shown in Figure 31.

25 experiments were performed in total over two days, and the results of the optimisation are shown in Figure 32 (with the full optimisation data summarised in appendix section 2.6.2). The results show the LHC sampling covered the design space efficiently, exploring a range of different reaction conditions. Optimal conditions for this reaction could be seen at the edge of the design space at high temperatures, low liquid flow rates, and at a range of different concentrations. This is in good agreement with the DoE data collected previously which also investigated the effects of liquid flow rate and temperature. The starting material concentration had little effect on the reaction, however, from a process standpoint a higher concentration would achieve a higher throughput of product. Therefore, optimal conditions would be seen at the highest yielding, highest concentration reaction conditions at experiment 24. A multi-objective

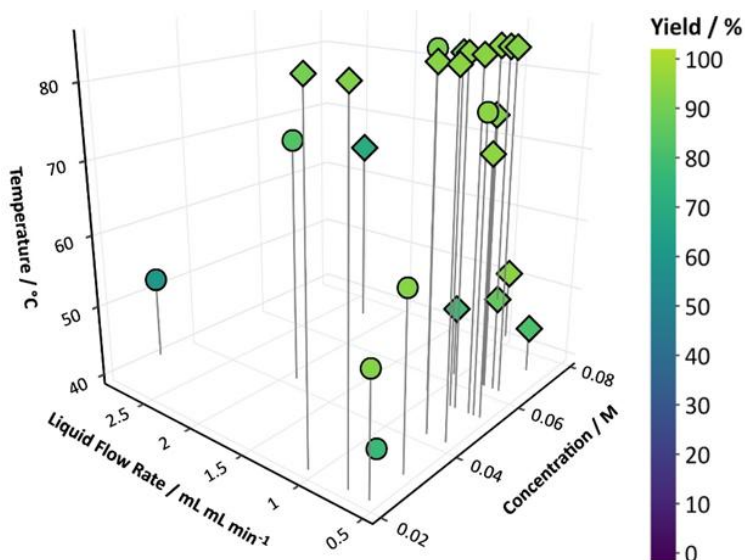


Figure 32. SNOBFIT optimisation results for the reduction of nitrobenzene, where ○ – LHC experiments and ◇ – refinement experiments. Fixed conditions: catalyst – 0.5 g, pressure – 40 bar, and H₂ flow rate – 50 mL min⁻¹.

Table 3. Repeat reaction data taken offline at the start and end of the reactions each day.

Repeat Experiments	Yield / %
1	78.0
2	74.6
3	71.6
4	74.7

optimisation that optimises for STY and yield would need to be used to explore this further.

It is important to monitor catalyst deactivation during all optimisations, as different process conditions may lead to more/less deactivation of the catalyst over time. When the conditions are changed, it is important to ensure that the yield seen for that experiment is only representative of the process conditions applied to the reactor and not a change in the activity of the catalyst. Therefore, during all optimisations, repeat reactions were performed every four/five experiments and sampled offline. The results of these repeat reactions are not included in the optimisation data or given to the algorithm. The results from these repeat reactions for the SNOBFIT optimisation are summarised in Table 3. This showed that there was an initial decrease in the yield from repeat experiment one to experiment two. However, over the two day reaction there was no further permanent decrease in yield of the reaction, indicating that the activity of the catalyst remained relatively stable throughout the optimisation, and that the difference in the yield of the reactions is likely due to noise.

2.3.4 Gas-liquid separator

To fully integrate the system with the computer based optimisation platform and connect the reactor to online analysis, an effective gas-liquid separator was required. This was important to ensure that only the liquid phase was sampled into the online analytics, as a sample containing both gas and liquid would impact the results of an experiment leading to a blank or low concentration sample. This would then be read by the optimisation algorithm as a poor/low yielding result, and the conditions suggested for subsequent reactions would be incorrect, affecting the overall performance of the algorithm. The previous optimisation and characterisation reactions used an adapted cyclone for gas-liquid separation. However, when changing the liquid flow rate during

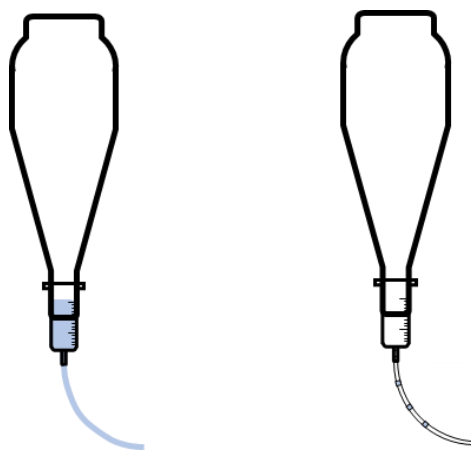


Figure 33. Different flow rate scenarios with a cyclone gas liquid separator. Left - high liquid flow rates, right - low liquid flow rates.

the optimisation, this would result in either too little liquid flowing through the tubing, causing gas bubbles, or too much liquid collecting at the bottom of the cyclone, which would result in inaccurate results, as the steady state liquid from the reactor could not be sampled accurately (Figure 33).

Commercial Zaiput separators have been shown in the literature to be effective at separating multiphase systems, with many examples of liquid-liquid separations reported (Figure 34).^{14,17} Gas-liquid separations at low pressures have also been reported with Zaiput membrane separators, with some examples shown in three-phase heterogeneous hydrogenations.^{15,18,19} Therefore, in an attempt to achieve accurate separations, a Zaiput membrane separator was tested using the recommended hydrophilic membrane (IL-900) for gas-liquid separation.²⁰ The reactor was connected up with a gas flow rate of 50 mL min⁻¹ and a liquid flow rate between 0.5 – 3 mL min⁻¹, as would be required for online optimisations.

The liquid phase (methanol) was able to permeate through the membrane as the wetted phase, and the gas was retained. However, some of the liquid phase remained in the gas outlet, suggesting that the overall flow rate was too fast/the internal volume of the Zaiput was too small for the full separation of both phases to be achieved. The gas flow rate was lowered to 20 mL min⁻¹ and the Zaiput was retested. Unfortunately, even with adapted flow rates of the two phases, full separation could not be produced. The gas flow rate cannot be lowered more than this as during the reaction, as the hydrogen reactant must be always in excess to the liquid phase, to achieve sufficient mass transfer during the reaction.

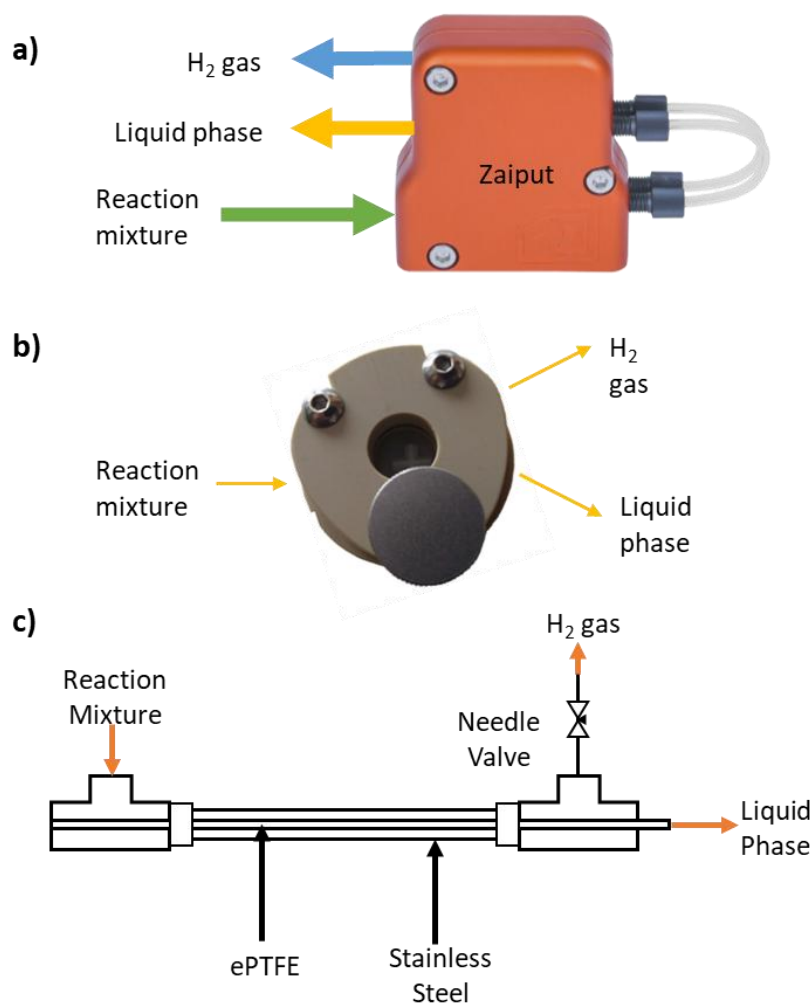


Figure 34. Gas-liquid separators tested in this work. a) Zaiput membrane separator, b) fReactor, and c) tube-in-tube separator.

With the commercial gas-liquid separator unsuccessful, more bespoke designs were considered. The use of a fReactor for gas-liquid separation was reported by Guan *et al*, which allowed the liquid phase to flow out of the lower outlet of the reactor, and the gas phase could exit from the fReactor outlet facing upwards towards a BPR.²¹ This was attempted for the same flow rates as described above. At high liquid flow rates, the fReactor filled with liquid and this phase was forced through the exit at the top outlet of the fReactor with the gas phase. At low liquid flow rates, both the gas and liquid phases exited through the bottom outlet of the fReactor. This showed that at the required flow rates, this design could not provide full and consistent separation.

Provided by Dr Stephen Ferguson at the University of College Dublin, a tube-in-tube separator with a porous ePTFE internal tubing was tested for gas-liquid separation.²² The group had previously published work on its novel construction, and effective use in liquid-liquid separations. Images of the internal and external structure

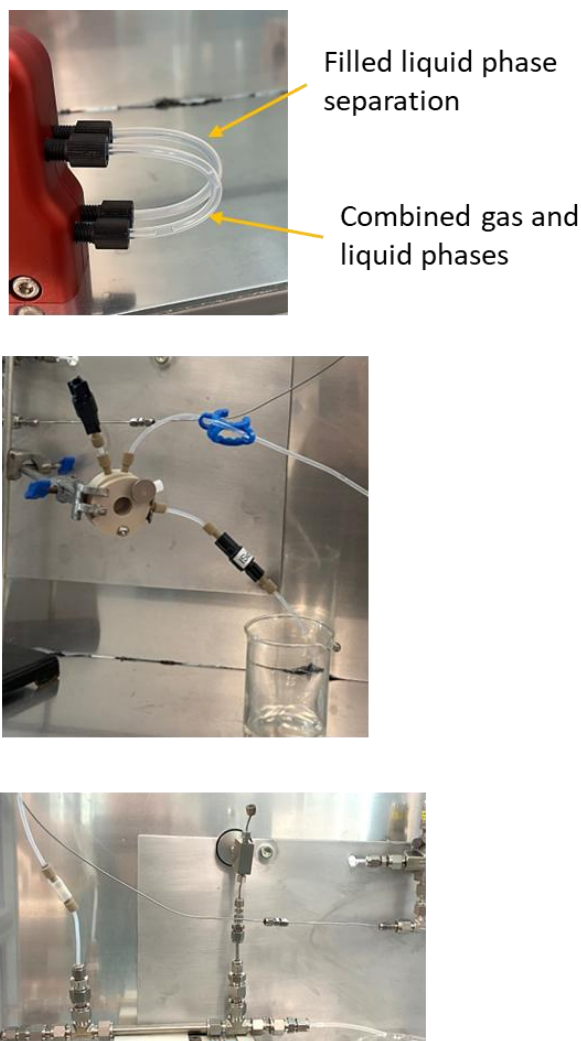


Figure 35. Pictures of the gas-liquid separators evaluated in this work.

and are shown in Figure 34 and Figure 35. A needle valve on the gas outlet stream provides a slight back pressure to the outer cavity of the tube-in-tube. This forces the liquid phase to permeate through the porous ePTFE tubing and complete phase separation was achieved. The needle valve could be adjusted to increase/decrease the back pressure as required, but adequate phase separation was found to be possible over the range of desired flow rates without the need for human intervention to adjust the needle valve. If a wider range of flow rates were investigated during an automated self-optimisation, the system would need to be adapted to incorporate an automated needle valve, similar to that described by Harvie²³ or O'Brien.¹¹ The outlet could be optically monitored, and a motorised needle valve could be adjusted autonomously to achieve an appropriate back pressure for phase separation.

With an effective gas-liquid separator now integrated into the automated PBR platform, online analysis could be connected to the liquid flow stream via a Vici sampling

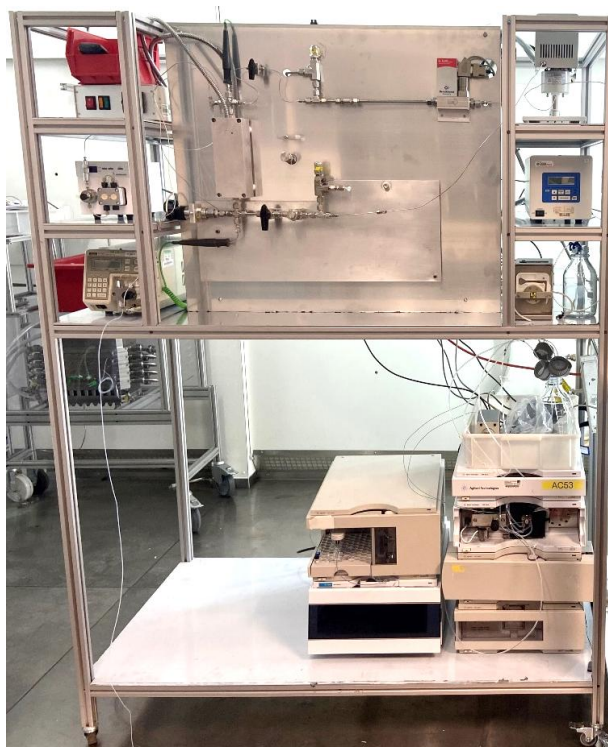


Figure 36. Image of the complete automated PBR setup with tube-in-tube gas liquid separator and online analysis via a HPLC.

valve (Figure 36). An Agilent 1100 HPLC was connected to the sampling valve to provide online analytics, meaning the system was closed-loop for automated control (a flow decision diagram for the online optimisation platform is outlined in appendix section 2.5.3).

2.3.5 Nitrobenzene Bayesian self-optimisation

The previous manual optimisation was performed with a SNOBFIT algorithm, to explore the design space and find optimum reaction conditions. A Bayesian optimisation algorithm with an adapted expected improvement acquisition function (BOAEI) was used for the online self-optimisation of the nitrobenzene reduction reaction (decision flow diagram outlined in section 2.5.5 of the appendix). BOAEI has been shown to be an efficient algorithm and finds optimum conditions in a minimum number of experiments. It was previously reported by Clayton *et al.* for its use in a multistep telescoped optimisation of an aryl ketone synthesis.²⁴

A three-variable single objective (to maximise yield) optimisation for the reduction of nitrobenzene was conducted with the variable bounds:

- Temperature – 40 – 85 °C.
- [Nitrobenzene] – 0.02 – 0.08 M.
- Liquid flow rate – 0.5 – 3 mL min⁻¹.

The algorithm was initialised with a LHC, seven initial experiments, and the results of the optimisation are shown in Figure 37 (full optimisation data can be found in section 2.6.3 and a typical HPLC chromatogram is shown in 2.5.2.5). The algorithm efficiently found optimum conditions with a product yield of 98% at high temperatures, low liquid flow rates, and high concentrations after only two refinement experiment (nine total experiments including LHC). Unlike the SNOBFIT optimisation, BOAEI did not explore the effect of concentration on the reaction, with most refinement experiments being performed in the same corner of the design space. Higher concentrations and higher liquid flow rates would be preferred to increase the throughput of the reaction and improve process metrics. A multi-objective optimisation could be performed in order to optimise for both yield and throughput, but these often require more experiments to be conducted to achieve a good understanding of all objectives. This is often a problem for heterogeneous systems as it would result in lengthy optimisations, which would increase the probability of catalyst deactivation. When comparing the BOAEI automated self-optimisation to the previous OVAT and DoE approaches the optimum conditions for the reaction were found in fewer experiments. The two OVAT

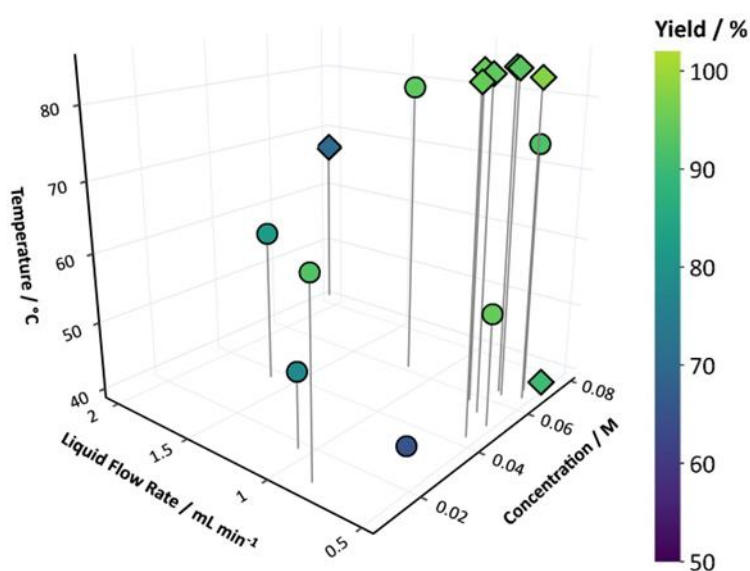
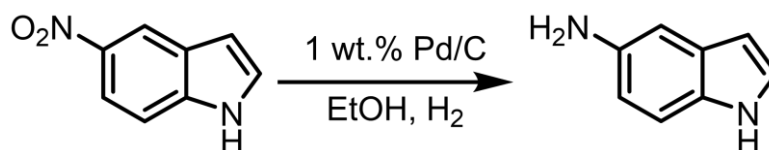


Figure 37. BOAEI self-optimisation for nitrobenzene reduction, where ○ – LHC experiments and ◇ - refinement experiments. Fixed conditions: catalyst – 0.5 g, pressure – 40 bar, and H₂ flow rate – 50 mL min⁻¹.

experiments only investigated the effect of temperature and flow rate and required ten experiments compared to the nine required for the BOAEI optimisation. The DoE explored three reaction variables with 20 experiments performed in total due to the investigation of four discrete pressures. A typical 2^3 full factorial design DoE with a centre point would require nine experiments (with an additional two experiments needed for centre point repeats to be explored) which is comparable to the BOAEI optimisation. However, in systems where the optimal conditions are not in the corner of the design space, a full factorial DoE would not be sufficient in finding the optimal conditions, and a BOAEI algorithm based optimisation with LHC initial sampling would likely be a more efficient way to investigate and optimise the design space.

2.3.6 5-Nitroindole Bayesian self-optimisation

To demonstrate the use of the platform for another substrate, the reduction of 5-nitroindole was performed in the system (Scheme 4). In the previous model system, the reduction of nitrobenzene, the reaction was well understood prior to performing the optimisation, due to it being used for the characterisation of the reactor platform. Previous conditions reported by Jones *et al.* were used to influence the concentrations and solvents used in this optimisation.²⁵ With this reaction, only a stability test of the catalyst was investigated before performing the self-optimisation. This was attempted in order to demonstrate that little pre-work is required before an optimisation can be performed in this platform. Stability tests were conducted over two days to assess if there would be any catalyst deactivation during an optimisation, Figure 38. An initial small decrease in the activity at the beginning of the reaction can be seen, indicative of the catalyst overcoming an early high activity period, due to a high concentration of hydrogen being present on the surface of the catalyst (from the activation protocol). Once the adsorption/desorption mechanisms had reached equilibrium, the catalyst is shown to achieve a steady activity and there is no further change in the yield seen, which



Scheme 4. The reduction of 5-nitroindole with Pd/C JM catalyst to 5-aminoindole.

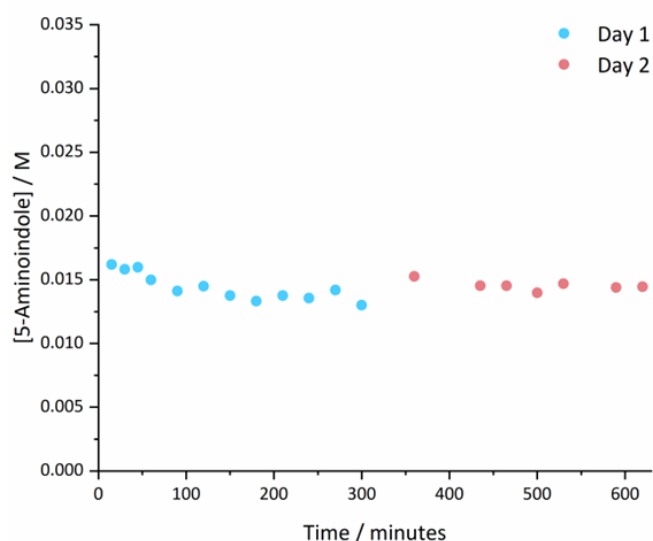


Figure 38. Concentration profile for the stability tests in the reduction of 5-nitroindole. Fixed conditions: catalyst – 1.2 g, concentration – 0.02 M, liquid flow rate – 0.5 mL min⁻¹, temperature – 50 °C, pressure – 40 bar, and H₂ flow rate – 50 mL min⁻¹.

is an essential prerequisite for performing an accurate optimisation. This initial stability test also allows information about the yields of the reaction to be seen, which influences the design space that is investigated by an optimisation. If the yield of the reaction is too high, the catalyst loading could be lowered in order to fully investigate the effect of different reaction variables. In this case, the yield of the reaction at this set of reaction conditions meant the following variables bounds were explored:

- Temperature – 40 – 85 °C.
- [5-nitroindole] – 2 – 20 mM.
- Liquid flow rate – 0.5 – 3 mL min⁻¹.

The results of the optimisation are shown in Figure 39 and all experimental data are summarised in section 2.6.4 of the appendix. The design space was initially explored with seven experiments from the LHC, before the algorithm was initialised, where it quickly found the optimum conditions in only ten experiments (with only a 3% difference in yield between experiments nine and ten). The LHC efficiently sampled across the design space and provided enough information for the BOAEI algorithm to find the optimum conditions after only two refinement experiments (example HPLC spectrum shown in 2.5.2.6). It can also be seen from the figure that once the BOAEI algorithm had found the optimum condition, it repeated them with small variations to the process conditions. This optimisation showed that a minimum number of iterations were

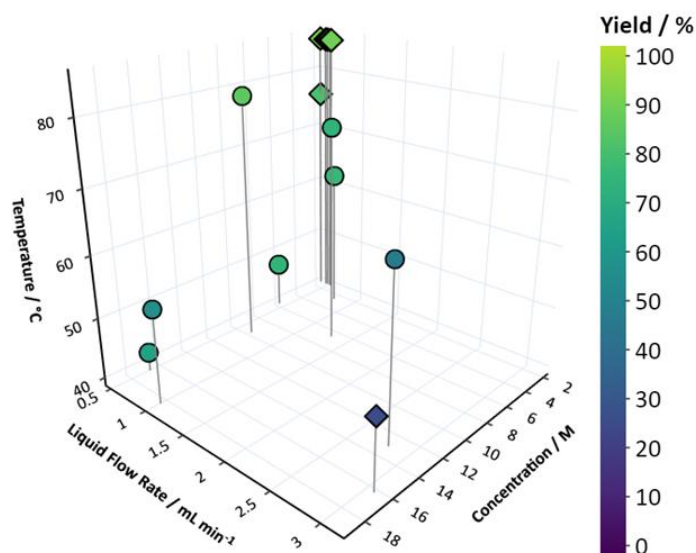


Figure 39. BOAEI self-optimisation for 5-nitroindole reduction, where $\circ$ – LHC experiments and $\diamond$ - refinement experiments. Fixed conditions: catalyst – 1.2 g, pressure – 40 bar, and H_2 flow rate – 50 mL min^{-1} .

required to find the global optimum, and the design space was explored sufficiently in the initial LHC to correctly inform the algorithm where the area of high interest would be. This case study is a simple hydrogenation reaction with no other side products produced. With more complicated systems which suffer from selectivity issues, it is expected that many more reactions would be required to find the optimum conditions.

2.4 Conclusion

Here a bespoke automated PBR platform was developed and characterised to be used for the self-optimisation of heterogeneous reduction reactions. It was developed to mimic the same reaction conditions that are achieved in commercial PBR platforms. The system included important safety features to perform heterogeneous hydrogenations effectively and safely. An initial model nitrobenzene reduction reaction was used to evaluate the reproducibility of the system and to investigate the commercial JM 1 wt.% Pd/C pellets stability to be used in an online optimisation. A tube-in-tube gas liquid separator was incorporated into the system to provide a control feedback loop to allow automated self-optimisations to be performed on the reduction of nitrobenzene and 5-nitroindole, with the BOAEI algorithm effectively finding optimum conditions in a minimum number of experiments.

2.5 Experimental

2.5.1 Chemicals

Nitrobenzene (99.5%, Acros Organics), aniline (99.5%, Acros Organics), hydrogen gas (99.99%, BOC Gas), nitrogen gas (99.998%, BOC Gas), methanol (>99%, Sigma Aldrich), biphenyl (99.5%, Sigma Aldrich), extrudate Pd/carbon pellets (product code:113784, 1 wt.% Pd, JM), 5-nitroindole (98%, Fluorochem), 5-aminoindole (97%, Sigma Aldrich), Ethanol (>99.8%, Sigma Aldrich) were all purchased from suppliers and used without further purification.

2.5.2 PBR platform

2.5.2.1 Reactor

Reservoir solutions were prepared and made fully homogeneous by dissolving the reagents in the solvent and stirring under ambient conditions.

- Pump 1: Reactant and internal standard in solvent.
- Pump 2: Solvent.
- Mass Flow Controller: H₂ gas

A Knauer Azura 41.S dual piston pump and a Jasco PU-980 pump were used to flow the liquid reactants into the reactor (1-10 mL min⁻¹), and consistent flow rates were maintained using IDEX P-762 (75 PSI) BPR cartridges on their outlets. A Bronkhorst EI-Flow Prestige MFC (5-100 sscm) was used to control gas flow rates and was calibrated for hydrogen gas. A Jasco BP-2080 plus BPR was used to control the pressure of the system. A Eurotherm temperature controller and heating cartridges were used alongside an aluminium block, fitted to surround the packed bed column, to control the temperature of the system. R3A series pressure relief valves were set to 10 bar above the overall pressure of the system for the individual reactions. A Vici EUHA-CI4WE.2 sampling valve was placed after the gas-liquid separator and would sample the reaction for online analysis. Online analysis was performed by an Agilent 1100 HPLC fitted with an Agilent Poroshell 120 EC-C8 HPLC column with 2.7 µm particle size, and L x ID of 5 cm x 4.6 mm. Offline analysis was performed by an Agilent Technologies 7890B GC-FID

system fitted with a HP-5 column, with a temperature range of -60 – 325 °C, 30 m in length, a diameter 0.32 mm, and a film thickness 0.25 µm. The packed bed used in this chapter was a stainless steel column (1/2" OD, 3/8" ID, 0.065" wall thickness) and the remaining setup was made from stainless steel tubing (1/16" OD, 1/32" ID), with a maximum system pressure of 50 bar. The details of the tube-in-tube gas liquid separator are reported by Harding *et al.*²² The porous ePTFE tubing used in this system was from Zeus Industrial Products (1/4" OD, 0.118 ID, 1.15 g cm⁻³).

2.5.2.2 Typical procedure

1. The system was flushed with N₂ gas (50 mL min⁻¹) for 30 minutes to remove any air/oxygen from the system.
2. The system was flushed with H₂ gas (50 mL min⁻¹) for 30 minutes to activate the catalyst.
3. The system was flushed with H₂ gas (50 mL min⁻¹) and solvent (0.5 mL min⁻¹) to further activate the catalyst.
4. The solvent pump was stopped, and the starting material pump was started (0.5 mL min⁻¹). The system was equilibrated with reactant solution and H₂ gas for two hours.
5. The optimisation was started.
6. When the optimisation was finished for the day, the entire system was flushed with H₂ gas (50 mL min⁻¹) and solvent (1 mL min⁻¹) for one hour to remove any leftover starting materials from the catalyst.
7. The solvent pump was stopped, and the system was flushed with only H₂ to remove residual solvent from the column.
8. The reactor pressure was reduced to three bar and the gas flow rate was stopped. The column was isolated by closing the valves at the top and bottom of the reactor. The rest of the reactor system was then depressurised.
9. When starting the reaction the next day, steps 1-4 were repeated to reactivate the catalyst. The optimisation was then restarted.

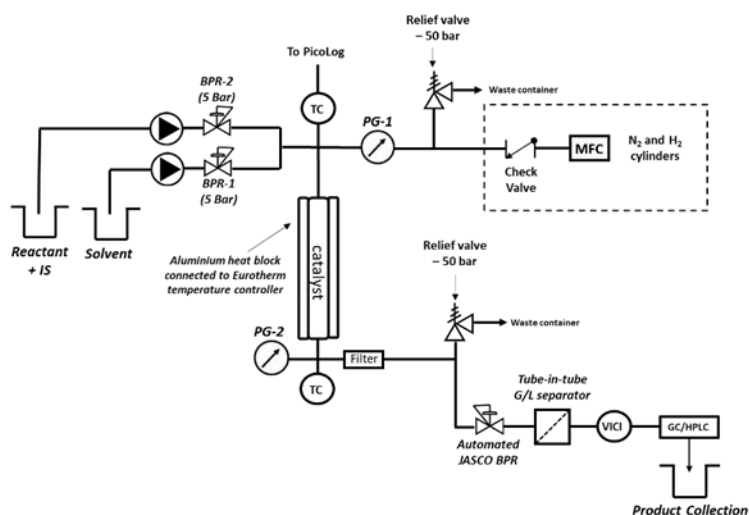


Figure 40. PBR platform used to perform heterogeneous reduction reactions.

2.5.2.3 Column packing

The same column packing procedure was used for all optimisations. The JM 1 wt.% Pd/C pellets and glass beads (2 mm OD, Merck) were weighed out. The column packing procedure as reported by Al-Dahhan *et al.*²⁶ was followed to ensure accurate packing of the column. A 1 cm plug of cotton wool was placed at the bottom of the reactor and then filled with the desired mass of catalyst pellets and glass beads. The

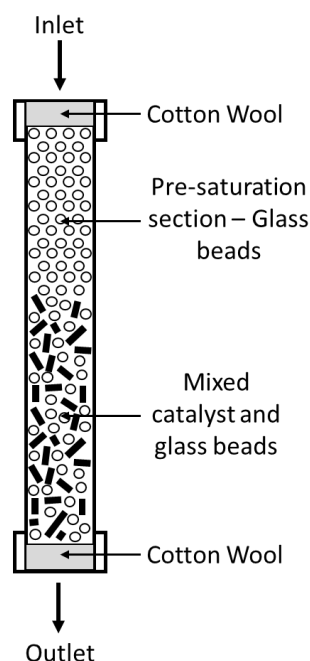


Figure 41. Column packing in PBR platform.

remainder of the column was filled with glass beads and another 1 cm cotton wool plug was placed on top of the beads at the top of the column. The cotton wool would ensure that the pellets would not move around into other parts of the reactor. It would also help stop large pieces of carbon pellets that were crushed during the reaction from blocking the tubing and filter in the downstream part of the reactor. The glass beads would create a pre-saturation section where both gas and liquid phases could mix before reaching the catalyst pellets, to increase mass transfer of hydrogen to the liquid phase (Figure 41).

2.5.2.4 Example GC chromatogram – nitrobenzene reduction

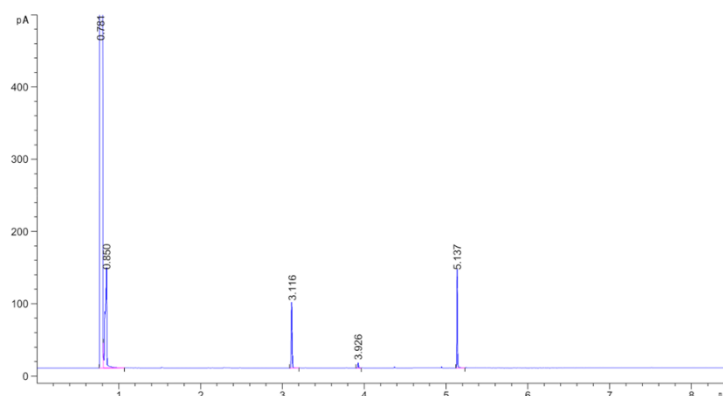


Figure 42. Example GC chromatogram for the hydrogenation of nitrobenzene.

Table 4. Peak picking for Figure 42, showing product (P), starting material (SM), and internal standard (IS).

Peak Position / min	Peak Identification
0.781, 0.850	MeOH solvent
3.116	Aniline (P)
3.926	Nitrobenzene (SM)
5.137	Biphenyl (IS)

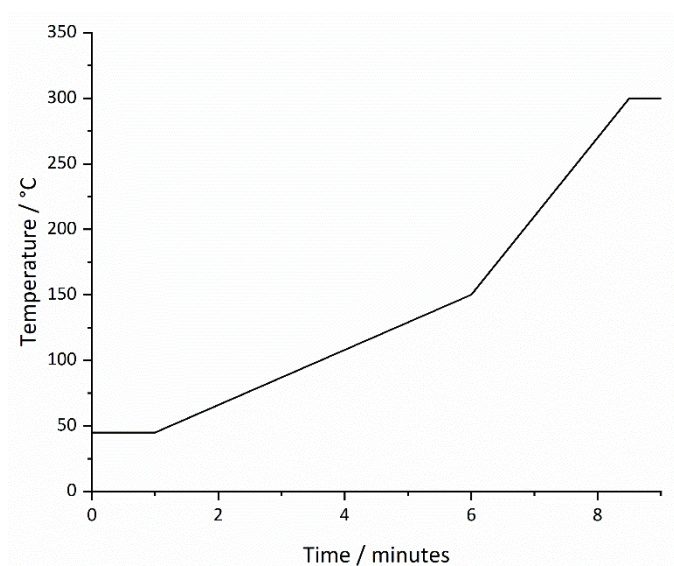


Figure 43. GC temperature protocol.

2.5.2.5 Example HPLC chromatogram – nitrobenzene reduction

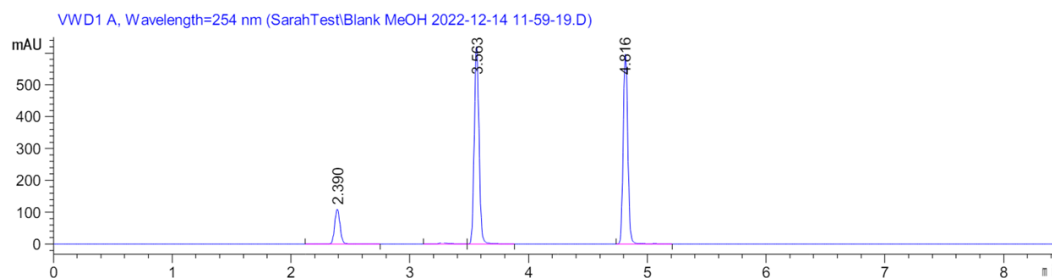


Figure 44. Example HPLC chromatogram for the reduction of nitrobenzene self-optimisation.

Table 5. Peak picking for Figure 44, showing product (P), starting material (SM), and internal standard (IS).

Peak Position / min	Peak Identification
2.390	Aniline (P)
3.563	Nitrobenzene (SM)
4.616	Biphenyl (IS)

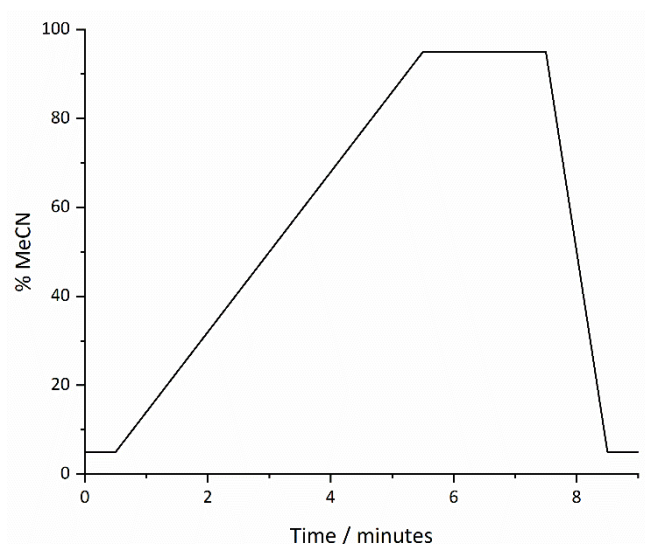


Figure 45. HPLC method solvent gradient for the nitrobenzene and 5-nitroindole reduction self-optimisations.

2.5.2.6 Example HPLC chromatogram – 5-nitroindole reduction

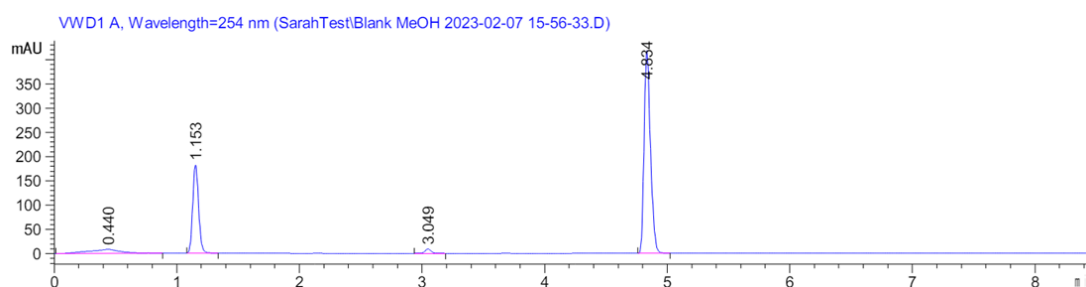


Figure 46. Example chromatogram for the 5-nitroindole reduction self-optimisation.

Table 6. Peak picking for Figure 46, showing product (P), starting material (SM), and internal standard (IS).

Peak Position / min	Peak Identification
0.440	Solvent
1.153	5-Aminoindole (P)
3.049	5-Nitroindole (SM)
4.834	Biphenyl (IS)

2.5.3 Optimisation platform decision flow diagram

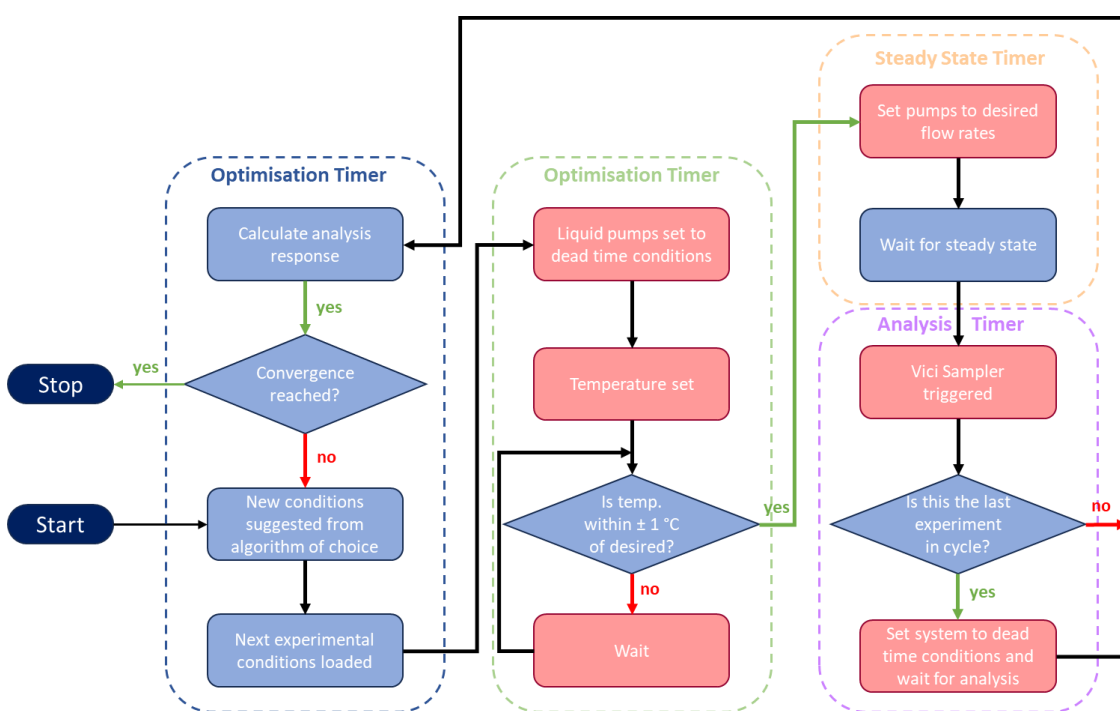


Figure 47. Flow diagram for optimisation procedure performed by the MATLAB platform during an optimisation experiment.

2.5.4 SNOBFIT algorithm decision flow diagram

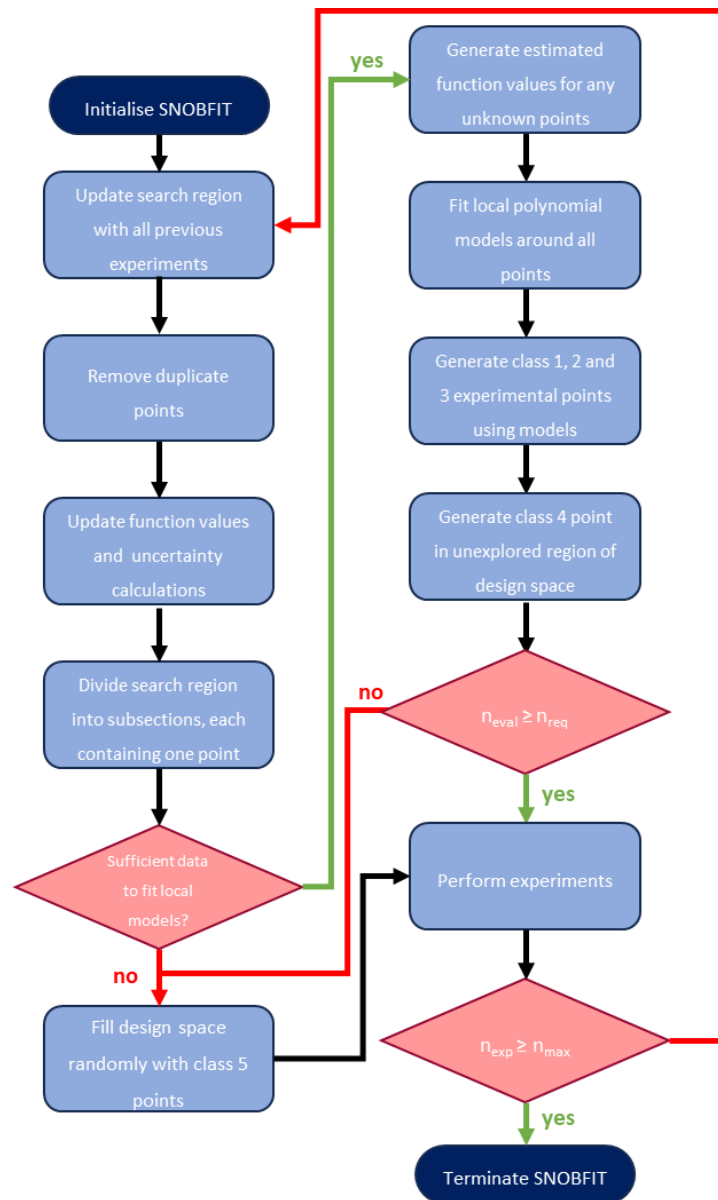


Figure 48. Flow diagram for SNOBFIT optimisation algorithm where n_{exp} = total number of experiments performed, n_{max} = maximum number of experiments allowed, n_{eval} = number experiments generated on this algorithm iteration, and n_{req} = number of experiments required by each algorithm iteration.

2.5.5 Bayesian algorithm decision flow diagram

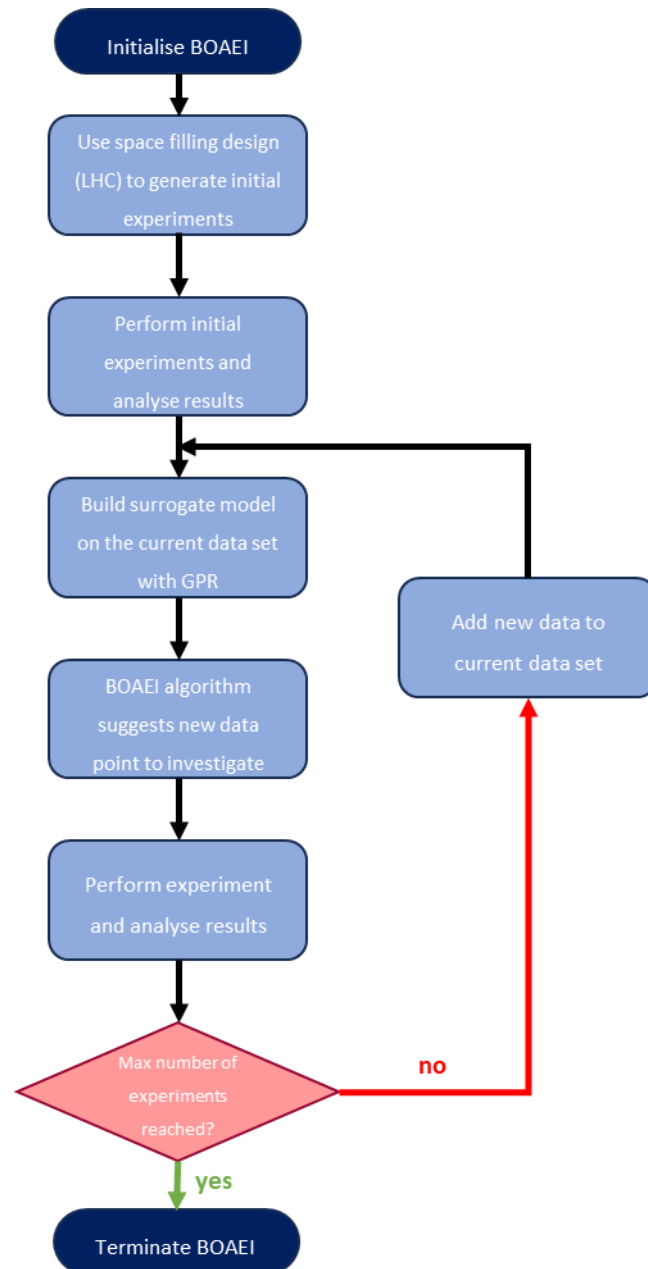


Figure 49. Flow diagram for BOAEI algorithm.

2.6 Appendix

2.6.1 DoE results

Table 7. Experimental conditions and results for the DoE of nitrobenzene reduction.

Exp. No.	Liq. Flow Rate / mL min ⁻¹	Temp. / °C	Yield / %			
			5 bar	10 bar	20 bar	40 bar
1	0.50	40.0	62.2	60.4	68.3	71.9
2	3.00	40.0	25.4	23.6	35.9	38.2
3	1.75	62.5	48.8	42.6	59.6	61.4
4	3.00	85.0	43.6	51.3	60.2	62.7
5	1.75	62.5	36.9	49.7	54.8	63.5
6	0.50	85.0	84.3	83.7	81.7	82.7
7	1.75	62.5	46.7	43.2	52.7	56.2

2.6.2 SNOBFIT optimisation results - nitrobenzene

Table 8. Optimisation data for nitrobenzene reduction with SNOBFIT algorithm.

Exp. No.	Exp. Type	Variables			Flow rate / mL min ⁻¹		Objective
		Liq. Flow Rate / mL min ⁻¹	Temp. / °C	Conc. / M	Nitrobenzene	MeOH	Yield / %
1	Initial	0.51	62.7	0.028	0.18	0.33	93.6
2	Initial	0.8	40.2	0.031	0.31	0.49	77.3
3	Initial	0.98	84.9	0.052	0.38	0.6	92.1
4	Initial	2.88	51.5	0.03	1.08	1.8	60.1
5	Initial	1.82	73	0.04	0.91	0.91	83
6	Initial	0.55	78.6	0.05	0.34	0.21	94.4
7	Initial	0.51	55.8	0.02	0.13	0.38	93.4
8	Refinement	2.15	66.7	0.07	1.88	0.27	70.7
9	Refinement	0.59	46.3	0.07	0.51	0.08	81.6
10	Refinement	0.67	85	0.02	0.17	0.5	92.7
11	Refinement	0.5	73.9	0.05	0.31	0.19	95.3
12	Refinement	0.66	85	0.04	0.33	0.33	94
13	Refinement	0.97	49.7	0.06	0.73	0.24	78.8
14	Refinement	0.51	85	0.04	0.38	0.13	94.7
15	Refinement	0.59	85	0.06	0.44	0.15	94.1
16	Refinement	0.59	85	0.05	0.37	0.22	94.7
17	Refinement	0.72	76.6	0.06	0.45	0.27	93.4
18	Refinement	0.64	85	0.06	0.48	0.16	94.1
19	Refinement	0.74	85	0.05	0.46	0.28	92.5

20	Refinement	0.67	80.8	0.08	0.67	0	92.5
21	Refinement	1.11	72	0.07	0.97	0.14	85.2
22	Refinement	0.99	85	0.02	0.25	0.74	90.2
23	Refinement	0.71	85	0.06	0.53	0.18	94
24	Refinement	0.7	85	0.05	0.44	0.26	95
25	Refinement	0.64	52.8	0.06	0.48	0.16	87

2.6.3 BOAEI optimisation results – nitrobenzene

Table 9. Optimisation data for BOAEI self-optimisation of the reduction of nitrobenzene.

Exp. No.	Exp. Type	Variables			Flow Rate / mL min ⁻¹		Objective
		Conc. / M	Liq. Flow Rate / mL min ⁻¹	Temp / °C	Nitrobenzene	MeOH	Yield / %
1	Initial	0.028	0.642	40.8	0.224	0.418	65.0
2	Initial	0.015	1.010	50.6	0.191	0.819	77.7
3	Initial	0.046	0.492	55.7	0.286	0.206	94.5
4	Initial	0.034	1.568	61.7	0.662	0.906	82.1
5	Initial	0.008	0.795	66.1	0.081	0.714	92.5
6	Initial	0.065	0.531	75.1	0.432	0.099	92.0
7	Initial	0.058	1.108	81.2	0.805	0.303	93.8
8	Refinement	0.070	0.498	40.4	0.436	0.062	90.1
9	Refinement	0.062	0.498	84.0	0.384	0.115	97.7
10	Refinement	0.040	0.510	85.0	0.255	0.255	94.7
11	Refinement	0.060	0.590	85.0	0.443	0.148	93.4
12	Refinement	0.050	0.590	85.0	0.369	0.221	94.1
13	Refinement	0.061	0.620	85.0	0.474	0.146	94.0
14	Refinement	0.054	0.680	85.0	0.456	0.224	95.0
15	Refinement	0.080	2.050	66.7	2.050	0.000	70.0

2.6.4 BOAEI optimisation results – 5-nitroindole

Table 10. Optimisation data for 5-nitroindole reduction with BOAEI algorithm.

Exp No.	Exp Type	Variable			Flow Rate / mL min ⁻¹		Objective
		Liq. Flow Rate/ mL min ⁻¹	Temp. / °C	Conc. / mM	5-Nitroindole	EtOH	Yield / %
1	Initial	0.617	43.2	17.22	0.531	0.086	65.64
2	Initial	1.403	75.3	7.32	0.512	0.891	74.10
3	Initial	0.778	79.7	10.29	0.400	0.377	85.78
4	Initial	2.878	67.0	13.61	1.957	0.921	46.66
5	Initial	1.110	55.1	18.88	1.049	0.061	56.40
6	Initial	0.890	63.3	3.42	0.151	0.738	76.46
7	Initial	0.542	47.6	6.36	0.173	0.368	75.04
8	Refinement	3.133	51.1	16.74	2.616	0.517	25.68
9	Refinement	0.503	85.0	2.00	0.050	0.453	92.16
10	Refinement	0.634	85.0	2.00	0.063	0.570	95.03
11	Refinement	0.649	85.0	2.01	0.060	0.589	89.50
12	Refinement	0.574	85.0	2.01	0.057	0.517	90.77
13	Refinement	0.600	85.0	2.00	0.060	0.540	86.21
14	Refinement	0.503	75.6	2.01	0.050	0.450	81.14

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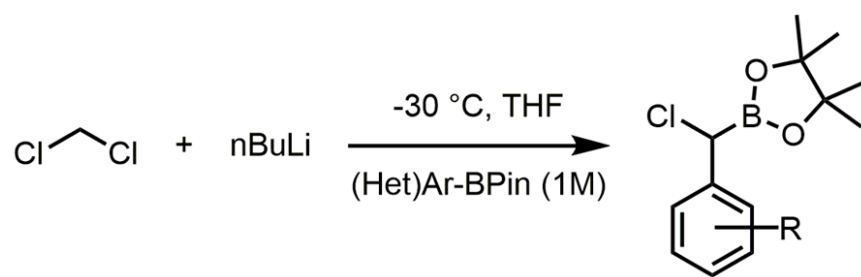
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Chapter 3 : API Process Development – The Self-optimisation of Osimertinib Nitrodiamine Reduction

3.1 Introduction

The pharmaceutical industry is beginning to integrate continuous flow processes into their manufacturing systems, but this comes with many challenges.¹ Processes are traditionally dominated by STRs, as they are versatile and can handle many types of chemistries. STRs allow for high concentrations of reagents, a range of different solvents and gases to be used, and are standardised equipment in many industry sectors.² Often pharmaceutical companies are working to strict deadlines for product delivery, meaning that a redesign of the process to transfer to continuous flow chemistry can fall outside the allotted timescales.³ Flow chemistry can also require significant capital investment,⁴ as new equipment is required at all stages of drug development to ensure that the process can be optimised and produced on scale.

However, there can be significant benefits to transferring some of these chemical processes to continuous flow, including the option to access higher pressures, better control of toxic or explosive intermediates, and using temperatures above the boiling points of solvents for reactions in a safer, more controlled way.^{5,6} Hazardous chemistries that were previously too dangerous to perform at scale in batch, such as highly exothermic ones, can be transferred to continuous flow, which handles comparatively smaller amounts of reagents at any one time, increasing heat transfer/exchange, allowing precise temperature control of the reaction.⁷ An example where precise temperature control is crucial is reactions which require cryogenic process conditions, making them hard to scale up in batch processes due to the difficulties in dissipating heat in large batch vessels.⁸ Specifically, the use of thermally unstable dichloromethylithium has been reported for the production of β,β -dichloromethyl carbinols as an intermediate for further functionalisation to epoxides, aldehydes and styrenes, as well as in the formation of boronic esters.⁹ These moieties are of significant importance as building blocks for APIs. Often this reactant is limited to its use in small scale batch reactions due to the need for low cryogenic temperatures ($<-78\text{ }^{\circ}\text{C}$). However, Hafner *et al.* demonstrated the use of continuous flow for the inline generation and rapid consumption of dichloromethylithium to form



Scheme 5. The continuous flow synthesis of boronic pinacol esters reported by Hafner *et al.*⁹

functionalised boronic pinacol esters at only -30 °C (Scheme 5). This demonstrates how continuous flow chemistry, when applied to the right reactions, can have significant benefits over standard batch chemistries, opening up new chemical pathways towards scale up.

Multiphase systems that require high pressures to increase the mass transfer of gaseous reactions into the liquid phase, can also benefit from continuous operation. Removing the need for large headspaces of hydrogen in traditional STR, minimises the explosion risk, making heterogeneous hydrogenation reactions more attractive in continuous flow (among the many other benefits of continuous manufacturing).¹⁰ In 2022, it was reported by Masson *et al.* that there were only 27 publications on Scopus detailing the application of heterogeneous hydrogenations in continuous flow from authors in the pharmaceutical or agrochemical sector.¹¹ 21 one of these were published with academic collaborations, showing that this technology is less developed in these industrial sectors, despite heterogeneous hydrogenations accounting for 10-20% of all reactions performed in the pharmaceutical industry.¹²

The modern day synthesis of APIs demands fast and efficient discovery and the optimisation of new chemical reaction pathways. Continuous flow has been shown to be an excellent enabling technology when integrated with automation and machine learning algorithms.¹³

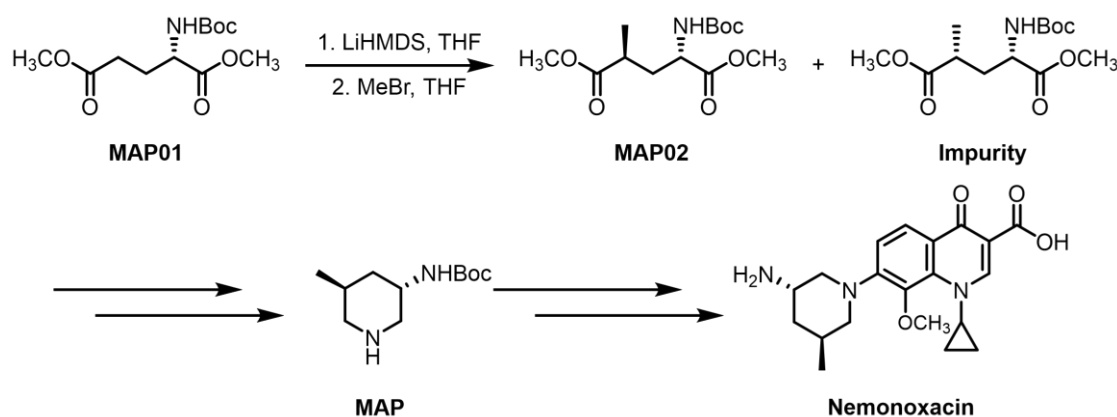
3.1.1 Application of self-optimisation to continuous flow in API synthesis

Typically, a reaction is optimised OVAT, for example increasing only temperature before then investigating another parameter at the chosen optimal temperature. This can be laborious and time consuming and may also lead to the chemist missing the

global optimum conditions of a system, due to overlooking the interactions between multiple reaction variables.¹⁴ The application of machine learning algorithms and artificial intelligence (AI) to chemistry aims to increase the speed and efficiency with which that optimal reaction routes and conditions are found, with the hope of bringing useful products/APIs to market in shorter timescales, which has a global benefit as medicines are transferred to patients faster.^{15,16}

One such application of self-optimising algorithms was reported by Fitzpatrick *et al.* in the use of cloud based servers for the autonomous self-optimisation of three APIs, Tramadol, Lidocaine, and Bupropion.¹⁷ The bespoke automated continuous flow system could be controlled remotely, across borders, via an internet connection to find the optimal process conditions for the three reactions and was monitored by IR to create a closed-loop feedback control platform. Optimised conditions for all three reaction steps investigated were found within hours, considering conversion, throughput, and the waste of reactants, in the form of excess equivalents, in the objective function. This work demonstrated the application of self-optimisation for important API reaction steps, where researchers in other parts of the world could control continuous optimisations. This work also established a possible solution to issues with a lack of equipment and resources for the implementation of continuous flow in academia.

The use of a BO algorithm (qNEHVI) for both single and multi-objective optimisations was used by Zhu *et al.* for a key reaction step in the production of Nemonoxacin, an antimicrobial drug effective at targeting antibiotic resistant bacteria strains.¹⁸ The six variable, two-step optimisations were used to produce MAP02, which is a main reaction step in forming the key intermediate MAP (shown in Scheme 6). The



Scheme 6. The synthesis of MAP and Nemonoxacin from MAP01.¹⁸

multi-objective optimisation was used to maximise the yield and enantioselectivity for MAP02 and improved these objectives from 70.5% and 97.1% in batch, to 83.8% and 97.2% respectively in continuous flow. The typical two-step one-pot batch synthesis used a temperature of -78 °C, which is energy intensive and difficult to maintain in a large scale batch system. This could be reduced to -37 and -41 °C for step one and step two respectively in continuous flow, which would have many benefits in terms of energy and environmental costs for scale up.

These examples demonstrate how continuous flow and optimisation algorithms can have a beneficial impact on optimising key API reaction steps for established chemical reactions.

3.1.2 Osimertinib nitrodiamine

Osimertinib (AZD9291), also known commercially as Tagrisso, is an on-market drug used to treat non-small-cell lung carcinomas (including those with a specific gene mutation T790M), and is named as one of AstraZeneca's five 'blockbuster' drug molecules.¹⁹ The orally administered drug acts to irreversibly and selectively inhibit the epidermal growth factor receptor for tyrosine kinase (EGFR-TKI) in patients that have EGFR-TKI sensitising or EGFR T790M resistant mutations.²⁰ The drug was discovered in 2011, and was first approved for medical use in 2015 in the US, and 2016 in Europe. It is synthesised via a seven step route which is disclosed in the composition matter patent application that was filed in 2012.²¹

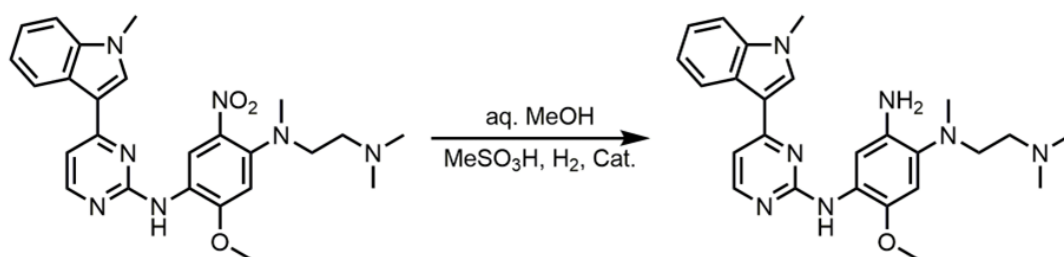
With process development still ongoing within AstraZenecas on-market technical team, this drug is of interest for improved route design and optimisation. Köckinger *et al.* in 2020 reported the optimisation and scale up for the initial acylation and nitration of a key osimertinib building block in a telescoped continuous flow process.²² Continuous flow offers benefits over the existing batch manufacturing process for these reaction steps, as the nitration of organic compounds can often lead to explosive intermediates and runaway reactions, meaning accurate process control is critical for safe scale up.²³ Acylation of the amine functionality allows protection from possible side reactions, and was essential for improving the overall yield of the two-step reaction. The group presented the optimised process, producing an isolated yield of 82%

for the final product, with a throughput of 0.46 kg hr⁻¹ in the scaled up pilot plant platform.

Another step that had previously been investigated for improved process design, is the nitro reduction for AZD9291 nitrodiamine (Scheme 7), with a recent European patent granted in 2020 for this reaction step.²⁴ The patent showed a change from using iron in aqueous ammonium chloride originally used in the manufacturing process, to a Pt or Pd on carbon based catalyst in the presence of an acid. Typically with the iron catalyst, iron-based residues would form as a byproduct to this reaction step, requiring lengthy and costly processing steps to yield the pure osimertinib aniline product. Swapping to a Pd or Pt/C based catalyst alleviates these issues and could cleanly produce the product without the need for such reprocessing procedures.

Most literature examples that discuss improvements to this step describe the production of new novel catalysts that can be used to perform the reduction reaction.^{25,26} The batch process is performed on scale in a STR, however, it is a strong candidate for transfer to continuous flow. With the ease of separation of the heterogeneous catalyst, and a reduction in plant downtime (little cleaning in between reaction runs), flow offers benefits of improved safety and process control using small tubular reactors.²⁷ Temperature control is particularly important for exothermic reactions such as this, where it is imperative to monitor the catalyst exotherm and control the temperature precisely in order to avoid runaway reactions.¹¹

Initial screening work for the transfer to continuous flow at AstraZeneca in a H.E.L. FlowCAT was performed by Kevin Leslie in 2020, investigating the effects of catalyst type, temperature, pressure, hydrogen equivalence, concentration, and liquid flow rate on the selectivity and yield of the aniline product. The optimum conditions found using an OVAT approach yielded 100% product with a 5 wt.% Pt/C granular



Scheme 7. The nitro reduction of osimertinib nitrodiamine to form the osimertinib aniline product.

catalyst from Evonik (2 g), 70 °C, ten bar pressure, three mole equivalents of hydrogen, 0.3 M starting material concentration, and 0.75 mL min⁻¹ liquid flow rate. The application of optimisation algorithms allows for a swift identification of the optimum reaction conditions, minimising the number of experiments required. This chapter will investigate a self-optimising approach to the synthesis of this API intermediate.

3.2 Aims

The aim of the work in this chapter is to assess the applicability of continuous flow for the heterogeneous hydrogenation of this important API reaction step. The reduction of osimertinib nitrodiamine is currently commercially performed in a large STR, but the process offers an opportunity for a beneficial transfer to continuous flow. The reaction will be performed in batch and screened to identify an appropriate catalyst and determine important kinetic parameters. The process will then be transferred to continuous flow where the reaction will be autonomously self-optimised to find the optimal reaction conditions. The results of these optimisations will be assessed for their pharmaceutical application and compared to the previous optimal conditions found by AstraZeneca.

3.3 Results

In this work, the reaction will be screened in both batch and continuous flow. In batch the reaction will be screened with a traditional OVAT approach, to understand the effect of each reaction variable on the yield of the reaction.

3.3.1 Catalyst screening in batch

To find an appropriate catalyst for the reduction of osimertinib nitrodiamine, a catalyst screen was first performed in batch. Six Pd and Pt/C catalysts from two different manufacturers (Evonik and JM) were tested for their activity in this reaction, and their properties are summarised in Table 11. The catalysts were screened in a H.E.L. HP ChemSCAN, that is designed specifically for benchtop parallel catalyst screening in batch

Table 11. List of catalysts and their average diameters screened in the HP ChemSCAN for their activity in the nitro reduction.

Supplier	Catalyst Type	Average Support Size / μm
Evonik	5% Pt/C	200
Evonik	5% Pd/C	200
Evonik	5% Pd(OH) ₂ /C	200
JM	5% Pd/C	400
JM	5% Pd(OH) ₂ /C	400
JM	4% Pt/C	400

STRs.²⁸ Each STR can be independently controlled and monitored, with their temperature, pressure, and hydrogen uptake separately recorded. A summary of the reaction conditions for each catalyst is outlined in appendix section 3.7.2. Performing an initial catalyst screen on a small scale (7 mL) minimised the amount of precious metals wasted and allowed any intermediates or side products to be evaluated and characterised. Hydrogen uptake data is summarised for all six catalysts in Figure 50. Initial uptake data showed a slow hydrogen uptake for four catalysts out of the six (Evonik 5% Pt, JM 5% Pd, JM 5% Pd(OH)₂, and JM 4% Pt). Therefore, the reaction temperature for these STRs was increased from 30 to 45 °C after 100 minutes. It can be seen from the graph that this caused an increase in the rate of reaction, with all four catalysts hydrogen uptake increasing at a faster rate. All of the Evonik catalysts performed well with both Evonik Pd based catalysts reaching full conversion after only 200 minutes. The Evonik catalysts have a smaller support diameter, which may cause an

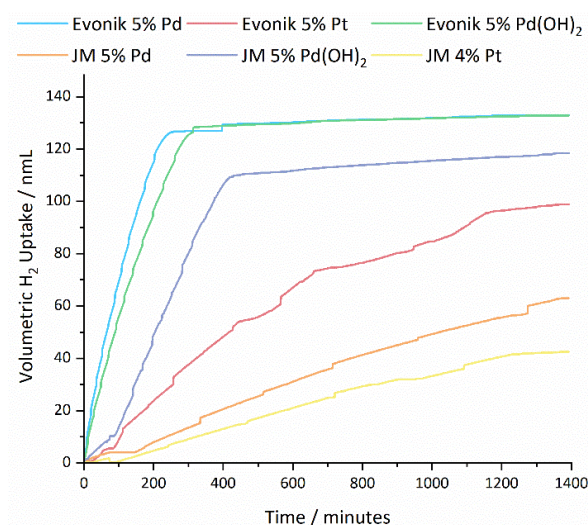
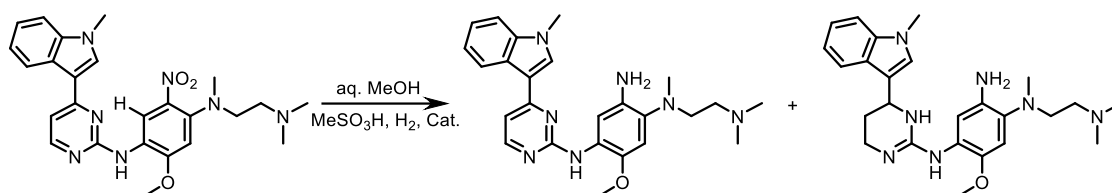


Figure 50. Hydrogen uptake data for the catalyst screen of six Pd and Pt/C catalysts, 30 or 45 °C and 5 bar.



Scheme 8. The reduction of osimertinib nitrodiamine to the desired product and the over-hydrogenated byproduct.

increase in the active surface area of the catalyst, or there may be a difference in the PdNP size, location or morphology compared to the JM catalysts. However, no characterisation of the catalysts was performed in this work. The JM 5% Pd(OH)₂ catalysts also performed well after the temperature was increased to 45 °C, showing that the catalyst required a higher temperature to be fully activated for this process. Although all Pd based catalysts performed well in this reaction, it could be seen from ultra-high performance liquid chromatography-mass spectrometry (UHPLC-MS) analysis from samples taken at the end of the reaction, all Pd based catalysts formed an undesired side product where the pyrimidine ring had also been hydrogenated shown in Scheme 8 – with an MS peak at 450 m/z present (UPLC-MS spectra shown in appendix section 3.8.2). Due to the lack of selectivity with the Pd based catalysts, for further batch and flow tests, the Evonik 5% Pt/C catalyst was chosen as it could achieve a good conversion with full selectivity for the desired product.

3.4 Kinetics testing in batch

Reaction conditions were screened in batch in a Biotage Endeavor parallel batch STR platform where eight parallel reactions were performed on a small scale (4 mL) with independent process control and monitoring for each reactor.²⁹ This would allow different reaction conditions to be tested simultaneously in separate vessels. The following variables would be investigated using an OVAT approach while keeping all other reaction variables constant:

- Osimertinib nitrodiamine starting concentration – 0.075 – 0.3 M.
- Catalyst mass – 4.5 – 18 mg.
- Temperature – 40 – 70 °C.
- Pressure – 1 – 10 bar.

The reaction variables for each experiment are summarised in section 3.8.3 of the appendix and the hydrogen uptake data for each experiment is shown in Figure 51. It can be seen in Figure 51a that changing the concentration of starting material in the reaction had little impact on the overall rate of the reaction, as all reactions proceeded with the same rate of hydrogen uptake. The catalyst amount used in the reaction had a significant impact on the reaction rate (Figure 51b), and the graph demonstrates an increase in the steepness of the gradient for the reactions with greater amounts of catalyst used, showing a faster rate of hydrogen uptake. This is also shown in the graph in section 3.8.4, demonstrating a linear increase in the k_{obs} with catalyst concentration. The pressure of the reaction also had an impact on the rate of reaction, with an increase in pressure leading to an increase in the rate of hydrogen uptake (Figure 51c). This may be due to the increase in the mass transfer of hydrogen gas to the liquid phase at higher pressure, as there is a linear relationship between these two variables (Henry's Law). This is also illustrated in the graph in section 3.8.4 with a linear increase in the k_{obs} with increasing hydrogen concentrations, caused by higher pressures in the reactor. Finally

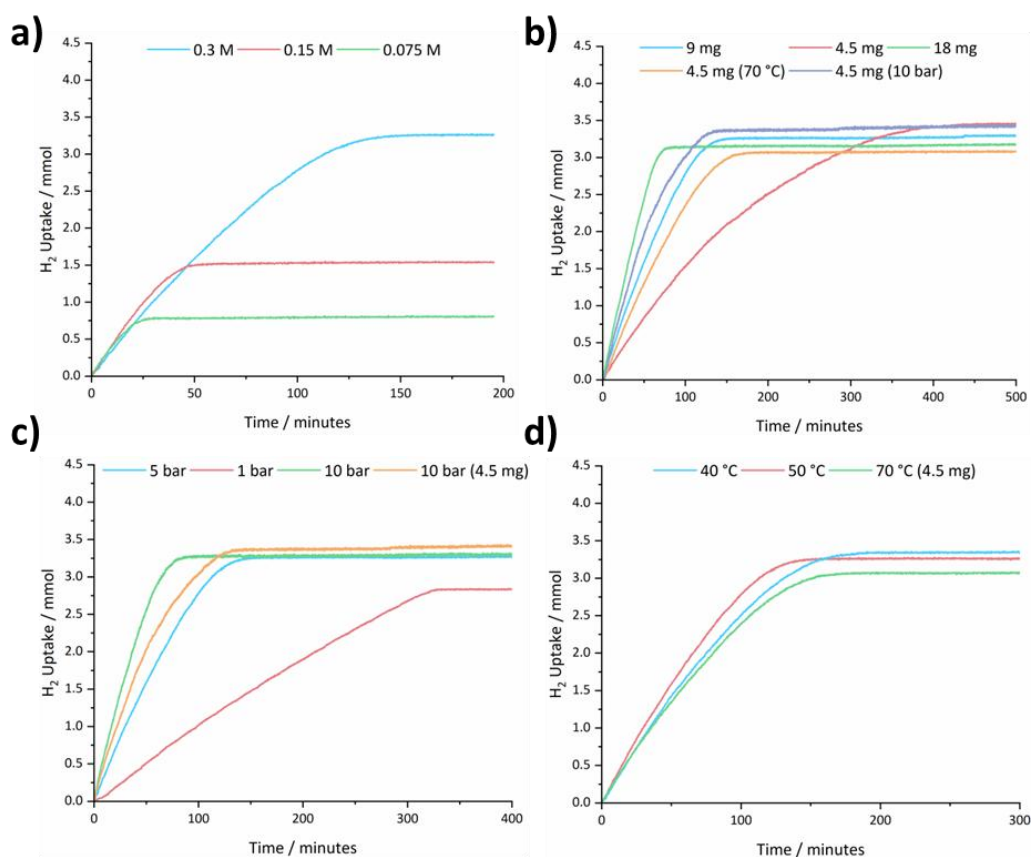


Figure 51. Hydrogen uptake data for all kinetic testing when changing OVAT, a) concentration, b) catalyst mass, c) pressure, and d) temperature.

an increase in temperature was also seen to increase the rate of reaction with a sharper gradient achieved at a higher temperature. A reaction at 70 °C proceeded too quickly for accurate kinetic analysis with 9 mg of catalyst, so the catalyst amount was halved and showed a similar rate to the reaction as the 40 °C reaction, even with a lower catalyst loading.

The hydrogen uptake data was converted into the consumption of starting material over time during each reaction, which could be used to calculate observed rate constants from the initial linear gradient of the graph. The rate was found to be zero order with respect to the concentration of starting material, and the rate equation is that shown in equation 1.

$$Rate = k [H_2][Cat.] = k_{obs} \quad (1)$$

The rate constant k could then be calculated from the observed rate constants, which are summarised in Table 12 (all runs were performed at the same temperature). The hydrogen concentration for each reaction was calculated from the solubility of hydrogen at 55 °C at the reaction pressure (taken from the DynoChem database). The average rate constant for this reaction was found to be 289 mol L⁻¹ min⁻¹ at 55 °C. Rate constants (Table 13) could also be calculated for the runs at three temperatures, and were used to calculate activation energies, using the Arrhenius equations (equation 2 and 3).

$$k = A e^{-\frac{E_a}{RT}} \quad (2)$$

$$\ln(k) = -\frac{E_a}{R} \cdot \frac{1}{T} + \ln(A) \quad (3)$$

Table 12. Summary of reagent concentrations and rate constants for kinetic screening.

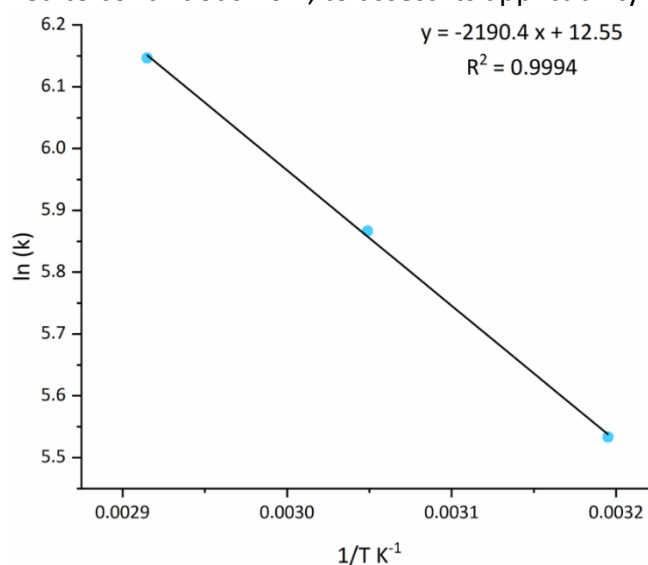
Run	Conc. SM / mol L ⁻¹	k _{obs} / mol L ⁻¹ min ⁻¹	[H ₂] / mol L ⁻¹	[Cat.] / mmol L ⁻¹	k / mol L ⁻¹ min ⁻¹
1	0.300	0.0026	0.0177	0.577	255
2	0.150	0.0036	0.0177	0.577	353
3	0.075	0.0032	0.0177	0.577	314
4	0.300	0.0012	0.0177	0.256	264
5	0.300	0.0045	0.0177	1.115	220
6	0.300	0.0009	0.0035	0.577	442
7	0.300	0.0043	0.0353	0.577	211

Table 13. Summary of the rate constants for kinetic runs in batch at different reaction temperatures.

Run	Temperature / °C	k / mol L ⁻¹ min ⁻¹
1	40	253
2	55	353
3	70	467

Where k is the rate constant in mol L⁻¹ min⁻¹, E_a is the activation energy in J mol⁻¹, R is the gas constant in J mol⁻¹ K⁻¹, T is the temperature of the reaction in K, and A is the pre-exponential factor.

A plot of $\ln(k)$ vs $1/T$ can be used to calculate the activation energy as the gradient of the linear $y = mx + c$ plot yields the value of E_a/R from equation 3. The calculated activation energy from the plot in Figure 52 was 18 kJ mol⁻¹. It is difficult to compare this to examples in the literature, as investigations into this reaction step are not widely reported. However, the R^2 value is close to 1, showing a good fit of the experimental data. This data set is limited to only three points, so more experimental points are required to get an accurate value for the activation energy of this process. When compared to other nitro reductions in the literature such as nitrobenzene (12 - 104 kJ mol⁻¹),^{30,31} nitrophenol (30 - 10 kJ mol⁻¹)³² and *p*-chloronitrobenzene (35 - 68 kJ mol⁻¹)³³ a range of activation energies are reported for a number of different catalysts.³⁵ After the reaction variables were investigated in batch, the hydrogenation could be transferred to continuous flow, to assess its applicability to this reaction step.

**Figure 52.** Arrhenius plot for the reduction of osimertinib nitrodiamine at different temperatures in batch to calculate the activation energy.

3.5 DoE in flow

The transfer to continuous flow was initially performed during a placement at AstraZeneca. A three variable two-level full factorial DoE with centre point repeats was conducted in a commercial H.E.L. FlowCAT PBR platform to investigate the effect of changing multiple variables at the same time (Figure 53). The variable bounds for the reaction were:

- Temperature – 40 – 70 °C.
- Liquid flow rate – 0.75 – 1.50 mL min⁻¹.
- Hydrogen mole equivalents – 1.25 – 3.00.

The reaction was run at the set reaction conditions for eight residence times, to ensure that steady state had been reached before a sample was taken from the outlet stream of the reactor for quantitative UHPLC-MS analysis offline. The results of the DoE are shown in Figure 54 and all experimental conditions and responses summarised in 3.8.5. The Pt/C catalyst (1 g) was shown to have a high activity for this reaction, with almost all of the experiments yielding over 90% conversion to the aniline product at relatively mild reaction conditions. The lowest yielding reaction was seen at a low hydrogen equivalents, low temperature, and low liquid flow rate. The effect of hydrogen equivalents was not clear from the DoE experiments conducted. All experiments were conducted in an excess of hydrogen gas, with the lower bounds chosen here to be 1.25 mole equivalents. If this bound was lowered below 1, the effect of hydrogen equivalents may have become clearer, but these experiments did show that a hydrogen flow rate of 37.5 mL min⁻¹ was sufficient in supplying enough hydrogen for the reaction.

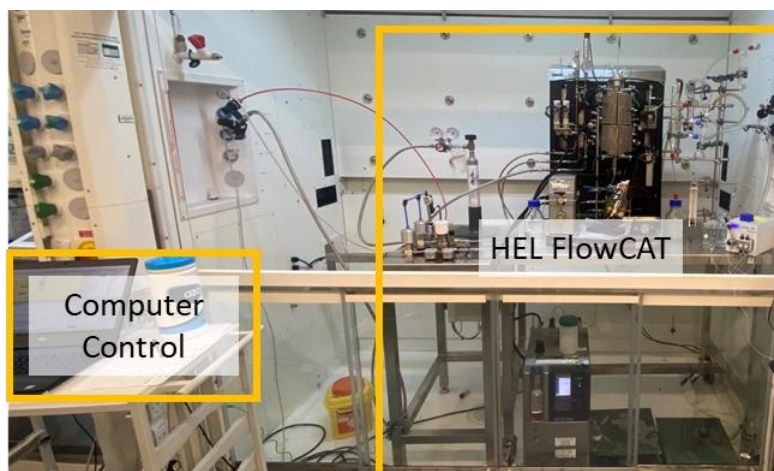


Figure 53. H.E.L. FlowCAT setup in the lab, showing the H.E.L. FlowCAT and its control computer.

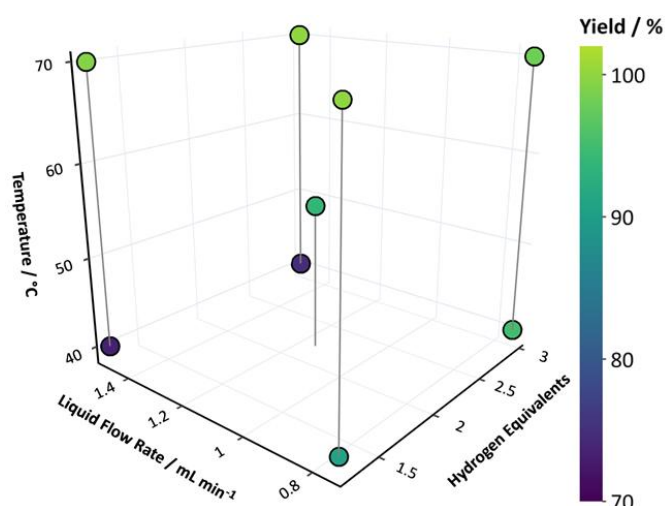


Figure 54. DoE data for the reduction of osimertinib nitrodiamine in the H.E.L. FlowCAT. Fixed conditions: catalyst – 1 g, pressure – 10 bar, and concentration – 0.3 M.

All DoE data was inputted into MODDE (version 12.1) and fitted with a multiple linear regression (MLR) model and a summary of the data fit is shown in Figure 55a. No outliers were observed in the residuals normal probability plot outside of the allowed standard deviation in Figure 55f; therefore, all data points were included in the model fit. The model was refined in MODDE by removing any insignificant terms that related to individual main, interactions, or squared terms, and subsequently refitted. This improved both the model goodness of fit (R^2) and the accuracy of the model predictions (Q^2) which both have ideal values close to 1. The hydrogen pressure of the system was shown to be a noninfluential variable in this reaction and including that term led to lower R^2 and Q^2 values. However, both the temperature and liquid flow rate terms were shown to have an impact on the yield of the reaction, with temperature displaying the largest coefficient, indicating it had the most influence on the response. The data also showed a significant interactions term between the temperature and the liquid flow rate of the reaction, shown in Figure 55b, c, and e. This showed that at high flow rates, increasing the temperature had a larger effect on the yield of the reaction. This aids in process understanding, as the reaction could be performed at higher liquid flow rates when using higher temperatures to achieve both high yields and throughputs for the reaction. Conversely, if a higher temperature leads to a detrimental increase in process and energy costs, lower flow rates could be used at lower temperatures, resulting in only a small decrease in yield (5%). The observed vs. predicted plot in Figure 55d shows a reasonable fit of the data to the model with all data points lying close to the linear

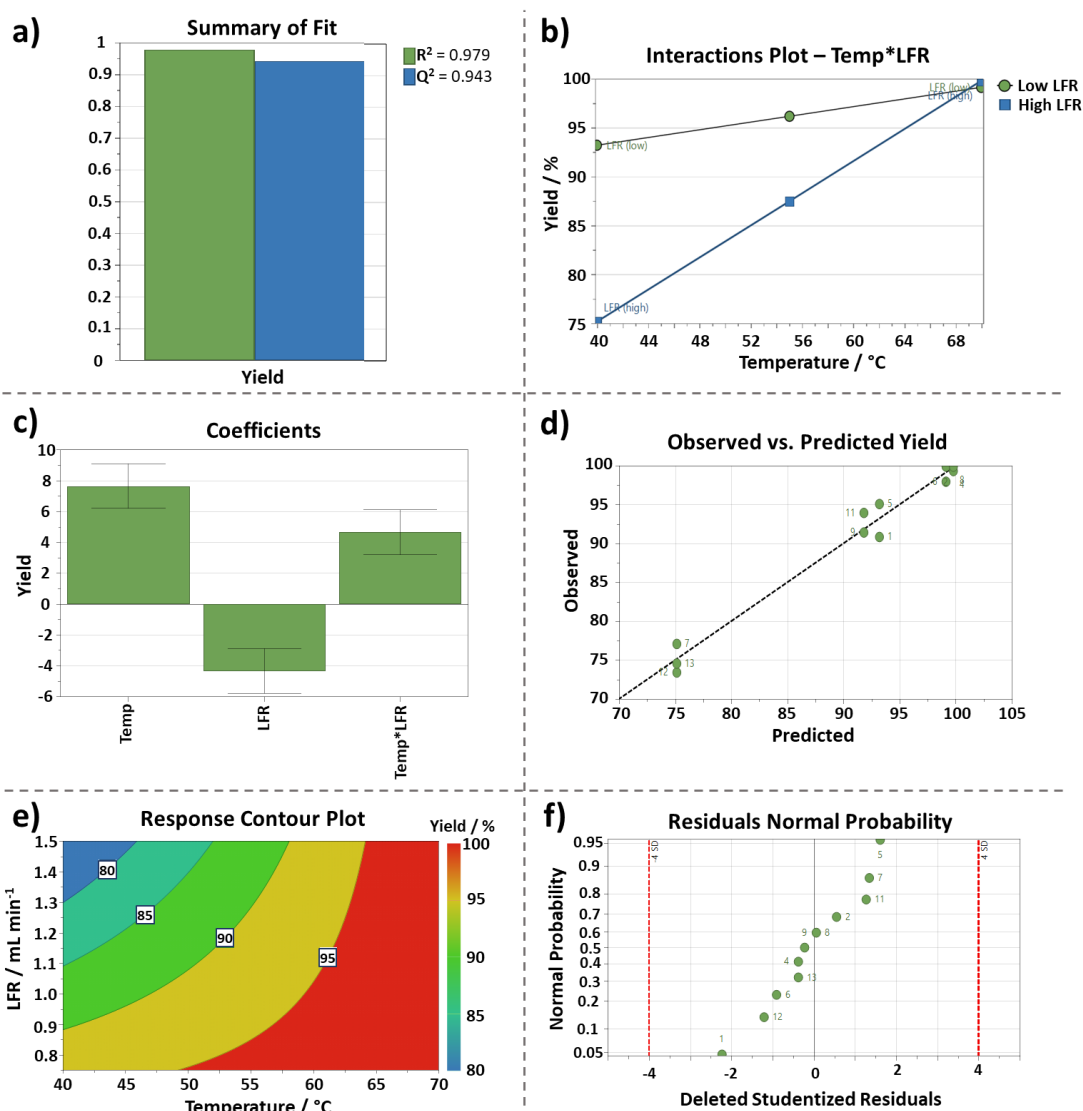


Figure 55. MODDE DoE fitting results, where LFR is liquid flow rate. a) A summary of the model fit where R^2 is the goodness of fit of the data to the model and Q^2 is the ability of the model to make accurate yield predictions. b) An interactions plot for the temperature and LFR variables. c) A coefficients plot showing the relevance of each variable on the yield of the reaction. d) A plot showing the observed vs. the predicted yields for the model. e) A contour plot showing the effect of temperature and LFR on the yield. f) A residuals normal probability plot with the allowed standard deviation given by the red dotted line.

diagonal line. However, the graph shows there is a large region between the 80 and 90 values that contains no experimental data points. To improve the model fitting and R^2 and Q^2 values, more experiments would be required to cover this area.

Modelling of the DoE data allowed for a good visualisation of the variables, the identification of insignificant terms, and also helped to highlight areas of the design space that would require more investigation in the future. This demonstrates the

usefulness of software such as MODDE as an easy to use data analysis tool, as little modelling knowledge was required to achieve a better process understanding.

3.5.1 BOAEI self-optimisation

The BOAEI algorithm previously described in Chapter 2 was used to perform single objective optimisations initialised using LHC (seven experiments) at the University of Leeds. Three catalyst loadings of the 5 wt.% Pt/C catalyst (500 mg, 100 mg, and 10 mg) were investigated and three individual optimisations were performed. As the DoE performed in the FlowCAT resulted in high yields for all but two of the experiments (with 1 g Pt/C catalyst), the catalyst amount was investigated to see if more variation in the yields of the reaction could be achieved. This would also mean that changing the catalyst amount could be investigated for its effect on the reaction yield as a discrete variable, which could provide information on how much of the catalyst was required, to avoid wasting excess precious metals. It could also allow the effect of catalyst deactivation to be seen, as some deactivation is likely to be experienced at lower catalyst loadings. The following variables and reaction conditions were investigated during the optimisation:

- [Osimertinib nitrodiamine] – 0.1 – 0.3 M.
- Liquid flow rate – 0.5 – 2 mL min⁻¹ (500 mg).
- Temperature – 30 – 70 °C (500 and 100 mg) and 45 – 85 °C (10 mg).

Due to the high concentration of the starting material used in this process (0.3 M), and to ensure the results of these optimisations were comparable to the batch and DoE experiments, the automated PBR platform previously described in Chapter 2 was adapted (section 3.7.5). If the 0.3 M reaction solution was injected into the inline HPLC, the variable wavelength detector (VWD) would become saturated due to this high concentration and accurate quantitative analysis would not be possible (even with a smaller 60 nL sample loop size for the Vici valve). Therefore, a dilution pump was placed after the tube-in-tube gas-liquid separator, before the Vici sampling valve, to dilute all samples down to an appropriate concentration for sampling into the HPLC for online analysis (0.1 M). The dilution pump flow rate would be included in the conditions generator and used by the BOAEI algorithm to calculate the flow rates required for the suggested reaction conditions.

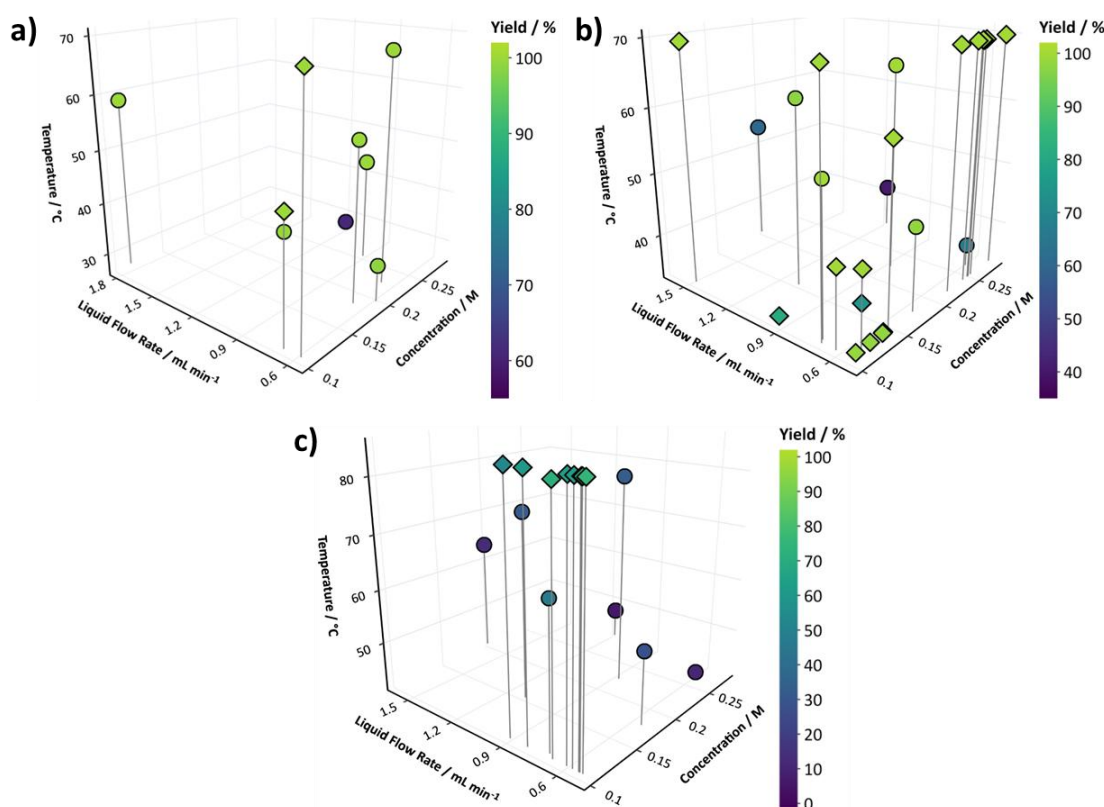


Figure 56. BOAEI optimisation data for the reduction of osimertinib nitrodiamine. a) 500 mg of Pt/C catalyst, b) 100 mg of Pt/C catalyst, and c) 10 mg of Pt/C catalyst, where ○ – LHC experiments and ◇ - refinement experiments. Fixed conditions: pressure – 10 bar and H₂ flow rate – 50 mL min⁻¹.

The results of all three BOAEI optimisations are shown in Figure 56 and all data is summarised in section 3.8.6. In both Figure 56a and b, which correspond to 500 mg and 100 mg catalyst loading respectively, it can be seen that there is very little variation in the yields of the reactions at different reaction conditions. Most experimental points achieved a yield of 95% or above of the osimertinib aniline product, with the remaining left as unreacted starting material, showing the activity of the catalyst for this reaction to be extremely high. If all the points in the optimisation are high yielding, then the effect of each variable on the yield of the reaction cannot be understood. In Figure 56c, with only 10 mg of the 5 wt.% Pt/C catalyst, the maximum yield achieved after a total of nine experiments was 78.2% for the osimertinib aniline product at high temperatures, low liquid flow rates (long residence times) and low concentrations. Although the reaction could no longer reach full conversion with only 10 mg of catalyst, the effect of each optimisation variable could now be clearly seen and evaluated. In optimisation three, the LHC explored the design space well and informed the algorithm effectively, as all refinement experiments were conducted in the highest yielding area of the design space

and the optimum conditions were found quickly after only two refinement experiments. All the optimisations results and yields are summarised in Figure 57, showing the maximum yield achieved chronologically during each optimisation. It can be seen more clearly from this graph that 100% yielding experiments were found in the LHC for both the 500 and 100 mg optimisations due to most of the design space being high yielding for these catalyst loadings. During the 10 mg optimisation, a high yield was found quickly after the initial LHC, but there was a drop off in activity from experiment 15, with little variations in the reaction conditions from the BOAEI algorithm. Although catalyst deactivation was seen during this optimisation, it likely did not affect the optimisation results due to the efficiency of the BOAEI algorithm finding the optimum quickly before significant deactivation of the catalyst occurred. This demonstrates the importance of using efficient algorithms to optimise heterogeneous processes. The deactivation was likely caused by catalyst fouling at such low catalyst amounts, which resulted in the blockage of active sites on the catalyst over time. Repeat reactions were sampled offline during all three optimisation, and also show this trend in a decrease in the activity of the catalyst over time during the optimisation (section 3.8.8). In optimisation two (100 mg of catalyst) many more experiments were conducted over multiple days and there was no observed decrease in the activity of the catalyst, with the yield consistently remaining

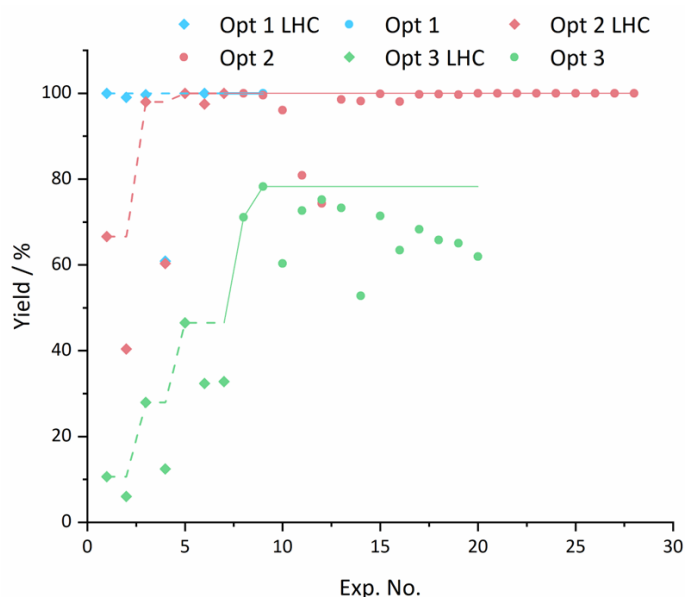


Figure 57. Optimisation data showing the yield of the reaction vs. the experiment number, where ○ – LHC experiments and ◇ – refinement experiments. The lines represent the highest yielding experiment achieved chronologically in each optimisation, where the dotted line is the LHC experiments and the solid line is the refinement experiments. Opt. 1 – 500 mg, Opt. 2 – 100 mg, and Opt. 3 – 10 mg.

at 100%. Although deactivation was not seen at higher catalyst loadings (over three days with 100 mg of catalyst), it is likely that deactivation of the catalyst was also present in these cases, but the loading was too high to observe it. This shows that for an industrial process, a higher amount of catalyst is required to minimise the effect of catalyst deactivation, to allow the process to be performed for many days or even weeks, to produce the product on a kilogram scale.

3.5.2 Process metrics

The data from all three BOAEI optimisations can be converted into industrially relevant process metrics so that all optimisation data can be compared from a process and sustainability aspect (summarised in section 3.8.7). The following equations were used to calculate the relevant process metrics for each experiment:

$$\text{Space – time yield (STY)} / g L^{-1}hr^{-1} = \frac{\text{mass of product (g)}}{\text{vol.of reactor} \times \text{reaction time}} \quad (4)$$

$$\text{Reaction Mass Efficiency (RME)} / \% = \frac{\text{mass of product}}{\text{total mass of reactants}} \quad (5)$$

$$\text{Turnover Number (TON)} = \frac{\text{moles product in one hour}}{\text{moles Pt}} \quad (6)$$

STY is a measure of the efficiency of the process and relates to the throughput of the reaction. A higher value indicates a process that can produce larger quantities of product over a specified time. RME shows the ‘greenness’ of a reaction and considers the percentage of the input mass that is converted to useful product. A larger RME is desired as it means the process is less wasteful, as more of the reactant mass ends up in the desired product. TON takes into account the moles of catalyst used in the reaction and the moles of product that can be produced under specific reaction conditions for a specified amount of time. It allows the amount of catalyst used in each of the optimisations to be compared and related to how much product can be made. The calculated values for each experiment are shown in Figure 58, where the data points for each optimisation are represented as different shapes. It shows that the 10 mg optimisation was able to achieve much higher TONs due to the small amount of catalyst used. However, it was not able to produce high RME or STY as the optimum conditions were found at low liquid flow rates and low concentrations, reducing the throughput of

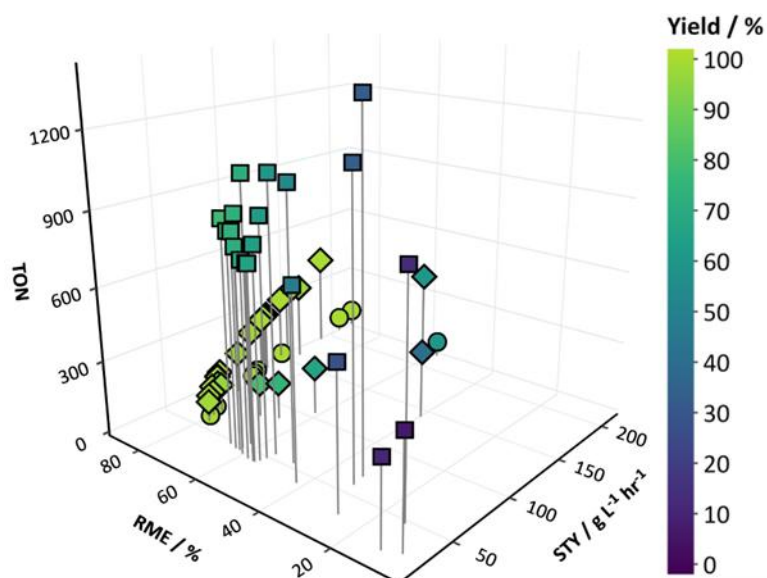


Figure 58. A summary of all the process metric data for the three optimisations, where $\circ$ = 500 mg Pt/C, $\diamond$ = 100 mg Pt/C, and $\square$ = 10 mg Pt/C catalysts.

the process. When only the catalyst optimisations for 100 and 500 mg are shown (Figure 59), it can be seen that the 100 mg catalyst is able to achieve high STY and RME like the 500 mg optimisation data points but exhibits a higher TON than those with 500 mg of catalyst. The catalyst contains precious metals, which are expensive and nonabundant, so limiting their use is beneficial for any process. Therefore, from these three optimisations, a catalyst loading of 100 mg would be suggested with the highest overall RME, STY, TON and yield found in experiment seven for optimisation two. The STYs in experiment seven do satisfy the scale requirement for a pharmaceutical process, as the

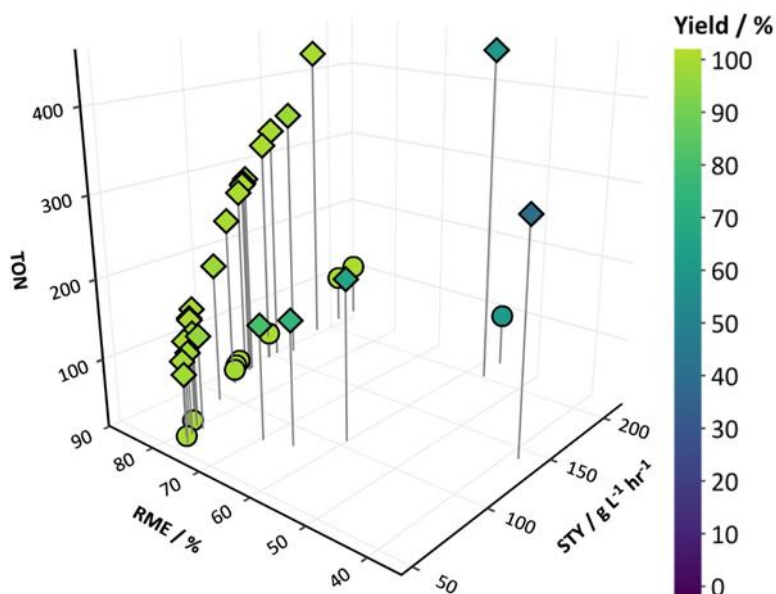
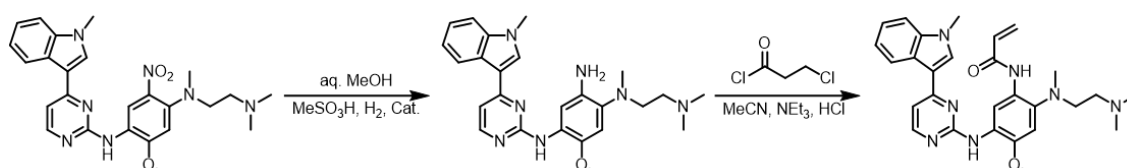


Figure 59. Process metric data for optimisation one and two, where $\circ$ = 500 mg Pt/C and $\diamond$ = 100 mg Pt/C.

reaction can produce $180 \text{ g L}^{-1} \text{ hr}^{-1}$, leading to a daily STY of $4.32 \text{ kg L}^{-1} \text{ day}^{-1}$. However, to provide an accurate suggestion for the optimal conditions to achieve the best process metrics at this catalyst loading, a multi-objective optimisation for all four parameters would be required. A further investigation into the lifetime of the catalyst would also be required. Optimisation two (100 mg of catalyst) was performed over 82 hours where the yield of the reaction remained at 100%. Using the STY in experiment seven, this would result in 14.8 kg L^{-1} of product for 82 hours. API requirements per year are in the hundreds of kilograms, therefore, to understand if the 100 mg catalyst loading is appropriate it would be important to investigate how long it would take for the catalyst to become permanently deactivated and require a bed replacement.

When compared to the process conditions found by AstraZeneca using an OVAT approach in continuous flow, lower catalysts amount, higher liquid flow rates, lower mole equivalents of hydrogen, and lower temperatures were found for the optimal conditions (at experiment seven in optimisation two). Although the reaction wasn't optimised for these process metrics, exploring the design space using DoE and with a self-optimising approach showed beneficial improvements to the process development.

Previous work reported in the literature shows the application of continuous flow to the seventh and final step for the synthesis of osimertinib. If combined with the heterogeneous hydrogenation discussed here (the sixth step in the total synthetic route), a telescoped synthesis for the final product could be performed (Scheme 9). This has many benefits, including the reduction in purification and crystallisations steps, leading to an overall decrease in solvent and waste for the process. Holmes *et al.* in 2016 described the use of a SNOBFIT optimisation algorithm to perform an automated, closed-loop self-optimisation to maximise the yield of the final product, osimertinib.³⁵ The four variable, single objective optimisation found optimum conditions at high equivalents of acid chloride, high temperatures, high ethylamine equivalents and median liquid flow rates of AZ9291 aniline starting material. Work ensuring that the



Scheme 9. The proposed continuous flow telescoped synthesis of osimertinib from osimertinib nitrodiamine.

reactions are suitable for telescoping, such as investigating the compatibility of solvents between steps, as well as the removal of reactive intermediates that may cause further reactions downstream in other reaction steps, would need to be considered. However, this work shows promise for the future continuous telescoped synthesis of this API.

3.6 Conclusion

This chapter describes the translation of an API reaction step in the production of osimertinib from its existing batch process to continuous flow. The reaction was first screened in batch to identify an appropriate catalyst, with the 5 wt.% Pt/C granular catalyst showing a good selectivity and activity in the reaction. Process conditions were screened in a parallel batch platform on a small scale (4 mL), showing high temperatures, high pressures, and high catalyst loadings yielded the fastest rate of reaction. The reaction was then transferred to a continuous flow system via a PBR, and the self-optimisation of the hydrogenation was performed at various catalyst loadings to gain a full understanding of the effect of different reaction variables in continuous flow. Optimal process conditions were found when converting all the flow experiments into industrially relevant process metrics, showing a catalyst loading of 100 mg allows for short residence times and high concentrations to improve the STY of the reaction to 4.32 kg L⁻¹ day⁻¹.

3.7 Experimental

3.7.1 Chemicals

5 wt.% Pt/C (Evonik), 5 wt.% Pd/C (Evonik), 5 wt.% Pd(OH)₂ (Evonik), 5 wt.% Pd/C (JM), 5 wt.% Pd(OH)₂ (JM), 4 wt.% Pt/C (JM), methanol (99.9%, Sigma Aldrich), water (HPLC-grade, Sigma Aldrich), methanesulfonic acid (99%, Thermo Scientific Chemicals), nitrogen gas (99.998%, BOC Gas), hydrogen gas (99.99%, BOC Gas) were all purchased from suppliers and used without further purification. AZ9291 nitrodiamine and AZ9291 aniline were supplied by AstraZeneca and used without purification.

3.7.2 H.E.L. ChemSCAN catalyst screen

For the catalyst screens, a H.E.L. High Pressure ChemSCAN unit (Figure 60) was used to perform six reactions in parallel. All catalysts and reagents were weighed, transferred into the high pressure steel vessels, and sealed and a summary of their masses is outlined in Table 14. They were then subject to the desired reaction conditions and their hydrogen uptake was recorded for 24 hours. The vessels were then depressurised and a sample was taken of the resulting reactant solution for analysis via a Waters Acquity H-Class Plus UPLC-MS.



Figure 60. Image of the H.E.L. HP ChemSCAN used in the catalyst screen for the reduction of osimertinib nitrodiamine.

Table 14. Masses, catalysts, and volumes used in catalyst screening tests.

Catalyst	Mass Osi. Nitro. / g	Mass cat. / mg	Vol. MeSO ₃ H / mL	Vol. MeOH / mL	Vol. H ₂ O / mL	Total Vol. / mL
5% Pt Evonik	1	82	0.2	4.0	2.2	7.0
5% Pd Evonik	1	44	0.2	4.0	2.2	7.0
5% Pd(OH) ₂ Evonik	1	44	0.2	4.0	2.2	7.0
5% Pd JM	1	44	0.2	4.0	2.2	7.0
5% Pd(OH) ₂ JM	1	44	0.2	4.0	2.2	7.0
4% Pt JM	1	102	0.2	4.0	2.2	7.0

3.7.3 Endeavour kinetics testing

OVAT kinetic experiments were conducted on the chosen catalyst using a Biotage Endeavor catalyst screening system designed for parallel pressurised reactions (Figure 61). All the reagents were weighed into glass vials, sealed, and placed into the Endeavor; reaction conditions are summarised in Table 15. The desired reaction conditions were applied to the individual reactors and their hydrogen uptake data was recorded. Once every reaction had reached completion (evident from the uptake plateauing), the reactors were depressurised and samples were taken of the resulting reaction mixture and analysed by a Waters Acquity H-Class Plus UPLC-MS.



Figure 61. The Biotage Endeavor catalyst screening platform used in the kinetic experiments.

Table 15. Masses, volumes, and reaction conditions in the kinetic experiments in the Biotage Endeavor.

Exp. No.	Mass Osi. Nitro. / g	Conc. / M	Mass Cat. / mg	Press. / PSI	Temp. / °C	Total Vol. / mL	Vol. H ₂ O / mL	Vol MeOH / mL	Vol. MeSO ₃ H / µL
1	0.57	0.3	9.0	74	55	4	1.24	2.27	120
2	0.28	0.15	9.0	74	55	4	1.33	2.42	58
3	0.14	0.075	9.0	74	55	4	1.38	2.51	29
4	0.57	0.3	4.5	74	55	4	1.24	2.27	120
5	0.57	0.3	18.0	74	55	4	1.24	2.27	120
6	0.57	0.3	4.5	74	70	4	1.24	2.27	120
7	0.57	0.3	4.5	150	55	4	1.24	2.27	120
8	0.57	0.3	9.0	15	55	4	1.24	2.27	120
9	0.57	0.3	9.0	150	55	4	1.24	2.27	120
10	0.57	0.3	9.0	74	40	4	1.24	2.27	120

3.7.4 H.E.L. FlowCAT DoE

The H.E.L. FlowCAT was used to conduct continuous flow reactions for the reduction of osimertinib nitrodiamine at AstraZeneca. The 5 wt.% Pt/C Evonik catalyst (1 g) and glass beads (200 μm , 9.4 g) were packed into a stainless steel column (30 cm length, 0.6 cm ID) and connected to the FlowCAT system. The system was pressurised and flushed with nitrogen to remove any air. The system was then flushed with methanol (1 mL min^{-1}) and hydrogen (20 mL min^{-1}) for five hours to activate the catalyst. The reactor was then dried under hydrogen and sealed under 3 bar of hydrogen pressure overnight. A reservoir of osimertinib nitrodiamine (70.7 g, 0.3 M) and methanesulfonic acid (14.5 mL, 0.44 mM) in water (157 mL) and methanol (285 mL) was prepared and made fully homogeneous by dissolving the reagents in the solvent and stirring under ambient conditions. The DoE was conducted over two days. At the end of each day the reactor was flushed with methanol and hydrogen for one hour to remove any residual starting material from the reactor. The column was then dried under hydrogen and isolated under three bar of hydrogen overnight.

3.7.4.1 Typical procedure

1. The system was pressurised to five bar and purged three times with nitrogen.
2. The system was pressurised to five bar and purged five times with hydrogen.
3. The system was pressurised to 10 bar and flushed with the reactant solution and hydrogen at 40 °C for one hour to condition the column.
4. The DoE reaction conditions were applied to the reactor and allowed to reach steady state over eight residence times and the reaction was sampled for UHPLC-MS analysis.
5. Subsequent DoE experiments were performed.
6. When the experiments were finished for the day, the reactor was flushed with hydrogen (20 mL min^{-1}) and methanol (1 mL min^{-1}) for one hour.
7. The reactor was then flushed with hydrogen (20 mL min^{-1}) for 10 minutes and then sealed under a three bar hydrogen pressure over night.
8. When returning the next day steps 1-7 were repeated.

3.7.5 Adapted PBR for self-optimisation

The automated PBR platform was adapted to have a dilution Knauer Azura 4.1S dual piston pump after the gas liquid separator. Due to the size of the Evonik catalyst granules, a smaller stainless steel column was used for the PBR (1/4" OD, 0.194" ID, 0.028 wall thickness) and a new aluminium heating block was fitted to the new column diameter. The same typical procedure for an optimisation was used as described in Chapter 2.

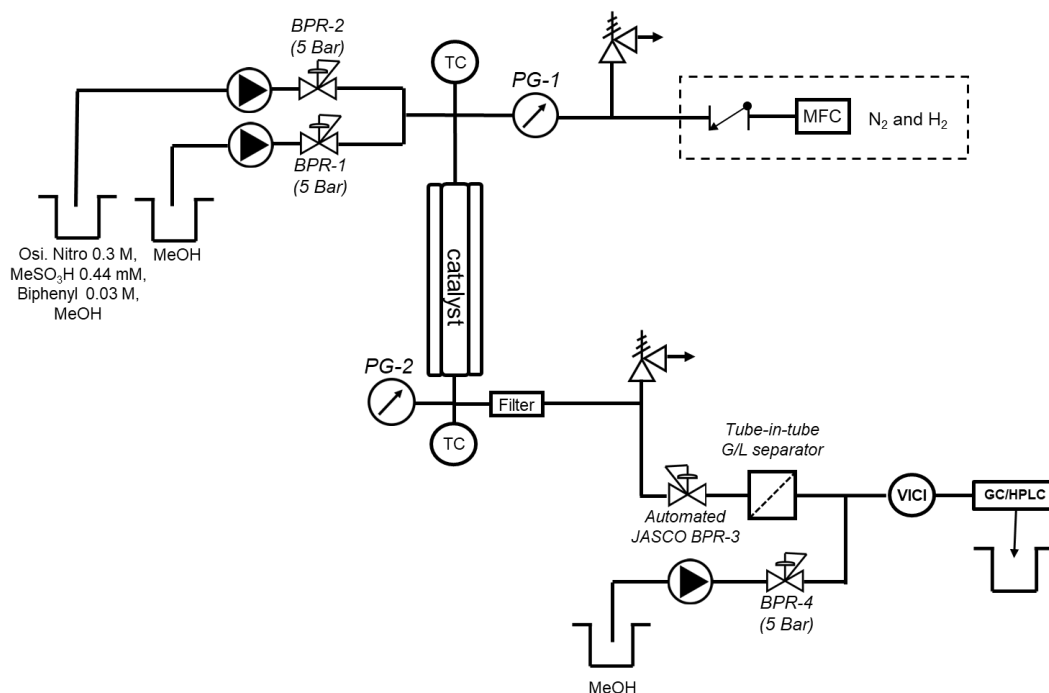


Figure 62. Adapted PBR platform used to perform the reduction of osimertinib nitrodiamine.

3.7.5.1 Typical HPLC chromatogram

Online analysis in the self-optimisation was performed by an Agilent 1100 HPLC fitted with an Agilent Poroshell 120 EC-C8 HPLC column with 2.7 μm particle size, and L x ID of 5 cm x 4.6 mm. A typical HPLC for the online optimisations is shown in Figure 63. A column oven temperature of 35 $^{\circ}\text{C}$, and a liquid flow rate of 1.5 mL min^{-1} were used in this HPLC method. The HPLC method used water with formic acid (0.1%) and ammonium formate (5 mM) as the aqueous phase and acetonitrile as the organic phase.

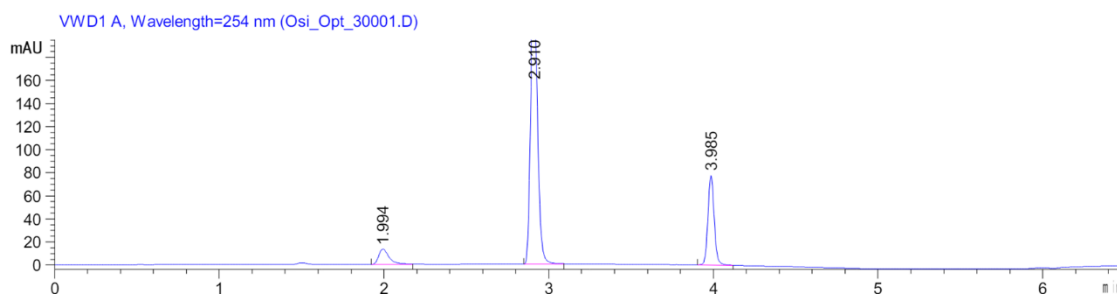


Figure 63. Example chromatogram for the reduction of osimertinib nitrodiamine.

Table 16. Peak picking for Figure 63, showing product (P), starting material (SM) and internal standard (IS).

Peak Position / min	Peak Identification
1.994	Osi. Aniline (P)
2.910	Osi. Nitro (SM)
3.985	Biphenyl (IS)

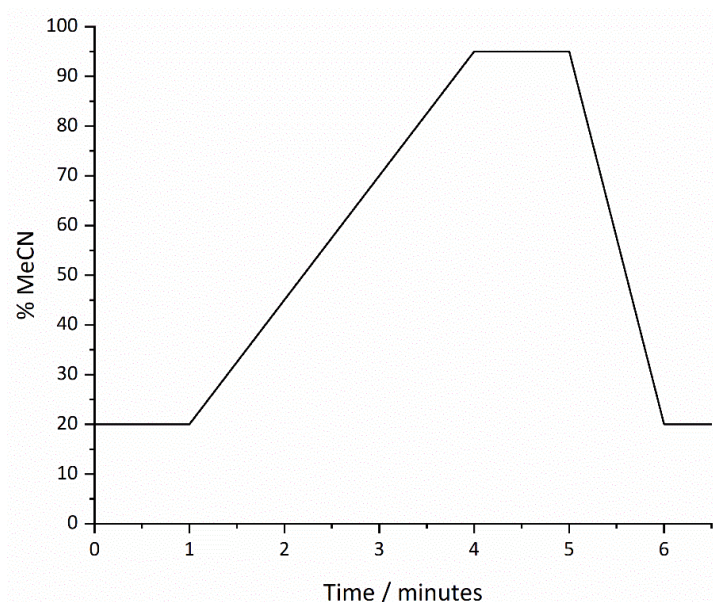


Figure 64. HPLC method solvent gradient for the reduction of osimertinib nitrodiamine self-optimisation.

3.8 Appendix

3.8.1 Catalyst screen

Table 17. Reaction conditions for initial catalyst screen.

Catalyst	Pressure / bar	Initial temp / °C	Temp increase?	Final temp / °C	Cat loading	Stirrer speed / RPM	Volume / mL	Total uptake / mmol
5% Pt Evonik	5	30	Yes	45	1:100	1000	7	4.41
5% Pd Evonik	5	30	No	30	1:100	1000	7	5.94
5% Pd(OH) ₂ Evonik	5	30	No	30	1:100	1000	7	5.93
5% Pd JM	5	30	Yes	45	1:100	1000	7	2.81
5% Pd(OH) ₂ JM	5	30	Yes	45	1:100	1000	7	5.28
4% Pt JM	5	30	Yes	45	1:100	1000	7	1.9

3.8.2 UHPLC-MS data for catalyst screen

3.8.2.1 Isolated starting material

Sample Name: Nitrodiamine SM

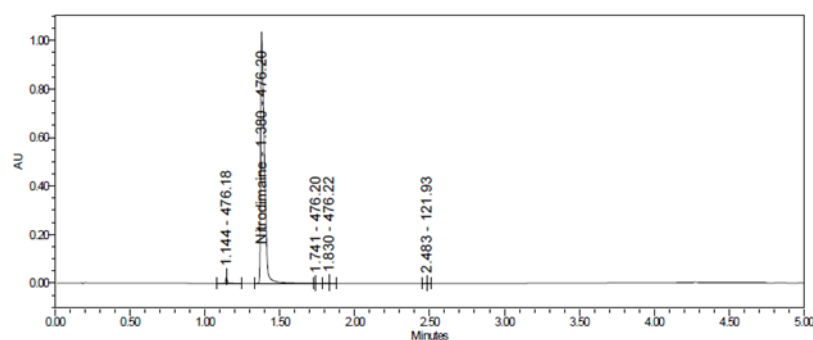


Figure 65. UPLC-MS chromatogram for the isolated nitrodiamine starting material.

3.8.2.2 Isolated desired product

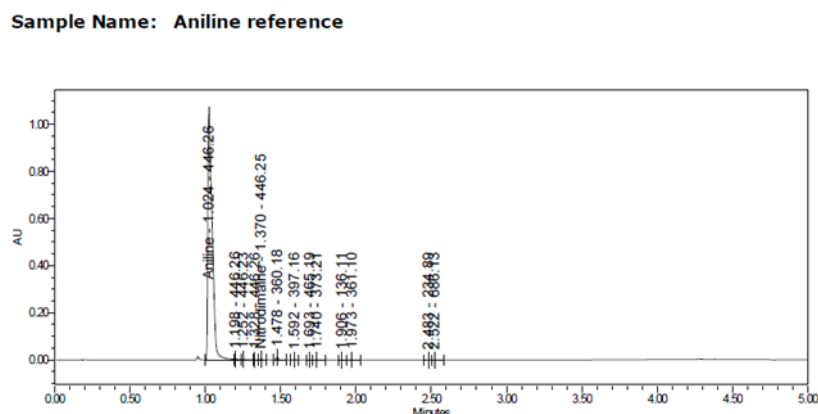


Figure 66. UPLC-MS chromatogram of the isolated desired osimertinib aniline product.

3.8.2.3 UHPLC-MS chromatogram for batch Pd based reactions

An MS spectra from the batch catalyst screen for the Pd based reactions is shown in Figure 67, showing overlapping peaks on the UHPLC-MS chromatogram corresponding to the aniline product and the fully hydrogenated side product.

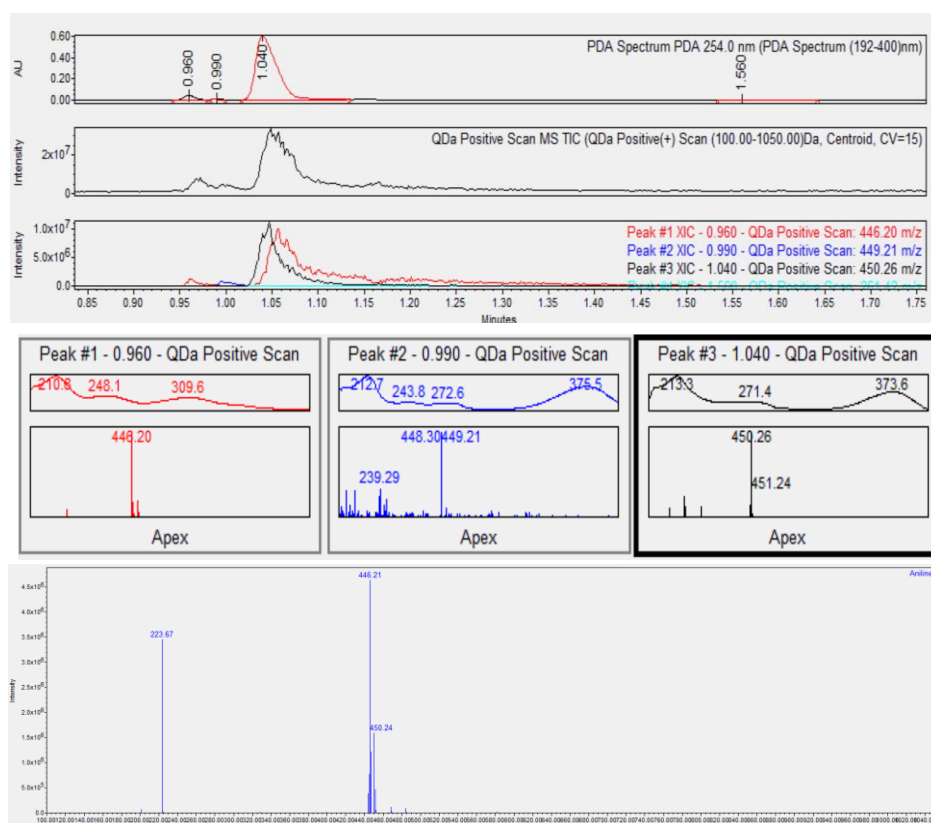


Figure 67. UPLC-MS data for the resulting solution of the nitrodiamine reduction with the 5% Pd/C Evonik catalyst.

3.8.2.4 UPLC-MS spectra for batch Pt based reactions

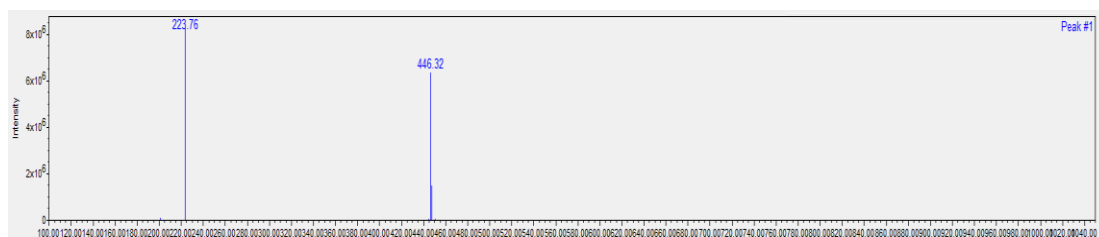


Figure 68. UPLC-MS data for resulting solution of the batch reaction with 5% Pt/C Evonik catalyst.

3.8.3 Kinetics testing

Table 18. A summary of reaction conditions used in the kinetics testing in the Endeavour batch platform.

Reaction No.	[Nitro] / M	Cat. Mass / mg	Pressure / barg	Temp / °C
1	0.3	9	5	55
2	0.15	9	5	55
3	0.075	9	5	55
4	0.3	4.5	5	55
5	0.3	18	5	55
6	0.3	9	1	55
7	0.3	9	10	55
8	0.3	9	5	40
9	0.3	4.5	5	70
10	0.3	4.5	10	55

3.8.4 Effect of [H₂] and [Cat.] on k_{obs}

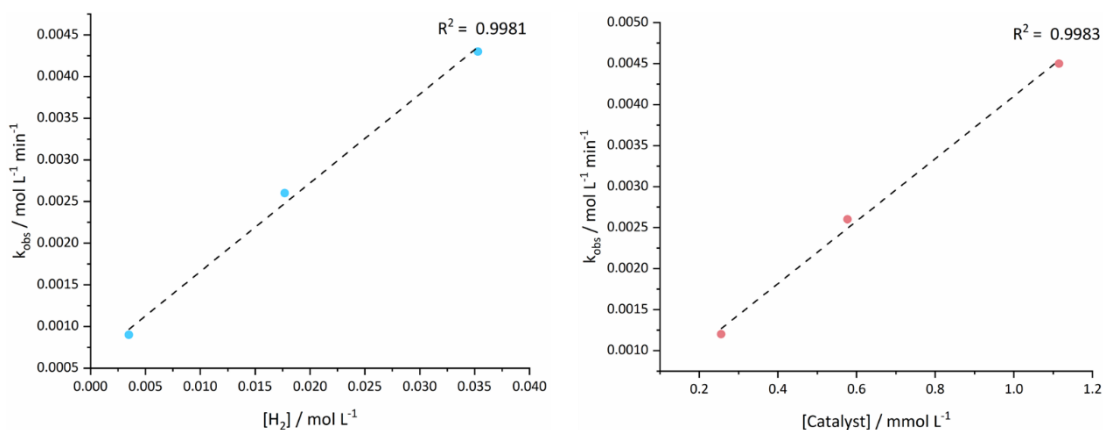


Figure 69. The linear relationship between k_{obs} and [H₂] (left), and [Cat.] (right).

3.8.5 Doe in FlowCAT

Table 19. Summary of the DoE results.

Exp. No.	Variables			H ₂ flow rate / mL min ⁻¹	Objective
	Temp. / °C	Liq. flow rate / mL min ⁻¹	H ₂ equiv.		Yield / %
1	40	1.50	3.00	90.00	74.53
2	70	1.50	3.00	90.00	99.9
3	70	0.75	1.25	18.75	99.9
4	55	1.13	2.13	47.75	99.54
5	40	0.75	1.25	18.75	90.85
6	55	1.13	2.13	47.75	91.42
7	40	1.50	1.25	37.50	73.46
8	70	1.50	1.25	37.50	99.3
9	55	1.13	2.13	47.75	93.9
10	70	0.75	3.00	45.00	97.94
11	40	0.75	3.00	45.00	95.07

3.8.6 BOAEI optimisation data

3.8.6.1 BOAEI – 500 mg Pt/C

Table 20. Optimisation data for the osimertinib nitrodiamine reduction with the BOAEI algorithm and 500 mg 5% Pt/C catalyst.

Exp. No.	Exp. Type	Variables			Flow Rate / mL min ⁻¹			Objective
		Liq. Flow Rate / mL min ⁻¹	Temp. / °C	Conc. / M	Osi. Nitro – Pump 1	MeOH – Pump 2	MeOH – Pump 3	Yield / %
1	Initial	1.196	27.9	0.289	1.150	0.046	2.254	60.89
2	Initial	0.557	33.7	0.190	0.352	0.205	0.500	99.06
3	Initial	0.825	41.9	0.131	0.361	0.465	0.257	99.70
4	Initial	0.879	46.2	0.246	0.721	0.158	1.284	100.00
5	Initial	0.633	55.7	0.225	0.373	0.260	0.485	100.00
6	Initial	1.815	58.6	0.177	0.673	1.142	0.203	100.00
7	Initial	0.637	68.5	0.111	0.460	0.177	0.744	100.00
8	Refinement	0.651	49.3	0.217	0.217	0.434	0.000	100.00
9	Refinement	0.555	70.0	0.225	0.185	0.370	0.000	100.00

3.8.6.2 BOAEI – 100 mg Pt/C

Table 21. Optimisation data for the osimertinib nitrodiamine reduction with the BOAEI algorithm and 100 mg 5% Pt/C catalyst.

Exp. No.	Exp. Type	Variables			Flow rate / mL min ⁻¹			Objective
		Liq. Flow Rate / mL min ⁻¹	Temp. / °C	Conc. / M	Osi. Nitro - Pump 1	MeOH - Pump 2	MeOH - Pump 3	Yield / %
1	Initial	0.566	37.5	0.260	0.483	0.083	0.883	68.04
2	Initial	1.159	40.9	0.280	1.094	0.065	2.123	41.16
3	Initial	0.524	46.8	0.170	0.297	0.227	0.367	99.07
4	Initial	1.617	53.1	0.200	1.059	0.558	1.560	64.95
5	Initial	0.682	56.0	0.100	0.235	0.446	0.024	99.56
6	Initial	1.060	62.5	0.150	0.520	0.540	0.499	99.47
7	Initial	0.840	65.9	0.220	0.605	0.235	0.974	98.87
8	Refinement	0.500	60.7	0.130	0.225	0.275	0.174	100.00
9	Refinement	0.502	45.9	0.110	0.178	0.324	0.034	99.54
10	Refinement	0.503	35.0	0.130	0.218	0.285	0.152	96.04
11	Refinement	0.904	35.0	0.100	0.301	0.603	0.000	80.89
12	Refinement	0.703	35.0	0.150	0.350	0.354	0.346	74.34
13	Refinement	0.500	35.0	0.100	0.167	0.333	0.001	98.55
14	Refinement	0.500	35.0	0.110	0.191	0.309	0.074	98.18
15	Refinement	0.595	45.6	0.100	0.199	0.397	0.000	99.85
16	Refinement	0.500	35.0	0.130	0.214	0.286	0.142	98.03
17	Refinement	0.669	70.0	0.100	0.223	0.446	0.000	99.74
18	Refinement	1.445	70.0	0.100	0.482	0.963	0.000	99.79
19	Refinement	0.500	70.0	0.210	0.351	0.149	0.552	99.68

20	Refinement	0.500	70.0	0.230	0.389	0.111	0.666	100.00
21	Refinement	0.500	70.0	0.270	0.458	0.042	0.875	100.00
22	Refinement	0.500	69.9	0.240	0.403	0.097	0.709	100.00
23	Refinement	0.500	70.0	0.250	0.409	0.091	0.726	100.00
24	Refinement	0.500	70.0	0.240	0.400	0.100	0.700	100.00
25	Refinement	0.500	70.0	0.240	0.401	0.099	0.702	100.00
26	Refinement	0.500	70.0	0.240	0.401	0.099	0.704	100.00
27	Refinement	0.500	70.0	0.240	0.400	0.100	0.700	100.00
28	Refinement	0.500	70.0	0.240	0.400	0.100	0.700	100.00

3.8.6.3 BOAEI – 10 mg Pt/C

Table 22. Optimisation data for the osimertinib nitrodiamine reduction with the BOAEI algorithm and 10 mg 5% Pt/C catalyst.

Exp. No.	Exp. Type	Variables			Flow rate / mL min ⁻¹			Objective
		Liq. Flow Rate / mL min ⁻¹	Temp. / °C	Conc. / M	Osi. Nitro - Pump 1	MeOH - Pump 2	MeOH - Pump 3	Yield / %
1	Initial	0.566	43.2	0.256	0.483	0.083	0.883	10.6
2	Initial	1.159	47.6	0.283	1.094	0.065	2.123	6.0
3	Initial	0.524	55.1	0.170	0.297	0.227	0.367	27.9
4	Initial	1.617	63.3	0.197	1.059	0.558	1.560	12.4
5	Initial	0.682	67.0	0.104	0.235	0.446	0.024	46.5
6	Initial	1.060	75.3	0.147	0.520	0.540	0.499	32.4
7	Initial	0.840	79.7	0.216	0.605	0.235	0.974	32.8
8	Refinement	0.649	84.0	0.100	0.216	0.432	0.000	71.1
9	Refinement	0.500	85.0	0.100	0.167	0.333	0.000	78.2
10	Refinement	0.778	85.0	0.100	0.259	0.519	0.000	60.3
11	Refinement	0.554	85.0	0.100	0.185	0.369	0.000	72.7
12	Refinement	0.500	85.0	0.100	0.167	0.333	0.000	75.2
13	Refinement	0.514	85.0	0.100	0.171	0.343	0.000	73.3
14	Refinement	0.876	85.0	0.100	0.292	0.584	0.000	52.8
15	Refinement	0.500	85.0	0.100	0.167	0.333	0.000	71.4
16	Refinement	0.579	85.0	0.100	0.193	0.386	0.000	63.4
17	Refinement	0.500	85.0	0.100	0.167	0.333	0.000	68.3
18	Refinement	0.516	85.0	0.100	0.172	0.344	0.000	65.8
19	Refinement	0.521	85.0	0.100	0.174	0.348	0.000	65.1

20	Refinement	0.550	85.0	0.120	0.220	0.330	0.000	61.9
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3.8.7 All process metric data

Table 23. All process metric data for optimisation one (500 mg), optimisation two (100 mg) and optimisation three (10 mg).

Exp. No.	Optimisation No.	STY / g L ⁻¹ hr ⁻¹	RME / %	TON	Yield / %
1	1	208	55.1	98	60.9
2	1	104	83.1	49	99.1
3	1	107	83.9	51	99.7
4	1	214	88.6	101	100.0
5	1	111	84.4	52	100.0
6	1	200	88.3	94	100.0
7	1	137	86.0	65	100.0
8	1	64	78.8	30	100.0
9	1	55	76.7	26	100.0
1	2	96	57.5	226	66.6
2	2	131	36.5	310	40.4
3	2	87	80.7	205	98.0
4	2	190	54.4	449	60.3
5	2	70	79.8	165	100.0
6	2	151	84.7	356	97.5
7	2	180	87.7	425	100.0
8	2	67	79.2	158	100.0
9	2	53	75.8	124	99.5
10	2	62	75.7	147	96.0
11	2	72	66.7	171	80.9

12	2	77	62.3	183	74.3
13	2	49	74.1	116	98.6
14	2	56	75.8	132	98.2
15	2	59	77.5	139	99.9
16	2	62	77.1	147	98.0
17	2	66	78.9	156	99.7
18	2	143	86.2	338	99.8
19	2	104	83.6	245	99.7
20	2	115	84.7	273	100.0
21	2	136	86.0	322	100.0
22	2	120	85.0	283	100.0
23	2	121	85.1	287	100.0
24	2	119	85.0	281	100.0
25	2	119	85.0	281	100.0
26	2	119	85.0	282	100.0
27	2	119	85.0	281	100.0
28	2	119	85.0	281	100.0
1	3	15	9.4	361	10.6
2	3	19	5.5	461	6.0
3	3	25	23.7	583	27.9
4	3	39	11.3	926	12.4
5	3	33	38.6	768	46.5
6	3	50	28.7	1182	32.4
7	3	59	29.3	1393	32.8
8	3	46	58.4	1079	71.1

9	3	39	62.0	916	78.2
10	3	46	50.6	1099	60.3
11	3	40	58.4	942	72.7
12	3	37	59.5	880	75.2
13	3	37	58.3	882	73.3
14	3	46	44.8	1082	52.8
15	3	35	56.5	836	71.4
16	3	36	51.3	860	63.4
17	3	34	54.1	799	68.3
18	3	34	52.3	794	65.8
19	3	34	51.9	794	65.1
20	3	40	50.9	957	61.9

3.8.8 BOAEI optimisation repeats

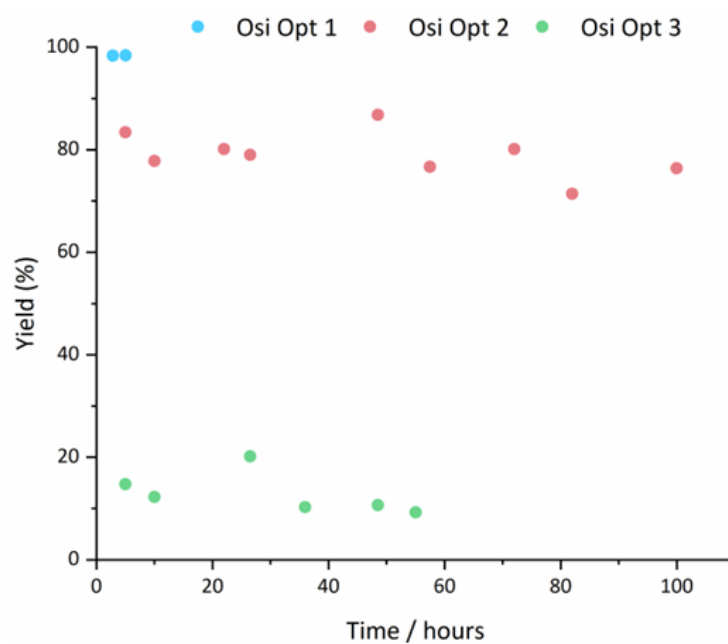


Figure 70. Repeat reaction data sampled offline during the self-optimisation of the reduction of osimertinib nitrodiamine at three different catalyst loadings. Repeat conditions: Opt. 1 - 500 mg, 1 mL min⁻¹, 40 °C, and 0.225 M. Opt. 2 - 100 mg, 1 mL min⁻¹, 45 °C, and 0.15 M. Opt. 3 - 10 mg, 1 mL min⁻¹, 50 °C, and 0.15 M.

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Chapter 4 : A Multistep Multiphase Telescoped Self-optimisation for the Synthesis of Paracetamol

4.1 Introduction

Sustainable chemical manufacturing is an important principle every industry must strive towards to limit their environmental impact. Environmental protocols set by governments are a way to ensure that companies are held liable for their processes chemical waste, such as the EU Integrated Pollution Prevention and Control (IPPC)¹ and Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), which is an EU law that aims to control and decrease the use of hazardous/dangerous chemicals that are common in the chemical industry.²

Continuous flow chemistry offers significant sustainability benefits over traditional batch reactors and satisfies many of the 12 principles of green chemistry, with less hazardous chemical synthesis, catalysts, and the use of renewable feedstocks highlighted in this chapter (Figure 71).^{3,4} Better process control, improved heat and mass transfer, and smaller plant footprints are among a few of the many benefits of

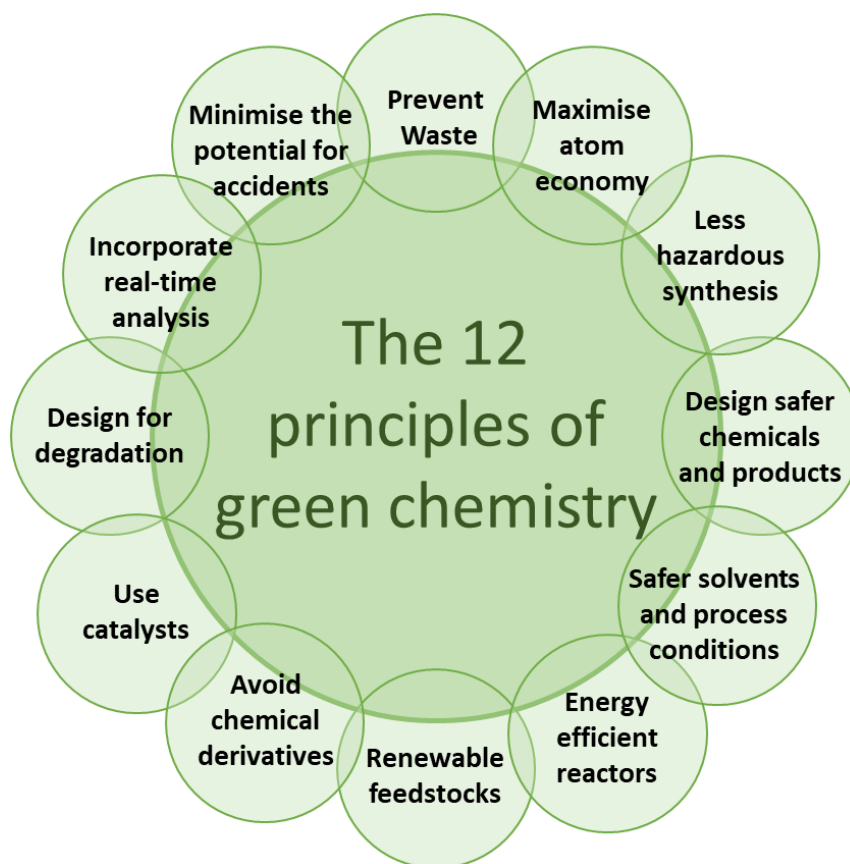


Figure 71. The 12 principles of green chemistry.

continuous flow that can improve the sustainability of a process. Any reduction in the number of reaction steps will improve the greenness of a process, as it leads to less raw material use, operating costs, and solvent waste. Traditionally, APIs are synthesised via single step batch reactions where one compound is synthesised and subsequently purified before being used in the next step of the reaction. Often these separate reaction steps can be located at different manufacturing sites, which may even include transporting chemicals across borders.⁵⁻⁷ The telescoping of reaction steps can lead fewer work up steps being required as often a single purification can be performed at the end of the entire telescoped process. Telescoping in continuous flow systems involves connecting the outlet of each reactor to subsequent reactors, to perform the next reaction steps, minimising the need for human intervention (and human error) and the possible handling of hazardous chemicals.⁸⁻¹¹ Telescoped flow systems have seen increasing interest in the literature over the last few decades, as advancements in in-line purification technologies,¹² PAT,¹³ and flow equipment has enabled the easy integration of this methodology for chemical manufacturing, with APIs of a particular interest for this chapter.^{14,15}

Sagandira *et al.* in 2021 reported a telescoped five-step transformation to synthesise stavudine in continuous flow, which is used as a chemotherapeutic agent for human immunodeficiency virus (HIV), acquired immunodeficiency syndrome (AIDS), and AIDS related conditions.¹⁶ Stavudine is listed as an essential medicine in South Africa for tackling the HIV and AIDs crisis, despite the World Health Organization's (WHO) recommendation to phase out the drug in 2009 due to its side effects. It remains an essential medicine due to its affordability in many poorer countries and is still produced by generic pharmaceutical companies, allowing the drug to be widely accessible. The individual five reactions steps were optimised using a OVAT approach before being combined in a fully telescoped process, achieving an 87% yield with a residence time of 19.9 minutes, which is a significant improvement on the previously reported batch procedures that take 13.5 – 28 hours. This demonstrates the use of continuous flow chemistry and telescoped synthesis to produce an important API with only one purification step required at the end of the reaction for the final product stavudine. The reduction in reaction time will have a substantial impact on the overall productivity of

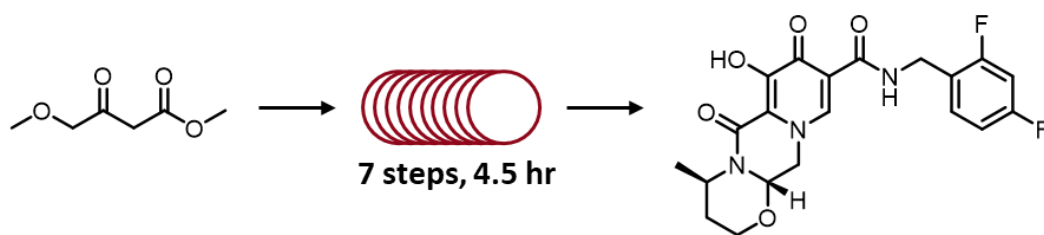


Figure 72. Telescoped flow synthesis to produce Dolutegravir reported by Ziegler *et al.*¹⁷

the process, making more product on shorter timescales, delivering important medicines to patients faster.

Ziegler *et al.* showed a seven-step synthesis in continuous flow to produce Dolutegravir, an HIV integrase inhibitor that was approved by the Food and Drug Administration (FDA) for use in 2013 and, since 2018, has been on the WHO list of essential medicines, Figure 72.¹⁷ The group demonstrated three separate flow operations could be used to complete the seven step total synthesis increasing the yield from the previously reported 6% to 24%. Continuous flow benefitted the synthesis by enabling rapid manufacturing time, a reduction in step count and a high reactivity and selectivity for the telescoped process. Only three isolation and purification steps were required, decreased from seven, saving solvent waste and reducing the number of work up steps. These advantages would lead to wider drug accessibility by reducing operating and manufacturing costs.

An eight-step continuous flow telescoped synthesis for (*S*)-rolipram, an anti-inflammatory drug and selective phosphodiesterase inhibitor, was reported by Tsubogo *et al.* from commercially available starting materials.¹⁸ A total of four packed bed columns were used for the eight step transformation, with different heterogeneous catalysts optimised and used in each reaction step. The group highlighted the importance of employing immobilised heterogeneous catalysts in API manufacturing, showing their ease of integration in continuous flow systems and the capability to produce uncontaminated products (when compared with homogeneous systems that require separations steps to remove catalysts from the final products). The full eight step synthesis involved no separations or isolations of intermediates, and the final optically pure product ((*S*)-rolipram) could be recrystallised in one step at the end of the reaction offline to give a throughput of close to 1 g day⁻¹. This throughput is relatively low compared to the requirements of APIs, which are in the region of hundreds of

kilograms, however, the group show a useful telescoped route for the end-to-end synthesis of (S)-rolipram with the outlook towards scale up.

These examples demonstrate the improvements and applications of telescoped continuous flow systems to produce important APIs. However, in all examples, each reaction step is first optimised using an OVAT approach before being combined in a telescoped process, which is time consuming and can lead to an unnecessary waste of resources in extra reactions being performed.

4.1.1 Telescoped self-optimisations

The use of automation and optimisation algorithms can be beneficial for the fast self-optimisation of telescoped processes. Closed-loop computer-controlled systems can be used in conjunction with PAT to explore experimental design space and optimise for a single or multiple desired objectives.^{19,20} The application of these algorithms to single step optimisations for single or multiple objectives has seen increasing attention in the past decade for a wide variety of chemistries.²¹⁻²⁷ However, their application to multistep processes is less reported, and many multistep processes are optimised for each step individually before being incorporated in to a telescoped system. Optimising multiple steps simultaneously may lead to fewer experiments being required, reducing solvent use and operational costs, or new optima being discovered if impurities from each step interact downstream with other reagents.²⁸

Sagmeister *et al.* reported the optimisation of a two-step seven variable system with 85 experiments for the synthesis for edaravone, an important API in the treatments of amyloid lateral sclerosis and stroke recovery.²⁹ The group made use of multiple spectroscopic PAT techniques (NMR and FTIR) in a bespoke modular platform, to perform real-time rapid spectroscopic measurements which were processed by chemometric models. The Thompson sampling efficient multi-objective (TSEMO) algorithm was employed to maximise the yield of step one, maximise the STY of step two, and to minimise the equivalents of triethylamine in step two. In 26 hours, optimum conditions were found yielding >95% of the imine product in step one, and an impressive space time yield of 5.42 kg L⁻¹ hr⁻¹.

Although real-time analytics such as FTIR and NMR provide rapid online data analysis of reactions, which can be useful for the fast identifications of optimum reaction conditions, they also require additional chemometric modelling. Using multiple PAT techniques in these telescoped systems can also become increasingly expensive, making the accessibility and application of this technology unachievable. Clayton *et al.* reported the optimisation of a two-step telescoped process with a Bayesian based optimisation algorithm, where a single HPLC setup was used for the accurate quantification of all reaction components in the multistep process.³⁰ A bespoke multipoint sampling system was developed to sample both reaction steps, limiting the number of PAT needed to gain full understanding of the effects of reaction variables on both steps. This example demonstrated that sampling each reaction step was critical, as it provided a better understanding of the reaction mechanism with the identification of a key vinyl reaction intermediate which would have been missed if the reaction was only analysed at the end of the entire telescoped process.

The development of new automated reactor platforms that can perform telescoped reactions is crucial to their integration in the wider pharmaceutical industrial application. Bedard *et al.* developed a modular reactor platform capable of performing automated closed-loop optimisations on a range of chemical reactions due to its plug and play reconfigurable modules (Figure 73).³¹ The group demonstrated the use of a SNOBFIT optimisation algorithm to perform the self-optimisation of single and multistep reactions including a Parr-Knorr pyrrole synthesis, a Buchwald-Hartwig cross coupling, a reductive amination, a Suzuki-Miyaura cross coupling and a photoredox reaction among others. The modular nature of the system allowed the reactors to be easily interchanged, to tolerate different chemistry and reaction requirements. This is useful for process chemists, who are often investigating a range of reactions and require a

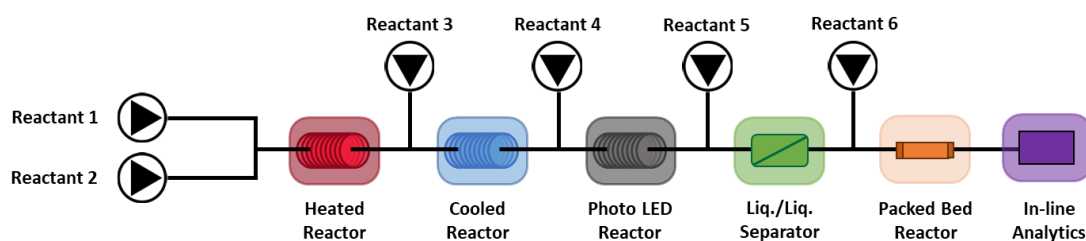
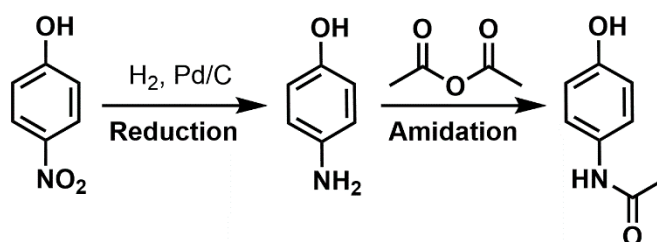


Figure 73. Reconfigurable reactor platform with interchangeable reactor bays developed by Bedard *et al.*³¹

general standardised equipment to explore each chemistry. The platform also integrates the options for purification through phase separation and the integration of different online analytics to fit the chosen chemistry including HPLC, FTIR, Raman spectroscopy and MS. The group demonstrated the use of the PBR module in a one-step heterogeneously catalysed Suzuki-Miyaura cross coupling self-optimisation. However, the combination of multiple steps with multiphase chemistry was not reported in this system.

The integration of solid catalysts to continuous flow is highly advantageous due to the ease of separations of the catalysts and a decrease in the processing time used to filter off spent catalysts. However, multiphase chemistry can be difficult to incorporate into self-optimising continuous flow telescoped systems due to the need to separate phases for accurate sampling and quantitative analysis. Catalyst deactivation is also a major concern in multistep optimisations as it takes longer for multiple steps to reach steady state, increasing the experimental time required for the optimisation of these processes. Nambiar *et al.* performed a multi-objective three-step optimisation of a telescoped process for discrete and continuous variables.³² This included an S_NAr , a heterogeneous multiphase nitro reduction and an amide coupling reaction. The group noted that due to issues with catalyst deactivation, the catalyst bed temperature had to be fixed at 125 °C to maintain catalyst stability during the optimisation, and the S_NAr reaction was optimised in a separate campaign. Only the equivalents of the nitro: acid starting materials was used as a variable to optimise the nitro reduction due to the difficulties with deactivation. This severely limits the experimental space the optimisation algorithm can explore for this reaction step, potentially leading to missed reaction optima.

This work aims to build upon these previous examples of self-optimising processes for telescoped reactions, to optimise a multiphase, multistep reaction for the



Scheme 10. The two-step synthesis of paracetamol.

synthesis of paracetamol (Scheme 10). Acetaminophen is a nonsteroidal anti-inflammatory painkiller, present on the WHO list of essential medicines.³³ Continuous flow offers benefits for on-demand fast synthesis of the drug and can provide a low-cost small footprint manufacturing method to provide drug accessibility for this API across the globe.

4.2 Aims

This chapter will explore a two-step process consisting of a multiphase heterogeneous hydrogenation, followed by an amidation reaction. The steps will be initially optimised individually, before being transferred and optimised as a fully telescoped process to maximise the product yield via remote automated control. The work will highlight the benefits of performing multistep optimisations for the development of pharmaceutical syntheses and calculate important green process metrics to compare single step and telescoped reactions.

4.3 Results

A two-step reaction for the production of paracetamol from 4-nitrophenol was investigated. When considering telescoping the process, an appropriate solvent had to be chosen for the two steps. Typically solvents such as alcohols are used for hydrogenations of nitro containing molecules,³⁴ however, the second step involves introducing acetic anhydride to the reaction, which would react with any alcohol present to form the corresponding ester and carboxylic acid. It can be beneficial to maintain the same solvent throughout a telescoped process, as it means no extra steps are required for solvent exchange, which is both energy and waste intensive. Therefore, the GSK solvent selection guide was utilised in order to find an appropriate green solvent for the telescoped system.³⁵ Derived from biomass, 2-methyltetrahydrofuran (2-MeTHF) has been shown to be a successful green solvent, often used as an alternative to dichloromethane and tetrahydrofuran.³⁶ It was selected as solvent for the two-step process as it would not interfere and react with any of the reactants, intermediates, or products.

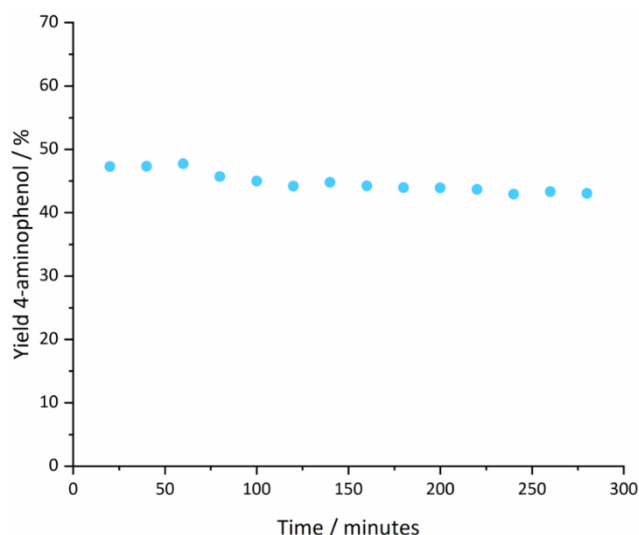


Figure 74. Concentration profile showing the stability of the catalyst in the reduction of 4-nitrophenol. Fixed conditions: catalyst – 0.9 g, pressure – 40 bar, H₂ flow rate – 50 mL min⁻¹, liquid flow rate – 0.5 mL min⁻¹, and temperature – 50 °C.

A catalyst stability test for the 1 wt.% Pd/C JM pelletised catalysts was initially performed for the heterogeneous hydrogenation step, to ensure that an optimisation could be performed with no/minimal catalyst deactivation. The results, in Figure 74, show an initial decrease in the yield of the reaction followed by a steady yield seen for the product over the six hour experiment. This same initial decrease in activity has previously been seen with all other reactions reported in previous chapters as the adsorption/desorption equilibrium of hydrogen to the catalyst surface is reached after one hour. This showed the catalyst to be stable under these process conditions and could be taken forward for use in a self-optimisation.

4.3.1 Single step optimisations

Each reaction step would initially be optimised one step at a time (OSAT) to be compared to the fully telescoped self-optimised approach. Details of each closed-loop automated reactor setup are shown in experimental sections 4.5.2 and 4.5.3. With initial stability testing performed, a single objective optimisation could be carried out on the first step, to maximise the yield with the following reaction bounds:

- [4-nitrophenol] – 0.01 – 0.05 M.
- Temperature – 40 – 85 °C
- Liquid flow rate – 0.5 – 2 mL min⁻¹ (SNOBFIT) and 0.5 – 1.5 mL min⁻¹ (BOAEI).

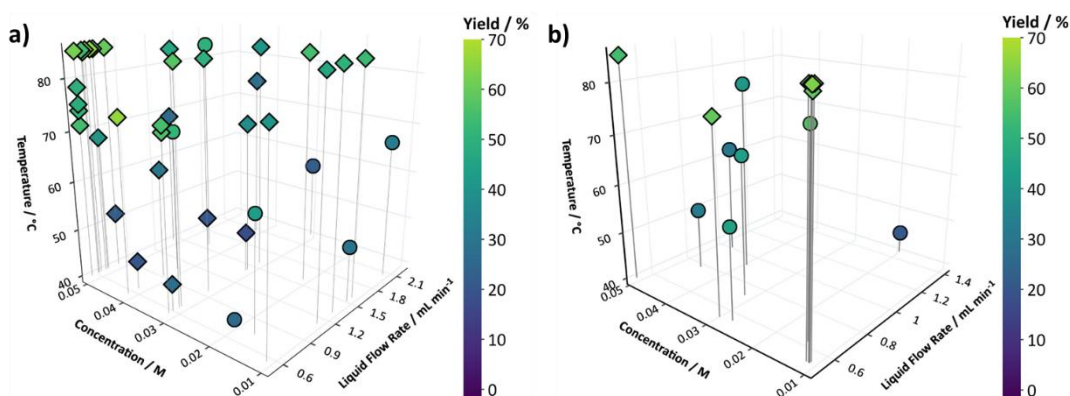


Figure 75. Optimisation data for step one, the reduction of 4-nitrophenol. a) SNOBFIT optimisation, and b) BOAEI optimisation, where $\circ$ – LHC experiments and $\diamond$ - refinement experiments. Fixed conditions: catalyst – 0.9 g, H_2 flow rate – 50 mL min^{-1} , and pressure – 40 bar.

Both SNOBFIT and BOAEI algorithms were tested for this reaction, with both initialised with a LHC space filling design. The results of both optimisations are shown in Figure 75. The SNOBFIT algorithm was used to optimise the reaction as it could explore the design space more, as every fourth experiment is set to explore (details in chapter 2). This would likely make the algorithm less efficient in finding the global optimum of the system but would perform more experiments covering the entire design space for better reaction understanding. The results show that the SNOBFIT algorithm explored the design space extensively with the 40 experiments performed, and optimal conditions were found at high concentrations of 4-nitrophenol, high temperatures and low liquid flow rates after ten experiments. However, with the BOAEI algorithm, optimum conditions were found after nine experiments, at high temperatures, low liquid flow rates, and low concentrations of 4-nitrophenol. The design space was explored much less in this optimisation, and any experiments performed after experiment nine were in the same area of the design space, as the algorithm believed this to be the optimum conditions. This shows that the LHC design was efficient in exploring the design space and influencing the BOAEI algorithm effectively. The differences in optimum concentrations found in both optimisations (0.05 M with SNOBFIT, and 0.01 M with BOAEI) was likely due to the small effect concentration has on this reaction step. In both optimisations, similar yields of reactions could be found at both high and low concentrations. If throughput was considered in the optimisation objectives, then a high concentration would be preferred to produce more product at the same flow rate. The deactivation of the catalyst was monitored to ensure there was no significant change in catalyst activity, as to not affect the optimisation of the

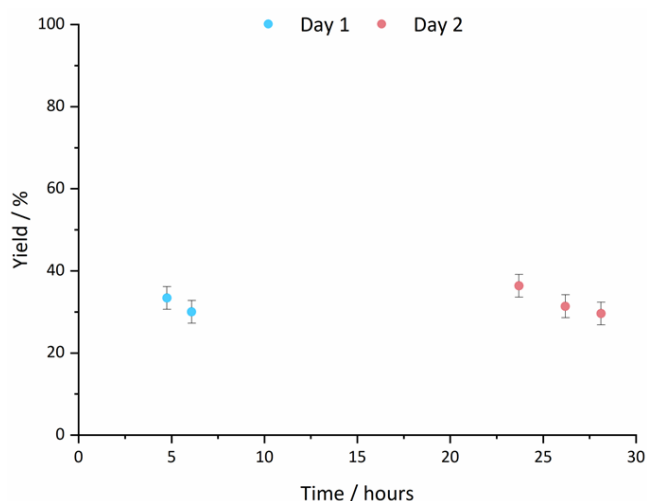


Figure 76. Deactivation data for two day step one BOAEI optimisation. Repeat conditions: concentration – 0.045 M, liquid flow rate – 1 mL min⁻¹, and temperature – 62.9 °C.

hydrogenation. This was done as previously described, by performing repeat reactions offline. The deactivation profile for the BOAEI optimisation in Figure 76 shows no significant deactivation of the catalysts during the optimisation over two days (<5%), showing the catalyst activity caused no issues to the results of the optimisation, and exhibited a good stability during this operating period.

A single step optimisation was also performed for the step two amidation of 4-aminophenol by Dr Holly Clarke. Initial variable bounds were set to:

- Residence time – 0.4 – 5.0 minutes.
- Equivalents – 1 – 5.
- Temperature – 25 – 200 °C.

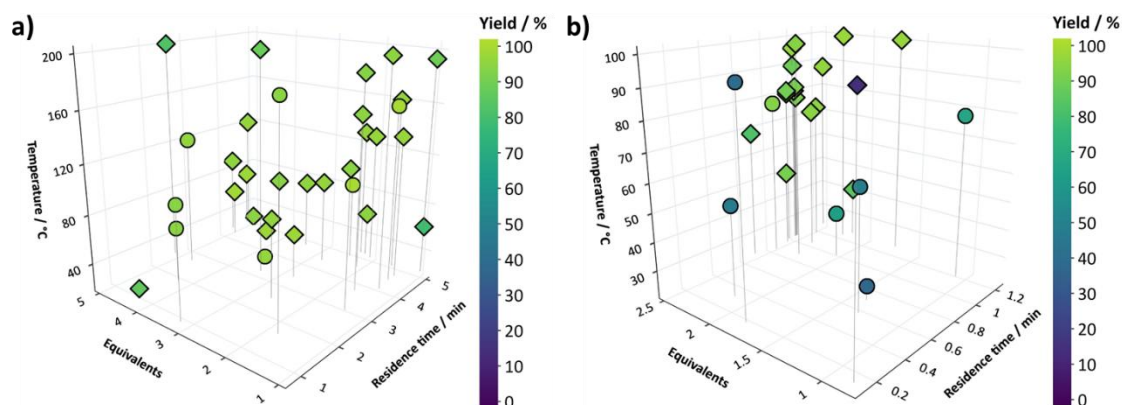


Figure 77. Optimisation data for step two, the amidation of 4-aminophenol. a) wide bounds, and b) narrow bounds, where ○ – LHC experiments and ◇ - refinement experiments.

32 experiments were performed in a BOAEI algorithm self-optimisation, and the results are shown in Figure 77a. This optimisation showed that when exploring the design space within these variable bounds, 28 experiments were over 90% yielding, with two optimal conditions (99.6%) found at long residence times, median equivalents, and high temperatures. However, a range of different conditions within the variable bounds could be used to yield >95% of the acetaminophen product. As most of the design space was high yielding, and in the interests of improving the sustainability of the process, narrower variable bounds were investigated for all three variables. A decrease in the equivalents of the acetic anhydride bounds would aim to reduce the waste of excess reagents. A decrease in the residence times investigated would lead to an increase in productivity, as a shorter residence time would increase the yield of product made over the same period of time. It would also lead to a decrease in the steady state wait time for each experiment, meaning the reaction can be optimised on a shorter timescale. A decrease in the temperature bounds would lead to a reduction in the energy requirements for the reactor, saving costs and electricity usage, which is particularly important when a process is scaled up. The new variable bounds were set to:

- Residence time – 0.10 – 1.25 minutes.
- Equivalents – 0.8 – 2.5.
- Temperature – 25 – 100 °C.

To maintain appropriate liquid flow rates for the HPLC piston pumps (with a 10 mL pump head), the reactor volume was decreased from 3 mL to 0.5 mL and a single objective BOAEI self-optimisation for yield was performed (results shown in Figure 77b). 10 out of the 25 experiments achieved >85% yields of the acetaminophen product, at high equivalents of acetic anhydride, high temperatures and a range of residence times. The variable that had the greatest overall effect on the yield of the reaction was the equivalents of acetic anhydride, with most of the high yielding experiments requiring an acetic anhydride equivalents of >2. This aligns with what has been reported in the literature as often neat acetic anhydride is used in the synthesis of paracetamol.³⁷ Although many high yielding points were found, the most optimal experiment would be a combination of high yield with a short residence time to improve the throughput of the reaction, which is found at experiment 11 with a residence time of 1.19 minutes, an equivalents of 2.2, and a temperature of 100 °C.

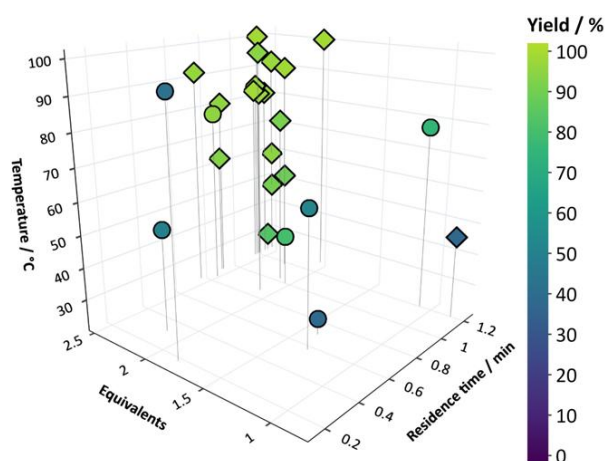


Figure 78. Optimisation data for step two, the amidation of 4-aminophenol with an IM reservoir, where ○ - LHC experiments and ◇ - refinement experiments.

A second optimisation of step two was performed to determine whether unreacted starting material from an incomplete reaction of step one would have any impact on the optimisation of step two. The optimum conditions found in the BOAEI optimisation of step one was used to create a reservoir of 4-aminophenol (65% yield) and unreacted 4-nitrophenol (35%). This reservoir was then used as the initial starting material stock solution, a model intermediate mixture (IM), for the optimisation of step two. The optimisation was performed with the same variable bounds as the narrower bounds BOAEI optimisation discussed previously and the results are shown in Figure 78. This optimisation showed that no other side products were produced from unreacted 4-nitrophenol, and that the optimum conditions were similar to those found previously, indicating that the unreacted reagent had no effect on the ability for the optimum to be found by the BOAEI algorithm.

4.3.2 Telescoped single objective optimisation

To combine both reactor systems and produce a fully autonomous telescoped platform, adaptations to both reactors were required. To allow the relationship of the chosen optimisation variables for each step to be fully understood, it was important that the reaction was sampled after both reactors. Employing a multipoint sampling system that could sample both reactions into one HPLC would limit the amount of analytical equipment needed to perform the optimisation (shown in Figure 79). Clayton *et al.* previously published the use of two sampling valves, that were daisy chained in loop to

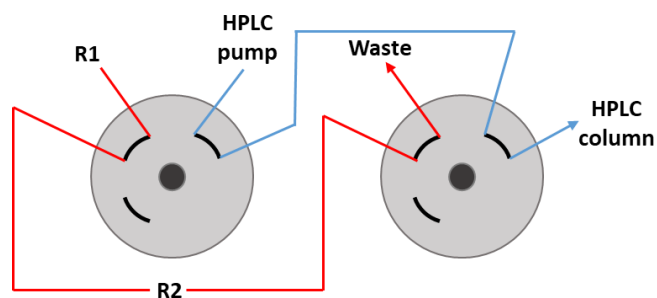


Figure 79. Multipoint sampling layout with two Vici valves.

one HPLC, to analyse a two-step process.³⁰ Once steady state had been reached in each reaction step, the first Vici sample valve would be triggered to sample the first reaction. After a predetermined time in the HPLC method, the second valve would be triggered to sample the second step, resulting in sequential analysis of both reaction steps on to a single chromatogram. This means that the optimisation algorithm would only have to identify the product peak on one chromatogram, simplifying the autonomous peak interpretation, and allowing the post-optimisation analysis of the yields of both steps at different reaction conditions.

It was also important that the gas could be removed from the liquid stream completely after the first reactor (R1). This is not only important for sampling of only the liquid stream into the HPLC but also to ensure that the residence times of reactor two (R2) were unaffected by the gas flow. In previous chapters a tube-in-tube reactor was utilised at ambient pressure on the outlet of the reactor to separate the gas and liquid phases. R2 required a pressure of 100 PSI in the reactor, facilitated by a 100 PSI IDEX cartridge based BPR on its outlet stream. The liquid outlet of the tube-in-tube would therefore need to be pressurised to 100 PSI. To allow accurate phase separation with the tube-in-tube, a 100 PSI cartridge based BPR was also integrated onto its gas outlet (shown in Figure 80). Combined with the needle valve, a slight pressure differential could be created across the tube-in-tube, allowing for complete separation of the gas and liquid phases at pressure.

The optimum yield of the individual optimisation of step one was found to be only 65% for the 4-aminophenol product with 0.9 g of catalyst used. To increase this yield, the catalyst loading in the PBR was increased to 1.5 g. The variables chosen for self-optimisation were:

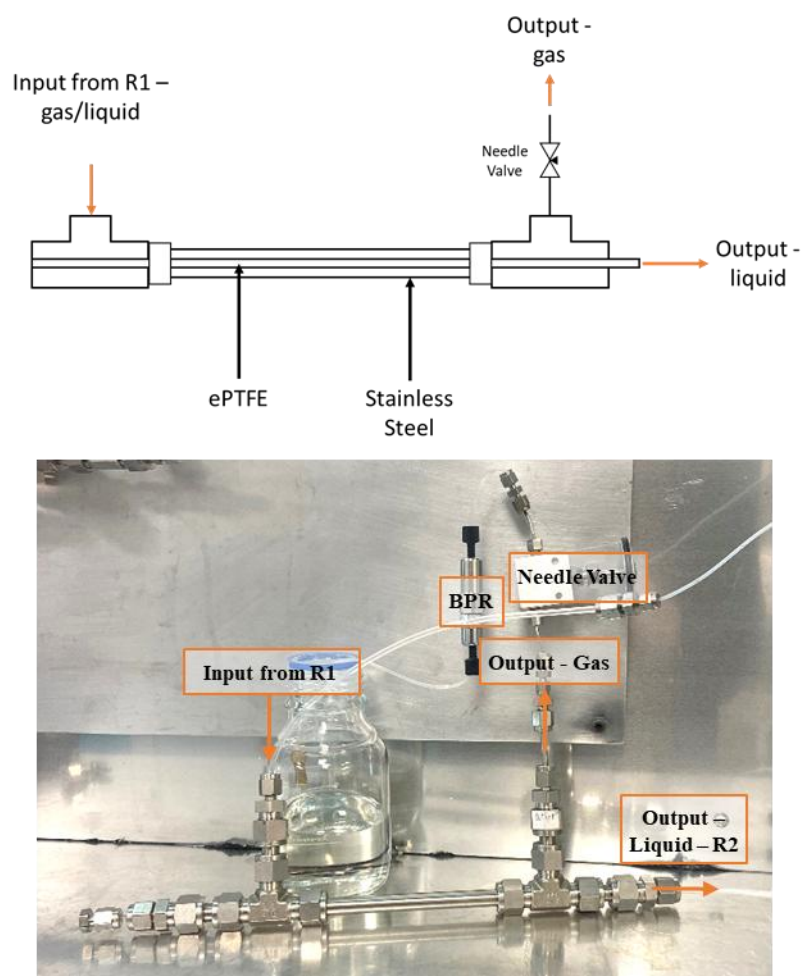


Figure 80. Adapted tube-in-tube separator for the telescoped reactor system.

- Temperature of R1 – 60 – 110 °C.
- Liquid flow rate of 4-nitrophenol – 0.5 – 2.0 mL min⁻¹.
- Temperature of R2 – 30 – 100 °C.
- Flow rate ratio – 0.20 – 0.55 (0.8 – 2.4 equivalents of acetic anhydride).

The flow rate ratio variable describes a ratio of the flow rates of the 4-nitrophenol pump in R1, to the acetic anhydride pump into R2. It was chosen as an optimisation variable instead of acetic anhydride equivalents as the yield of step one would be unknown until after the reaction was sampled. An individual sample of R1, after steady state was established, before sampling step two, would require a more complex HPLC method and significant modification to the optimisation code. To investigate the same bounds of equivalents of acetic anhydride in R2 and the liquid flow rate in R1 in the telescoped optimisation as the single step optimisations, the size of R2 was increased from 0.5 mL to 1.5 mL. This would allow accurate flow rates to be

achieved at the desired reaction conditions within the operational parameters of the piston pumps.

Concentration of the 4-nitrophenol starting material was not investigated in the telescoped optimisation as it was found to be the least important variable in the single step optimisation. This was shown by the variable having the largest kernel length scale (see appendix section 4.6.1), which indicates that it is the variable that had the least impact on the yield of the reaction. Therefore, to increase the throughput of the reaction a 4-nitrophenol concentration of 0.05 M for the reservoir was chosen. It is difficult to decouple the residence time of telescoped reactor steps as the liquid feed from the R1 is directly fed into R2 and diluted with more reagent feeds. If many steps are telescoped together, this will cause the flow rate in the subsequent reactors to be faster with each addition of more reagents. The flow from R1 could be split to try and address this, however this leads to the waste of material as some of the reaction stream would be lost and sent directly to waste. Therefore, it was decided that the residence time of R2 would not be investigated in the telescoped optimisation, and it would be entirely controlled by the other reaction variables.

With both systems combined into one reactor set up (further described in section 4.5.4), a four variable, two-step telescoped optimisation to synthesise paracetamol was performed with the BOAEI algorithm, and the results are shown in Figure 81 and summarised in section 4.6.7. An optimum yield of 85% for the final paracetamol product was achieved after a total of 12 experiments (nine initial conditions from the LHC and three refinement experiments). The LHC was successful in exploring the design space efficiently as only three experiments were required during exploitation via the BOAEI algorithm to find the optimum conditions for the reaction. Nine LHC experiments were required for the telescoped optimisation as the number of variables optimised was increased from three to four (the number of initial conditions is equal to $2n+1$, where n is the number of variables). The optimum conditions found were at high temperatures of R1, high acetic anhydride equivalents (high flow rate ratio) and low liquid flow rate of 4-nitrophenol, relating to a long residence time. Once the algorithm had found the optimum conditions at experiment nine, the temperature of R1, flow rate ratio, and the flow rate of 4-nitrophenol were kept constant by the algorithm, and only the temperature of R2 was investigated. In all single step

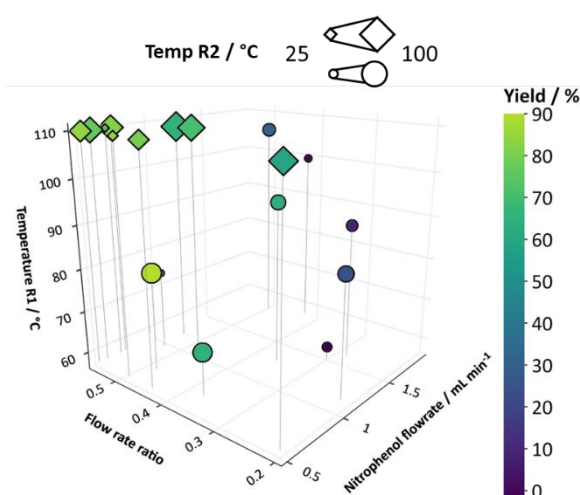


Figure 81. Optimisation data for the telescoped synthesis of paracetamol, where ○ – LHC experiments and ◇ - refinement experiments.

optimisations of step two, a high temperature was favoured (161 °C in wide bounds OSAT optimisation, and 100 °C in the narrow bounds OSAT and IM optimisations). However, in the telescoped optimisation a much lower temperature of 67 °C was found to be optimal. In all optimisations for step two, the temperature of R2 was found to be the least important variable in maximising yield, shown in the large kernel length scale value (4.6.1). This accounts for the difference in findings in the step two optimisations, showing a range of temperatures could be used to achieve high yields for the final product paracetamol. If only the OSAT optimisation were performed, this could have been missed, and higher temperatures would have been used in the two-step process, leading to unnecessary running costs in the system. Lower temperatures are favoured to decrease operating costs and energy requirements of the system, which has significant environmental and economic benefits.

The activity of the Pd/C catalyst used in R1 was monitored with repeat reactions which were taken every fourth experiment and analysed offline. The activity of the catalyst remained stable for the first two days, with minimal deactivation seen (<5%) in the repeat reaction data (shown in Figure 83). However, after 55 hours there was a sharp drop off in activity of the catalyst which was likely due to poisoning or fouling of the catalyst active sites by reactant molecules, leading to an irreversible loss in the activity of the catalyst. Therefore, the telescoped optimisation was stopped after 18 experiments, to ensure that this did not affect the results of the optimisation.

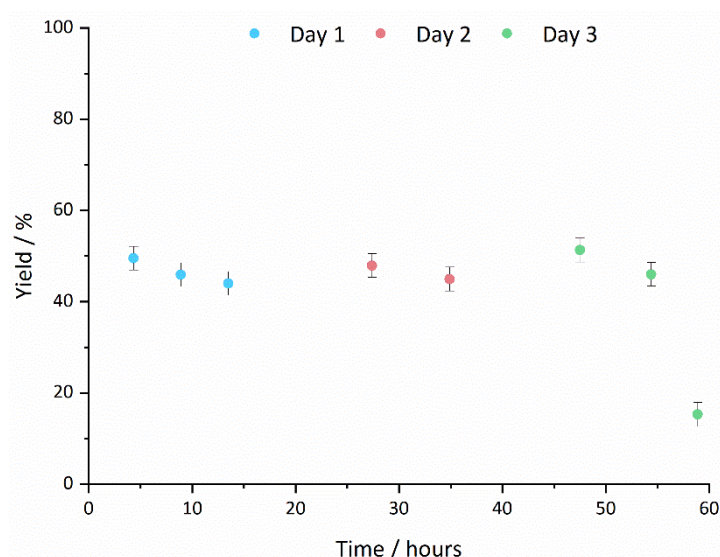


Figure 83. Deactivation data for telescoped three day optimisation. Repeat conditions: liquid flow rate – 1.09 mL min⁻¹ and temperature – 85 °C.

Figure 82 shows a comparison of the three BOAEI optimisations, the OSAT step one, the OSAT step two with narrow bounds, and the final telescoped optimisation. It can be seen in a plot of the yield achieved chronologically during each optimisation, that the BOAEI algorithm is highly efficient at finding the optimal conditions for each optimisation, with only two, three, or four refinement experiments required in each optimisation to reach the maximum yield. When comparing the total number of experiments required in each optimisation protocol (OSAT vs. telescoped), the bar chart shows that the individual OSAT optimisation approach collectively required many more experiments to be performed (20) to find the optimal conditions of each reaction. 12

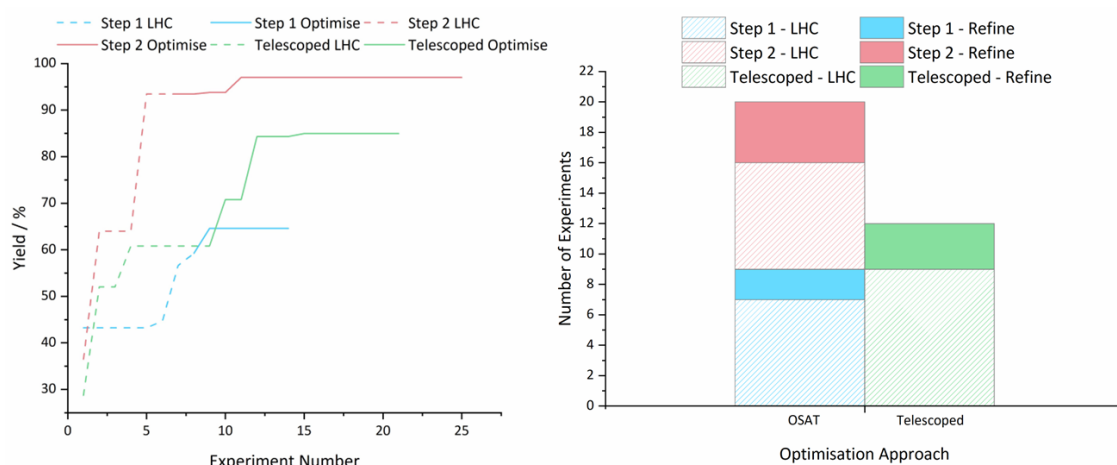


Figure 82. Comparison of the maximum yield achieved during each optimisation chronologically (left). Comparison of the number of experiments required in each optimisation to find the optimum conditions.

Table 24. Comparison of PMI values and the number of experiments performed to reach the optimum reaction conditions for the single step and telescoped optimisations.

Reaction Step	Total Mass / g hr ⁻¹	Mass of Product / g hr ⁻¹	PMI with 20% solvent mass	% of total mass from solvent	No. of expt. to reach optimum
OSAT – Step 1	26.9	0.021	299	96	9
OSAT – Step 2	21.6	0.072	61	99	11
OSAT – Combined	39.9	0.044	205	97	20
Telescoped	44.8	0.190	56	95	12

experiments were required in total to optimise both steps simultaneously in the telescoped process, which would lead to a significant reduction in the time and resources used to optimise the two-step reaction. This shows great promise for decreasing the waste produced when optimising processes, as optimum yields could be found in fewer experiments.

To objectively evaluate the optima determined by both the OSAT and telescoped approaches for the multistep reaction, process mass intensity values (PMI) were calculated at the optimum conditions found in each optimisation step, using equation 1.³⁸

$$PMI = \frac{\text{mass of all reactants} + \text{mass of catalysts} + \text{mass of solvents} / \text{kg}}{\text{mass of product/kg}} \quad (1)$$

PMI is used to evaluate the greenness of a process by taking the total amount of material used to produce a mass of product into account and was chosen by the Green Chemistry Institute Pharmaceutical Roundtable as their preferred mass based metric.²⁸ The pharmaceutical industry is also taking an active role in trying to reduce the PMI of their chemical processes, which is exemplified in the report by AstraZeneca of a 23% reduction in the PMI for their late stage project portfolio in 2022.³⁹ A PMI value of one is the most optimal as it implies that everything used in the process is converted into useful product. This is difficult to achieve for most processes, as a solvent is often used to dissolve solid reagents, and are not incorporated into the product, increasing the PMI value. Solvent-free syntheses are not often used, as solvents can act as a useful heat sink for exothermic reactions, improving the safety of these processes. This is not usually possible to justify in batch reactions due to safety issues, however, due to the excellent

heat transfer achievable in continuous flow platforms, this has been shown to be possible where neat reactions have been performed in flow with liquid reagents.⁴⁰

The yield of the two approaches could not be compared directly due to the changes in catalyst loading and reactor volume during the adaptation of the reactors to form the fully telescoped process. PMI was therefore an appropriate metric for comparison as it accounts for the extra mass and volume used. The PMI values calculated for the OSAT and telescoped processes were much higher than those reported in the literature. This was due to the low concentrations used in this work (0.05 M), to ensure a good solubility of the reactants in 2-MeTHF, as solids could not be tolerated in the continuous flow process (as they lead to pump and tubing blockages). Therefore, PMI values for 20% the mass of 2-MeTHF were calculated, as it is likely that some solvent could be recycled from process to process.^{28,41} When comparing the PMI values shown in Table 24 to a solution based example of the two-step synthesis for paracetamol, Geib *et al.* reported a value of 43, which is similar to the telescoped process presented here.⁴² However, this value does not account for the separation and work-up steps associated with the OSAT approach reported by Geib, which would likely lead to a much higher PMI value due to the extra purification step required. The PMI value was also calculated for the OSAT step one and step two processes at their respective optimal conditions if they were combined into a telescoped process. This shows the PMI values for the OSAT reactions can be significantly reduced when performing them in a telescoped process, mainly due to a reduction in solvent use in a telescoped system. In typical single step reactions, the product is purified, isolated, and crystallised at the end of every step to be used in subsequent steps. The next reaction step may take place in a separate facility, or even in another country which has associated transportation costs and lead to extensive waste of solvents. In a telescoped process, the product can be isolated and purified at the end of the entire telescoped synthesis, which limits the number of work up unit operations required. Table 24 shows the associated mass percentage of the solvent in each of the two-step approaches, showing over 95% of the total mass used in every reaction was related to the solvent. Therefore, any reduction in solvent use during these reactions is a significant improvement of the process and will decrease its environmental impact.

The PMI calculated for the telescoped process at the optimum conditions is lower than the combined OSAT optimised conditions. This is due to the increase in concentration of 4-nitrophenol from 0.01 M (optimum in OSAT BOAEI optimisation) to 0.05 M used in the reservoir for the telescoped BOAEI optimisation. This leads to an increase in the overall mass of paracetamol that could be produced in a specified time period, leading to a smaller PMI value. This again demonstrates the impact of concentration and solvent use on the sustainability of a process, particularly when a process is scaled up to a kg day⁻¹ production. When comparing these PMI values to those reported for API synthesis in the literature, a range of values were described of a similar magnitude to that of the 20% mass of solvent PMIs reported here.⁴³⁻⁴⁷ As PMI is an important metric in green chemistry, a multi-objective optimisation of PMI and STY would be useful for this telescoped system, to find more sustainable reaction conditions focussed on these values.

4.4 Conclusion

A comparison of single and multistep step optimisations was described in this chapter, showing the BOAEI optimisation algorithm to be efficient in exploring the experimental design space, and finding the optimum conditions in a minimum number of experiments in all applications presented. It was shown that a simultaneously self-optimised telescoped approach could reduce the number of experiments required to optimise the reaction conditions, with only 12 experiments needed to optimise the two-step synthesis of paracetamol, as opposed to the 20 experiments required in the combined OSAT optimisations. The telescoped process requires no purification or solvent exchange steps, decreasing the solvent waste for the process, and benefits from improved PMI metrics. The ability to optimise for discrete variables such as the catalyst type or catalyst loading would be beneficial in improving the yields of step one, and therefore the yield of the entire process. The improvement to all metrics analysed makes the telescoped process an extremely attractive proposition, not only for scale up manufacturing, but also for future telescoped automated optimisations that involve multiphase systems.

To further investigate this approach, the use of multi-objective optimisation algorithms would be beneficial to explore the trade-off between objectives such as yield, STY, reaction mass efficiency or process costs. This would expand and improve the greenness of this process, reducing the environmental impact of the production of APIs. Incorporating discrete variables, such as catalyst type or loading, into this multi-objective self-optimisation would also be useful in providing information about how much catalyst is required to minimise precious metal use.

4.5 Experimental

4.5.1 Chemicals

4-Nitrophenol (99%, Fisher), 4-aminophenol (98%, Fluorochem), biphenyl (99%, Merck), acetic anhydride (98%, VWR), acetaminophen (98%, Canyon Chemical), 2-methyl tetrahydrofuran ($\geq 99.5\%$, Sigma), extrudate Pd/carbon pellets (product code:113784, 1 wt.% Pd, JM), nitrogen gas (99.998%, BOC) and hydrogen gas (99.99%, BOC) were purchased from suppliers and used without further purification.

4.5.2 Hydrogenation reactor (R1) setup

The reactor system and typical optimisation procedures are described in the experimental section of Chapter 2.

- Pump 1: 4-nitrophenol (0.05 M), biphenyl (0.03 M), in solvent.
- Pump 2: Solvent.
- Mass flow controller : H₂ gas.

A Vici EUHA-CI4WE.2 sampling valve was used to sample the reaction into an Agilent 1100 HPLC, fitted with an Agilent Poroshell 120 EC-C8 HPLC column with 2.7 μm particle size (L x ID – 5 cm x 4.6 mm). A VWD detector at 254 nm, a column oven temperature of 35 °C, and a flow rate of 1.5 mL min⁻¹ were used (method gradient shown in Figure 84).

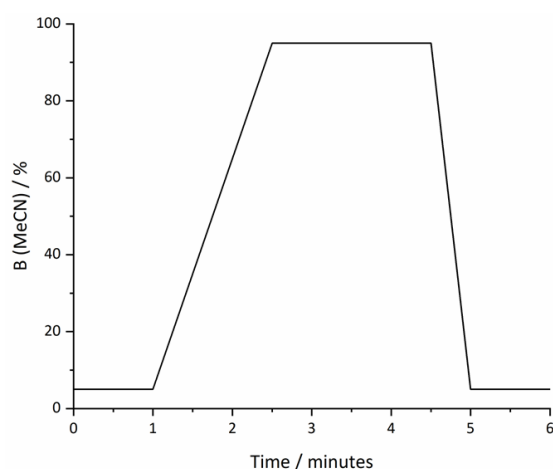


Figure 84. HPLC method gradient used for the OSAT experiments.

4.5.3 Amidation reactor (R2) setup

4.5.3.1 Reactor

A typical heated coiled plug flow reactor was used in the second step of the reaction. Reservoir solutions were prepared and made fully homogeneous by stirring under ambient conditions.

- Pump 1: 4-aminophenol (0.05 M), biphenyl (0.03 M) in solvent.
- Pump 2: Acetic anhydride (0.4 M) in solvent.
- Pump 3: Solvent.

Jasco P-980 pumps were used to control liquid flow rates in the reactor and IDEX BPR cartridges (75 PSI) were placed on the pump outlets to ensure consistent and accurate flow rates. The reactor was made from a 0.5 mL Polyfon PFA tubing of length 1.01 m (1/16" OD, 1/32" ID) and was coiled around an aluminium heating block. A Eurotherm temperature controller and heating cartridges were used in combination with the aluminium heating block to control the temperature of the system. A 100 PSI IDEX BPR was placed on the outlet of the reactor to maintain pressure in the system. A Vici EUHA-CI4WE.2 sampling valve was used to sample the reaction into an Agilent 1100 HPLC, fitted with an Agilent Poroshell 120 EC-C8 HPLC column with 2.7 μm particle size (L x ID – 5 cm x 4.6 mm). A VWD detector at 254 nm, a column oven temperature of 35 °C, and a flow rate of 1.5 mL min⁻¹ was used (method gradient shown in Figure 84).

This reactor was also used for the intermediate mixture experiments. The system was not adapted for this optimisation and was used as describe above but with a different stock solution reservoir.

4.5.3.2 Typical procedure

1. The system was flushed with IPA for 1 minute at 1 mL min⁻¹ per pump.
2. The system was flushed with solvent (2-MeTHF) for 2 minutes at 1 mL min⁻¹ per pump.
3. Pumps were connected to their respective reservoirs and the starting materials were flushed through the system for 2 minutes at 1 mL min⁻¹ per pump.
4. The optimisation was started.

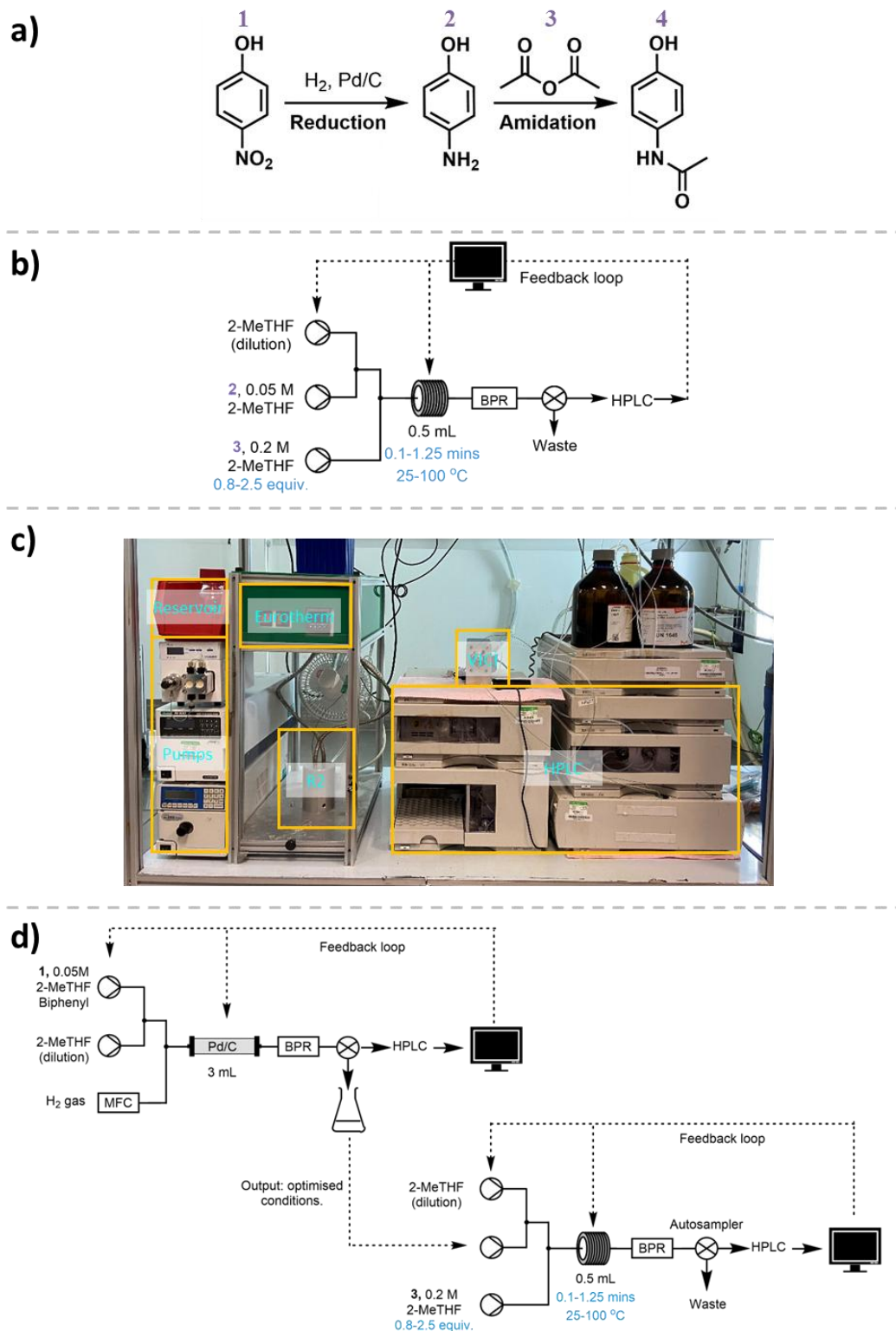


Figure 85. a) Scheme for the two-step synthesis of paracetamol, b) flow reactor used to perform the OSAT amidation reaction of 4-aminophenol to paracetamol, c) image of R2, and d) flow reactor used to perform the OSAT amidation reaction of 4-aminophenol to paracetamol for the step two – IM optimisation.

5. Once the optimisation is complete, the entire system was flushed with solvent again for 2 minutes at 1 mL min⁻¹ per pump.
6. The system was then flushed with IPA for 2 minutes at 1 mL min⁻¹ per pump and left under IPA to maintain pump health.

For the optimisation of step two-IM, the R2 system remained unchanged but the starting material reservoir was made up of the outlet mixture directly from R1. The overall reactor is shown in Figure 85d.

4.5.4 Combined telescoped reactor platform

Reservoir solutions were prepared by dissolving the desired reagents in solvent under stirring at ambient conditions. Reservoir solutions were replenished when required.

- Pump 1: 4-Nitrophenol (0.05 M) and biphenyl (0.032 M) in 2-MeTHF (250 mL).
- Mass Flow Controller: H₂ gas.
- Pump 2: Acetic anhydride (0.4 M) in 2-MeTHF.
- Pump 3: 2-MeTHF.

R1 remained unchanged from that described in Chapter 2. The PBR was made from stainless steel tubing (1/2" OD, 3/8" ID, 0.065" wall thickness) with 10.8 mL volume when empty, and 4 mL void volume when packed with 12.52 g glass beads (2 mm diameter) and 1.501 g 1% Pd/C JM catalyst pellets. The system was maintained under 580 PSI (40 bar) of pressure using a Jasco BP-2080 plus back pressure regulator. Reactor 2 was a cylindrical aluminium block with 1.5 mL Polyfon PFA tubing coiled (1/16" OD, 1/32" ID) and maintained under 100 PSI of pressure with a IDEX BPR cartridge. Two VICI Valco EUDA-CI4W sample loops (4-port) with 0.2 µL rotors were used for online sampling and monitoring of each step. The 100 PSI BPR on the outlet of the second reactor was used in tandem with a second 100 PSI BPR and a needle valve on the tube-in-tube separator gas outlet. The needle valve was tightened and loosened as needed to ensure optimal separation of the gas from the flow stream before passing into R2.

Online analysis was performed with a HP Agilent 1100 HPLC System fitted with an Agilent Poroshell 120 EC-C8 HPLC column with 2.7 μm particle size, L $\times$ ID 5 cm $\times$ 4.6 mm. Temperature of column was 35 $^{\circ}\text{C}$, wavelength of VWD was 254 nm, flow rate of 1.5 mL min⁻¹ (method gradient shown in Figure 86). It was made up of a six minute method which is doubled, where the autosampler after R1 is fired at zero minutes, and the autosampler after R2 is fired at six minutes.

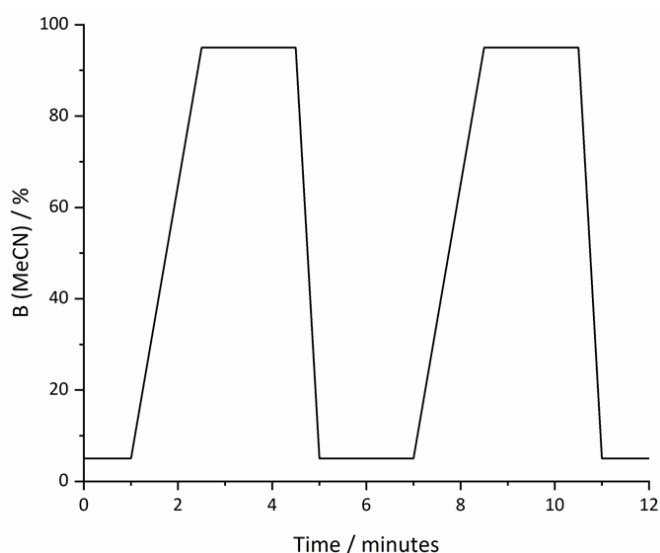


Figure 86. HPLC method gradient for the two-step telescoped hydrogenation and amidation reaction.

4.5.4.1 Typical procedure

1. R1 system was flushed with nitrogen gas (50 mL min⁻¹) for 30 minutes.
2. R1 system was flushed with hydrogen gas (50 mL min⁻¹) for 30 minutes.
3. R1 system was flushed with 2-MeTHF (0.5 mL min⁻¹) and hydrogen (50 mL min⁻¹) for six hours.
4. The 2-MeTHF pump was stopped, and the starting material pump was started (0.5 mL min⁻¹) for one hour.
5. R1 and R2 were connected via the tube-in-tube gas/liquid separator and all pumps were set to minimum flow rates and temperatures. The optimisation was then started.
6. When the optimisation was complete, the entire system was flushed with solvent (1 mL min⁻¹) and nitrogen (50 mL min⁻¹) for one hour.

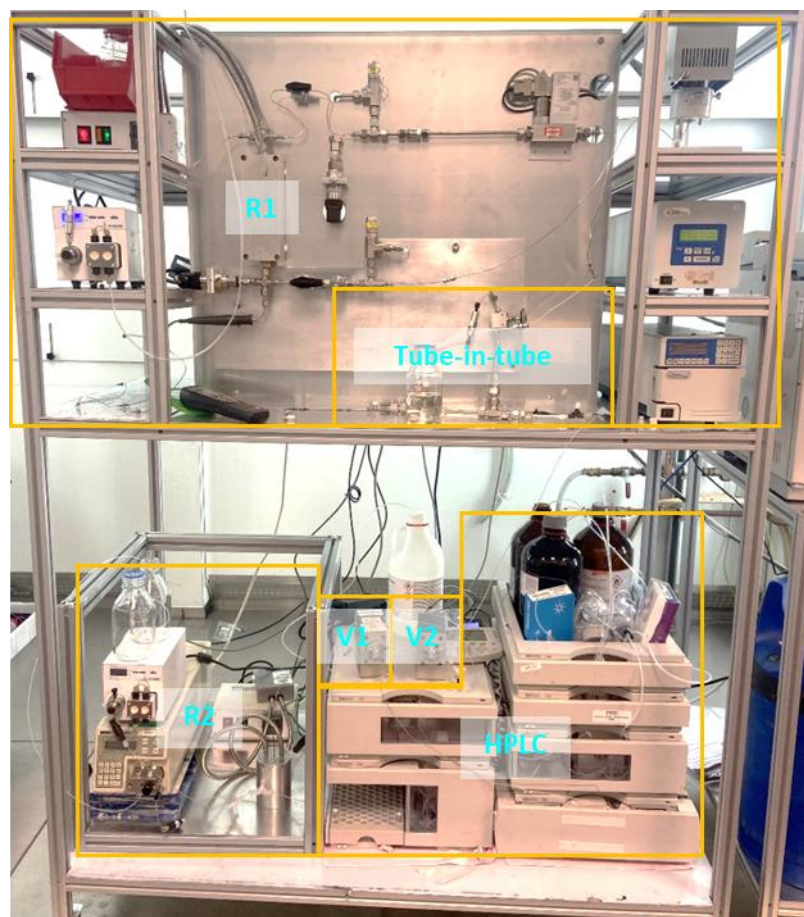


Figure 87. Reactor setup for combined telescoped two-step synthesis of paracetamol. R1 – reactor 1 heterogeneous PBR, R2 – PFA plug flow coiled reactor, V1 – vici sampling valve 1 for R1, and V2 – vici sampling valve for R2.

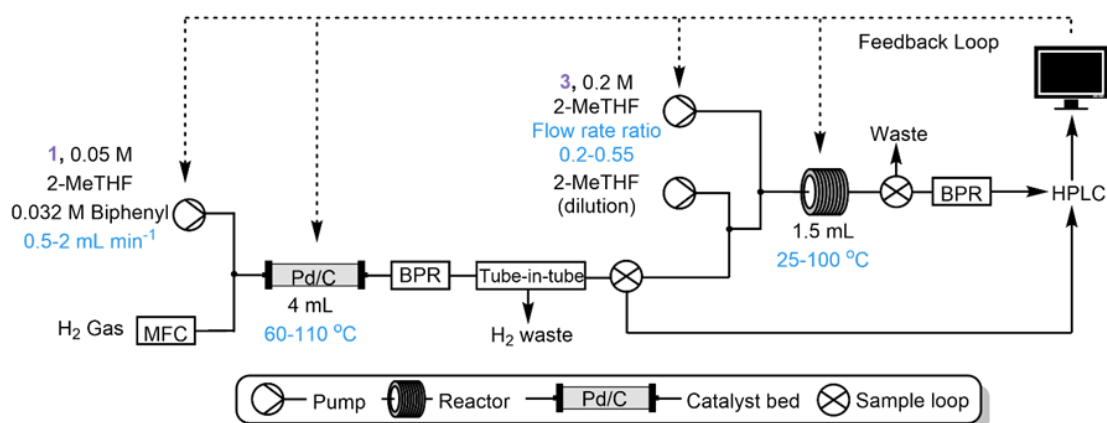


Figure 88. Continuous flow reactor set-up for the telescoped two-step synthesis of paracetamol from 4-nitrophenol. Numbers of the reagents relate to the scheme illustrated in Figure 85.

4.5.5 Online HPLC analysis

Example chromatograms for step one, step two and the telescoped multistep optimisations are shown below.

4.5.5.1 Step one

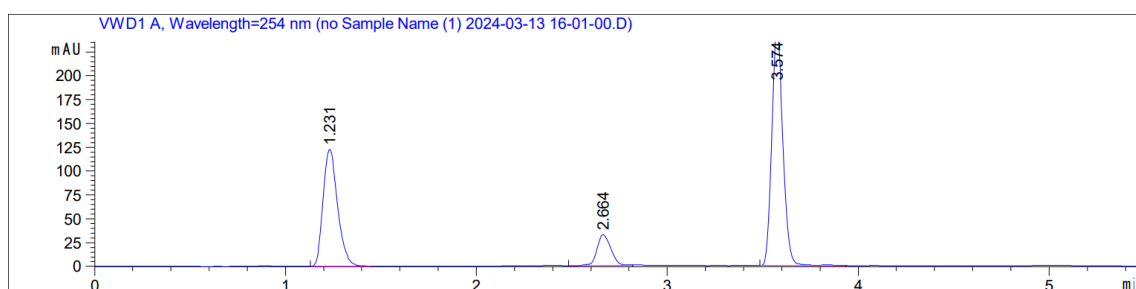


Figure 89. Example HPLC chromatogram for the hydrogenation optimisation of 4-nitrophenol.

Table 25. Peaks picking for Figure 89 in the hydrogenation optimisation for the product (P), internal standard (IS), and starting material (SM).

Peak position / min	Peak identification
1.231	4-Aminophenol (P)
2.664	4-Nitrophenol (SM)
3.574	Biphenyl (IS)

4.5.5.2 Step two

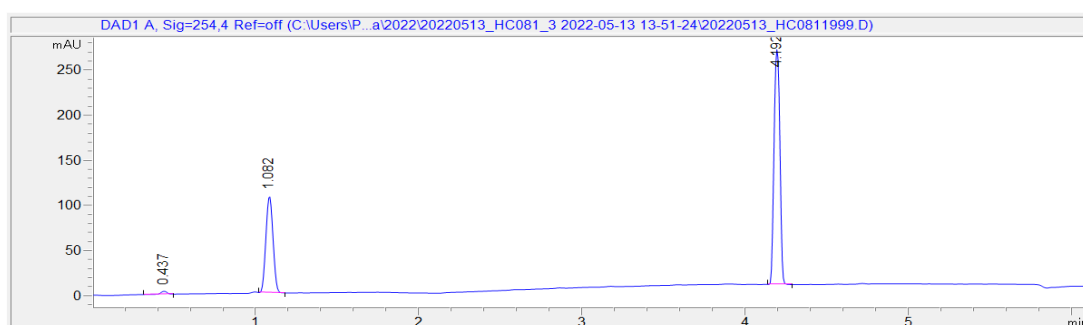


Figure 90. Example HPLC chromatogram for the amidation optimisation of paracetamol.

Table 26. Peaks picking for Figure 90 in the amidation optimisations for the starting material (SM), product (P), and internal standard (IS).

Wavelength / nm	Peak position / min	Peak identification
254	0.4	4-Aminophenol (SM)
220	1.1	Paracetamol (P)
220	4.2	Biphenyl (IS)

4.5.5.3 Telescoped

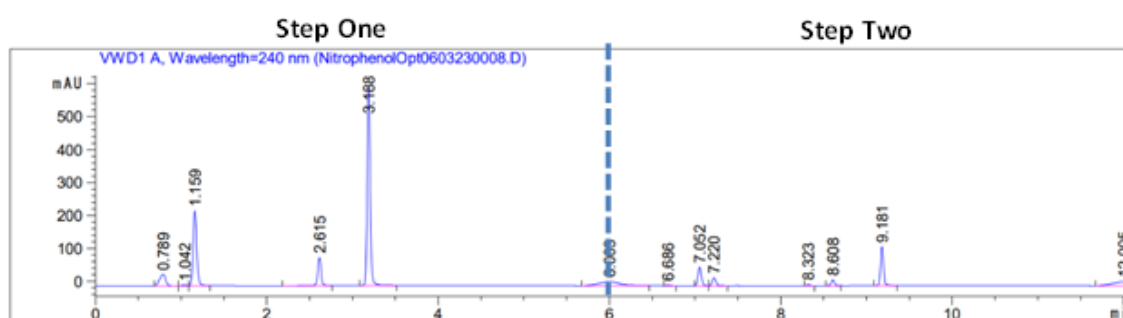


Figure 91. Example HPLC chromatogram for the telescoped hydrogenation-amidation optimisation of paracetamol where 0-6 minutes is the first sample from step one and 6-12 minutes is the second sample from step two.

Table 27. Peaks picking for Figure 91 in the telescoped hydrogenation-amidation optimisation of paracetamol for the product from step one (P1), starting material from step one (SM1), internal standard (IS), product from step two (P2), and by-product from step two (BP2).

Step/ Sample	Peak position / min	Peak identification
1	0.79	4-Aminophenol (P1)
1	1.16	Impurity
1	2.62	4-Nitrophenol (SM1)
1	3.19	Biphenyl (IS)
1	6.00	Solvent
2	6.69	4-Aminophenol (P2)
2	7.05	Impurity
2	7.22	Paracetamol (P2)
2	8.32	Diacetamate (BP2)
2	8.61	4-Nitrophenol (SM1)
2	9.18	Biphenyl (IS)
2	12.00	Solvent

4.6 Appendix

4.6.1 Kernal length scale values

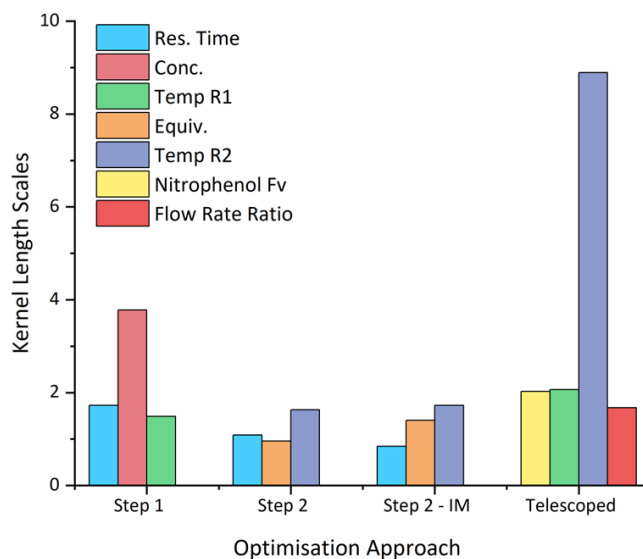


Figure 92. Comparison of the optimisation variables kernel length scales, showing their importance to the overall reaction output (larger value is the least important factors).

4.6.2 Optimisation data for step one – OSAT - BOAEI

Table 28. Optimisation data for OSAT step one single objective optimisation with the BOAEI algorithm.

Exp. No.	Exp. Type	Variable			Flow Rate / mL min ⁻¹		Objective
		Liq. Flow Rate / mL min ⁻¹	Temp. / °C	Conc. / M	4-Nitrophenol	2-MeTHF	Yield / %
1	Initial	0.685	68.1	0.030	0.414	0.270	43.25
2	Initial	1.422	44.6	0.019	0.538	0.881	20.52
3	Initial	0.965	62.9	0.045	0.874	0.091	30.42
4	Initial	0.739	52.8	0.044	0.648	0.092	31.82
5	Initial	0.880	78.7	0.038	0.664	0.214	41.17
6	Initial	0.521	58.2	0.026	0.272	0.248	44.68
7	Initial	0.594	77.9	0.013	0.160	0.434	56.63
8	Refinement	0.508	77.1	0.029	0.290	0.218	59.22
9	Refinement	0.502	85.0	0.010	0.100	0.400	64.58
10	Refinement	0.503	85.0	0.011	0.101	0.399	62.33
11	Refinement	0.502	84.9	0.010	0.100	0.400	63.30
12	Refinement	0.500	85.0	0.049	0.488	0.012	54.40
13	Refinement	0.508	85.0	0.010	0.102	0.407	63.20
14	Refinement	0.500	84.0	0.010	0.100	0.400	59.00

4.6.3 Optimisation data for step one – OSAT - SNOBFIT

Table 29. Optimisation data for OSAT step one single objective optimisation with the SNOBFIT algorithm.

Exp. No.	Exp. Type	Variable			Flow Rate / mL min ⁻¹		Objective
		Liq. Flow Rate / mL min ⁻¹	Temp. / °C	Conc. / M	4-Nitrophenol	2-MeTHF	Yield / %
1	Initial	1.490	84.3	0.043	1.280	0.210	50.37
2	Initial	0.730	40.0	0.021	0.300	0.430	26.10
3	Initial	0.680	62.2	0.016	0.210	0.470	43.12
4	Initial	1.430	51.1	0.010	0.280	1.150	29.05
5	Initial	0.600	73.3	0.030	0.360	0.240	51.82
6	Initial	2.230	56.7	0.030	1.340	0.890	22.55
7	Initial	1.960	67.8	0.010	0.390	1.570	32.19
8	Refinement	0.500	79.1	0.010	0.100	0.400	40.87
9	Refinement	0.540	45.4	0.030	0.320	0.220	27.00
10	Refinement	0.634	85.0	0.050	0.634	0.000	67.41
11	Refinement	0.500	74.5	0.040	0.400	0.100	66.16
12	Refinement	0.760	85.0	0.050	0.760	0.000	59.79
13	Refinement	1.350	48.4	0.040	1.080	0.270	21.12
14	Refinement	0.500	85.0	0.050	0.500	0.000	62.43
15	Refinement	0.500	71.2	0.050	0.500	0.000	54.85
16	Refinement	0.570	84.6	0.050	0.570	0.000	56.49
17	Refinement	1.350	70.8	0.030	0.810	0.540	37.99
18	Refinement	1.500	85.0	0.010	0.300	1.200	52.99

19	Refinement	0.500	78.4	0.050	0.500	0.000	50.31
20	Refinement	0.850	62.5	0.040	0.680	0.170	30.07
21	Refinement	1.500	85.0	0.020	0.600	0.900	54.97
22	Refinement	0.500	73.7	0.030	0.300	0.200	56.08
23	Refinement	1.990	75.4	0.040	1.590	0.400	28.24
24	Refinement	1.500	85.0	0.030	0.900	0.600	40.33
25	Refinement	0.500	75.2	0.050	0.500	0.000	48.70
26	Refinement	0.760	51.3	0.050	0.760	0.000	22.51
27	Refinement	1.000	85.0	0.040	0.800	0.200	46.43
28	Refinement	0.620	85.0	0.030	0.370	0.250	57.46
29	Refinement	0.500	74.9	0.030	0.300	0.200	55.05
30	Refinement	1.370	68.7	0.050	1.370	0.000	26.00
31	Refinement	1.240	85.0	0.010	0.250	0.990	50.47
32	Refinement	0.500	74.0	0.050	0.500	0.000	51.65
33	Refinement	0.560	85.0	0.050	0.560	0.000	54.43
34	Refinement	1.330	48.4	0.030	0.800	0.530	17.75
35	Refinement	1.050	84.6	0.010	0.210	0.840	46.24
36	Refinement	0.660	85.0	0.050	0.660	0.000	56.18
37	Refinement	0.600	45.7	0.040	0.480	0.120	20.47
38	Refinement	0.900	84.6	0.030	0.540	0.360	49.90
39	Refinement	0.590	85.0	0.050	0.590	0.000	59.94
40	Refinement	0.650	68.0	0.050	0.650	0.000	40.81

4.6.4 Optimisation data for step two with wide bounds - OSAT

Table 30. Optimisation data for OSAT step two single objective optimisation with wide variable bounds (BOAEI algorithm).

Exp No.	Exp. Type	Variables			Flow Rate / mL min ⁻¹			Objective
		Res. Time / min	Equiv.	Temp. / °C	4-Aminophenol	Acetic Anhydride	Solvent	Yield / %
1	Initial	3.37	3.40	28.1	0.357	0.303	0.231	96.30
2	Initial	1.76	4.14	66.2	0.682	0.705	0.317	94.84
3	Initial	4.71	2.35	86.2	0.255	0.149	0.233	99.59
4	Initial	0.76	3.07	109.4	1.572	1.206	1.151	93.98
5	Initial	2.52	4.53	126.5	0.476	0.540	0.175	95.79
6	Initial	4.29	1.28	161.7	0.280	0.090	0.330	99.61
7	Initial	1.51	1.68	185.3	0.793	0.333	0.857	94.80
8	Refinement	5.00	1.00	61.4	0.240	0.060	0.300	79.23
9	Refinement	3.24	2.64	58.8	0.370	0.244	0.311	97.88
10	Refinement	4.91	2.01	128.1	0.245	0.123	0.244	96.95
11	Refinement	5.00	1.00	193.3	0.240	0.060	0.300	89.40
12	Refinement	2.83	1.29	129.0	0.423	0.137	0.498	94.57
13	Refinement	4.52	1.28	136.8	0.266	0.085	0.314	96.82
14	Refinement	4.74	5.00	70.4	0.253	0.316	0.063	97.72
15	Refinement	3.87	1.23	200.0	0.310	0.096	0.369	95.12
16	Refinement	2.35	2.46	85.7	0.511	0.314	0.453	95.78
17	Refinement	5.00	2.17	58.9	0.240	0.130	0.230	95.00
18	Refinement	5.00	2.27	128.8	0.240	0.136	0.224	96.26
19	Refinement	4.86	1.52	161.1	0.247	0.094	0.276	95.77

20	Refinement	4.38	1.99	181.8	0.274	0.136	0.274	93.50
21	Refinement	4.10	4.79	62.4	0.293	0.351	0.088	98.43
22	Refinement	4.58	3.30	79.8	0.262	0.216	0.177	95.30
23	Refinement	4.79	5.00	120.0	0.250	0.313	0.063	96.24
24	Refinement	4.96	5.00	25.0	0.242	0.302	0.060	94.64
25	Refinement	2.53	5.00	199.9	0.475	0.593	0.119	83.04
26	Refinement	3.55	1.53	159.2	0.338	0.130	0.378	94.78
27	Refinement	4.28	5.00	87.7	0.280	0.350	0.070	95.19
28	Refinement	4.50	4.27	25.0	0.27	0.28	0.12	97.62
29	Refinement	3.03	3.24	200.0	0.395	0.320	0.273	88.01
30	Refinement	1.00	4.33	25.0	1.206	1.306	0.502	85.93
31	Refinement	5.00	4.30	67.4	0.240	0.258	0.102	93.90
32	Refinement	4.19	2.65	91.0	0.286	0.190	0.240	96.25

4.6.5 Optimisation data for step two with narrow bounds – OSAT

Table 31. Optimisation data for OSAT step two single objective optimisation with narrow variable bounds (BOAEI algorithm).

Exp No.	Exp. Type	Variables			Flow Rate / mL min ⁻¹			Objective
		Res. Time / min	Equiv.	Temp. / °C	4-Aminophenol	Acetic Anhydride	Solvent	Yield / %
1	Initial	0.65	1.33	27.5	0.308	0.102	0.360	36.48
2	Initial	0.95	1.97	39.0	0.211	0.104	0.213	64.00
3	Initial	0.28	2.09	53.7	0.727	0.379	0.711	47.76
4	Initial	0.53	1.26	63.8	0.378	0.119	0.448	48.56
5	Initial	0.80	2.43	78.2	0.251	0.153	0.224	93.44
6	Initial	1.14	1.04	79.1	0.176	0.045	0.218	66.94
7	Initial	0.14	1.76	95.3	1.406	0.619	1.491	39.16
8	Refinement	0.91	2.47	50.2	0.220	0.135	0.194	91.02
9	Refinement	0.83	2.22	99.5	0.241	0.134	0.228	93.81
10	Refinement	0.68	2.50	68.3	0.296	0.185	0.259	82.02
11	Refinement	1.19	2.20	100.0	0.167	0.092	0.159	97.03
12	Refinement	1.00	2.50	95.9	0.200	0.125	0.175	96.17
13	Refinement	1.12	2.41	73.5	0.179	0.108	0.161	94.88
14	Refinement	0.95	2.50	79.8	0.211	0.132	0.185	96.28
15	Refinement	1.25	2.16	40.9	0.160	0.086	0.154	84.71
16	Refinement	0.99	2.29	73.8	0.202	0.116	0.187	94.36
17	Refinement	1.25	1.70	100.0	0.160	0.068	0.172	96.94
18	Refinement	1.25	2.50	87.2	0.160	0.100	0.140	95.90
19	Refinement	0.10	0.80	100.0	1.990	0.398	2.587	13.66

20	Refinement	0.95	2.50	80.8	0.211	0.132	0.185	89.90
21	Refinement	1.01	2.50	81.6	0.197	0.123	0.173	91.32
22	Refinement	1.01	2.50	80.3	0.198	0.124	0.173	88.63
23	Refinement	1.00	2.50	89.6	0.200	0.125	0.175	88.90
24	Refinement	1.02	2.50	77.6	0.196	0.122	0.171	91.88
25	Refinement	1.01	2.50	80.3	0.199	0.124	0.174	91.71

4.6.6 Optimisation data for step two - IM

Table 32. Optimisation data for IM step two single objective optimisation (BOAEI algorithm).

Exp No.	Exp. Type	Variables			Flow Rate / mL min ⁻¹			Objective
		Res. Time / min	Equiv.	Temp. / °C	4-Aminophenol	Acetic Anhydride	Solvent	Yield / %
1	Initial	0.65	1.33	27.5	0.308	0.102	0.360	38.74
2	Initial	0.95	1.97	39.0	0.211	0.104	0.213	79.98
3	Initial	0.28	2.09	53.7	0.727	0.379	0.711	49.63
4	Initial	0.53	1.26	63.8	0.378	0.119	0.448	52.03
5	Initial	0.80	2.43	78.2	0.251	0.153	0.224	95.17
6	Initial	1.14	1.04	79.1	0.176	0.045	0.218	74.81
7	Initial	0.14	1.76	95.3	1.406	0.619	1.491	41.88
8	Refinement	0.88	2.50	80.3	0.226	0.141	0.198	95.36
9	Refinement	0.82	2.04	98.7	0.245	0.125	0.243	94.42
10	Refinement	0.87	2.50	62.1	0.229	0.143	0.200	93.23
11	Refinement	1.21	2.50	28.6	0.165	0.103	0.144	83.17
12	Refinement	1.14	0.80	48.1	0.176	0.035	0.228	37.29
13	Refinement	0.97	2.05	76.5	0.205	0.105	0.203	91.22
14	Refinement	0.73	2.50	91.5	0.274	0.171	0.239	96.43
15	Refinement	1.25	2.50	91.0	0.160	0.100	0.140	97.18
16	Refinement	1.20	2.50	80.7	0.167	0.105	0.146	97.77
17	Refinement	1.16	2.50	80.8	0.173	0.108	0.151	97.73
18	Refinement	1.12	2.50	82.1	0.179	0.112	0.156	98.52

19	Refinement	1.25	2.01	100.0	0.160	0.080	0.160	98.83
20	Refinement	1.13	2.50	83.7	0.177	0.110	0.155	97.62
21	Refinement	1.14	2.50	100.0	0.175	0.109	0.153	98.71
22	Refinement	1.12	2.20	91.1	0.179	0.098	0.170	98.42
23	Refinement	1.25	2.37	51.4	0.160	0.095	0.146	88.93
24	Refinement	1.25	2.50	58.5	0.160	0.100	0.140	94.84
25	Refinement	1.25	2.50	46.8	0.160	0.100	0.140	90.88

4.6.7 Optimisation data for telescoped two-step reaction

Table 33. Optimisation data for telescoped two-step single objective optimisation (BOAEI algorithm).

Exp. No.	Exp. Type	Variables				Equivalents Acetic Anhydride	Flow Rate / mL min ⁻¹		Yield (step 1) / %	Objective
		Nitrophenol / mL min ⁻¹	Temp. R1 / °C	Temp. R2 / °C	Flow Rate Ratio		Acetic Anhydride	Solvent		Yield (Step 2) / %
1	Initial	1.44	60.6	44.9	0.29	1.16	0.418	0.542	54.3	28.3
2	Initial	0.63	67.5	91.4	0.36	1.44	0.225	0.193	68.3	52.0
3	Initial	0.91	76.1	31.7	0.52	2.06	0.471	0.138	62.6	40.8
4	Initial	0.67	80.4	94.9	0.47	1.87	0.312	0.134	68.8	60.8
5	Initial	1.09	85.0	77.1	0.21	0.83	0.226	0.498	60.7	37.7
6	Initial	1.56	89.0	54.2	0.27	1.10	0.428	0.614	52.1	32.0
7	Initial	1.22	94.9	71.0	0.35	1.38	0.421	0.392	62.2	51.5
8	Initial	1.93	99.4	34.1	0.42	1.68	0.813	0.477	56.1	28.8
9	Initial	1.83	106.1	59.5	0.48	1.93	0.883	0.335	64.7	39.9
10	Refinement	1.01	109.9	83.2	0.46	1.85	0.468	0.206	78.6	70.8
11	Refinement	1.12	109.0	91.7	0.52	2.09	0.586	0.160	71.5	65.1
12	Refinement	0.50	110.0	67.0	0.55	2.20	0.275	0.058	86.8	84.3
13	Refinement	0.71	110.0	77.1	0.55	2.20	0.389	0.082	83.9	82.1
14	Refinement	0.50	110.0	90.4	0.20	0.80	0.100	0.233	82.0	59.0
15	Refinement	0.50	110.0	32.2	0.48	1.92	0.240	0.093	83.3	85.0
16	Refinement	0.50	110.0	64.0	0.43	1.72	0.214	0.119	83.6	79.6
17	Refinement	0.56	110.0	80.0	0.55	2.20	0.310	0.066	80.0	76.8
18	Refinement	0.67	110.0	25.0	0.55	2.20	0.368	0.078	76.8	71.5

4.7 References

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Chapter 5 : Catalyst Deactivation – Continuous Adaptive Optimisation

5.1 Introduction

Catalysts must not only be highly active and selective for a process, but they must also have a long lifetime and show minimal deactivation during their use in a reaction. Deactivation can be caused by many different mechanisms, with some common deactivation processes outlined in Table 34.¹⁻³ However, the literature available on deactivation mechanisms uses a wide range of interchangeable vocabulary to define these processes, making identification and categorisation difficult. Work by Martin *et al.* aims to unify the field, creating a generalised structure for the description of deactivation mechanisms, categorising all types into either a loss, a blockage or a modification deactivation mode.⁴ It is hoped that a clearer, fundamental understanding of the different types of deactivation mechanisms will not only help other scientists navigate literature examples more easily, but will encourage the adoption of operando methods to study the deactivation in all of the new, novel catalysts that are reported. The article summarises which techniques are appropriate for identifying the deactivation mechanism and is a great source of information for new scientists in the field. Deactivation can be characterised as temporary, where the catalyst deactivates but is able to be regenerated under certain process conditions, or permanent where the deactivation causes permanent loss to the activity of the catalyst.⁵ Many heterogeneous

Table 34. Details of some common mechanisms responsible for the deactivation of catalytic species.¹⁻³

Deactivation Mechanism	Description
Poisoning	Poisoning occurs through the strong chemisorption of species to the active sites of the catalyst, blocking them from being catalytically active.
Vapour Formation	A chemical reaction where the gas phase interacts with the catalyst and produces volatile compounds that deactivate the catalyst.
Vapour-Solid and Solid-Solid Reactions	An interaction of a species with the catalyst to produce an inactive catalyst phase.
Metal leaching	The loss of active sites on the support material through the dissolution into the reaction medium.
Attrition/Crushing	The degradation of the catalyst through mechanical failure e.g. crushing, attrition, and erosion.
Fouling	The physical deposition of molecules in the pores of the catalyst or on the catalyst surface decreasing the activity of the catalyst.
Sintering	The thermal degradation of the catalyst causing the loss of surface area, collapse of the support and/or chemical transformations of the catalyst.

systems make use of expensive precious transition metals such as Pt, Pd, and Ru, which are highly active for many processes but are scarce. Therefore, it is important that the catalysts can be used many times to make the process economical and sustainable. Reactivation of the catalysts can be highly beneficial for systems where the catalysts are used for long periods of time in industrial processes. It allows catalysts to be regenerated and recycled minimising the use and unnecessary waste of precious metals, reducing the cost of the process.¹ However, reactivation may cause problems with the productivity of a process as the reaction must be stopped while the reactivation protocol is applied and then restarted.

Periodic reactivation of catalysts can be useful for continuous processes as it requires minimal human intervention through the use of automation and minimises the need for the replacement of catalyst beds. Mohanta *et al.* presented an alkylation of 1,3-dicarbonyls with an Amberlyst®-15 catalyst in continuous flow, shown in Figure 93, that suffered deactivation over prolonged use (50 hours).⁶ A reactivation protocol involved flushing the catalyst column with a solution of HCl (0.1 M) in methanol every five hours which allowed the activity of the catalyst to be regained, similar to that at the start of the reaction. This led to an increase in the productivity of the process, as more products could be produced over a longer time period, showing the industrial applicability of this reactivation protocol. However, the yield of the reaction may decrease at different reaction rates in between reactivations, therefore a threshold based reactivation protocol, which involves monitoring the reaction output and reactivating the catalyst when the yield of the reaction decreases below a certain threshold, is much more useful. This would lead to a more consistent reaction output and means reactivation would only be applied, when necessary, possibly decreasing the waste of solvents if the reactivation was performed too often.

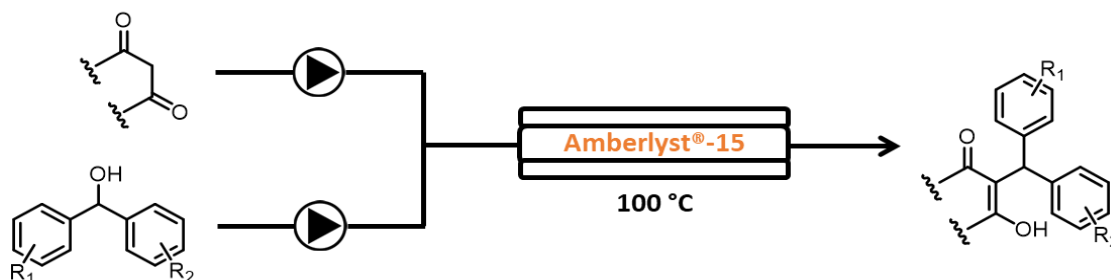


Figure 93. Continuous flow platform for the alkylation of 1,3-dicarbonyl with an Amberlyst®-15 catalyst reported by Mohanta *et al.*⁶

A common form of deactivation is fouling caused by coking, which involves the blockage of the catalytic sites or pores of the support with carbon species that are produced from the decomposition of organic reactants.¹ The carbon species deposit onto the active sites of the catalyst particle preventing other reactant molecules from being able to react here, lowering the activity of the catalyst and causing deactivation over time.⁷ Catalysts can often be regenerated from coke formation through the burning of the catalyst in controlled amounts of oxygen at high temperatures.⁸⁻¹⁰ Modification of the catalyst itself can also aid in controlling the extent of fouling during a reaction.¹¹ In the formation of an active nickel-based catalyst, Kong *et al.* combined Ni particles with a Ca promoter to reduce coke formation.¹² The adsorption capacity of CO₂ by the catalyst was increased to eliminate carbon species from blocking the active Ni catalyst sites on the Ca-Ni-SiO₂ support. This was successful as the catalyst only experienced 0.6% carbon formation on the catalyst particles when they were used in the CO₂ reforming of methane.

Deactivation via metal leaching from the support material is another common mechanism, often found in reactions that use liquid reactants.³ This can happen through the direct solubilisation of the metal in solution or through a chemical transformation of the solid to form a soluble species. Reactions that are performed at high temperatures and in polar solvents will always result in some metal leaching, making the solvent choice another important parameter to consider when developing heterogeneous catalytic processes. It is important that metal leaching is kept to a minimum during a process, as it would require the removal of these metals from the final product which is costly and creates large amounts of solvent waste. In a techno-economic analysis of the production of DMF from fructose by Kazi *et al.* in 2011, the group reported that the catalyst cost accounted for a third of the total equipment costs, showing that any loss of the catalytic species would result in a significant increase in the cost of this process.¹³ Many procedures have been implemented to successfully reduce metal leaching including changing the pH of the solution,^{14,15} implementing washing steps in between reactions to stabilise the support,^{3,16} and the use of less polar solvents.^{17,18}

Precise control over experimental conditions can help to prevent catalyst deactivation by thermal and chemical degradation. Highly exothermic reactions can cause the reactor to heat up rapidly which may lead to the pulverisation/sintering of

catalyst pellets leading to blockages in the reactor, reducing the efficiency of the process.¹⁹ Continuous flow systems for heterogeneous catalysts can alleviate these issues, as these setups benefit from improved process control and enhanced heat and mass transfer, allowing precise control over reaction exotherms.²⁰

Deactivation may not always be directly from the reactants or the product, it may be from additives or impurities that poison the catalyst under certain process conditions. Simon *et al.* reported a continuous flow platform designed to test heterogeneous catalysts for their functional group tolerances in industrially important multiphase hydrogenation transformations.⁵ The group showed the novel reactor platform could be used to screen the stability of a Pd/Al₂O₃ catalyst, immobilised on a coated static mixer, for the reduction of *o*-nitrotoluene to *o*-toluidine with 12 separate additives (Figure 94). The reaction was monitored by UHPLC and FTIR, allowing quantitative analysis of all reactants, intermediates, additives and products during flow ramps and changes to the reaction conditions. It was found that the catalyst showed a good stability for amine functionality, but complete poisoning of the catalyst was observed with sulphur containing compounds. It is important to understand these changes in activity with small additive quantities, and impurities from previous reactions may influence processes further downstream, especially in telescoped systems. Continuous flow operation allowed for the rapid generation of data relating to the

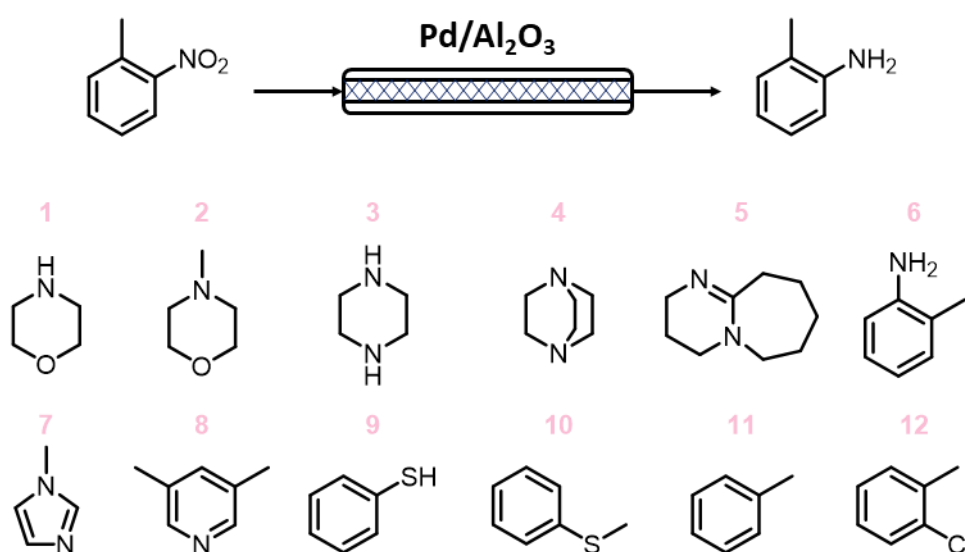


Figure 94. Reaction setup and additives investigated by Simon *et al.* in the functional group tolerance testing of an immobilised Pd/Al₂O₃ catalyst.⁵

influence of reaction impurities and additives on the stability of heterogeneous catalysts, through the integration of online and inline PAT.

5.1.1 Self-optimisation and catalyst deactivation

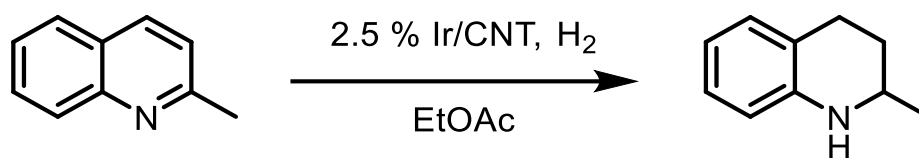
Automated self-optimising algorithms have been shown to be highly beneficial in the rapid identification of optimal reaction conditions for many processes.²¹ During the self-optimisation of reactions containing catalysts, deactivation must be monitored, to ensure that the response from the reaction is due to the reaction conditions, and not a change in the activity of the catalyst. This is usually monitored by performing repeat reactions, or by measuring the catalyst bed temperature, as a change in the exotherm of the reaction is related to the deactivation of the catalyst. Self-optimisations can be performed with catalysts that deactivate, but this requires an adaptation to existing optimisation approaches.

One way to perform self-optimisations on reactions that experience catalyst deactivation, is to replace the catalyst during the optimisation to a fresh stock solution or a fresh bed of catalyst (whether exploring a homo- or heterogeneous system) to ensure a consistent catalytic activity is experienced for all experiments. Liang *et al.* applied this method in the self-optimisation of the reduction of nitrobenzene and 5-nitroisoquinoline in a heterogeneous micro-PBR.²² A novel combined simplex and BO algorithm approach was implemented and repeat reactions were taken every three hours to evaluate any changes to the activity of the catalyst. If a decrease in the yield of the repeat reaction of greater than 3% was seen, the catalyst bed was replaced with fresh PBR and the optimisation was continued. This ensured consistent activity of the catalyst throughout the optimisations; however, this is a very wasteful method for addressing catalyst deactivation. The reactions made use of precious metals (Pd, Pt and Ni), which are expensive and nonabundant, meaning the recycling and reuse of these metals is highly important from a sustainability and economic standpoint.

A way in which deactivation has been addressed in a more environmentally friendly way is through incorporating a model of the deactivation of a catalyst into the optimisation algorithm. Kohl *et al.* reported the self-optimisation of a photocatalytic dye degradation with a Bayesian algorithm that incorporates deactivation into the surrogate

model of the optimisation.²³ The photocatalyst was immobilised on static mixers and experienced catalyst deactivation via fouling with unreacted dye molecules. The algorithm built a model for the deactivation of the catalyst, alongside optimising the reaction, based on the amount of material that had passed over the bed since the catalyst was last regenerated. The catalyst is regenerated periodically every three to five experiments in the optimisation, by passing a solution of H₂O₂ (1 M) over the catalyst bed for 40 minutes before flushing with deionised water and restarting the optimisation. The deactivation model can then be used to predict what the yield of the reaction would have been with no catalyst deactivation. This method requires no extra experiments as the algorithm can simultaneously investigate the model for the deactivation of the catalyst and optimise the yield of the photocatalytic reaction. This has improvements over other methods, which involve performing a separate study to model the deactivation, in that no extra reactions or material were required to understand the deactivation of the catalyst, saving time and resources. However, this example only discusses the single objective optimisation of a two-variable system. Increasing the number of variables investigated will increase the complexity of the deactivation and reaction models, making predictions more difficult and requiring many more experiments.

When a catalyst cannot be regenerated, approaches must be developed to account for the change in catalyst activity over time. Fabry *et al.* outlined a method for an adaptive optimisation that could be used to detect sudden changes in process input conditions during a reaction on plant to re-optimize the system.²⁴ An adapted simplex algorithm was reported that would perform repeat reactions every other experiment to check for changes to the optimum conditions found in the initial simplex optimisation. If a decrease in the yield of >5% was detected, the simplex would re-optimize the system and find optimal reaction conditions within the new design space. This was demonstrated on a heterogeneous hydrogenation with online FTIR analysis to quantitatively analyse the resultant reaction stream and create an online feedback loop to self-optimize the reaction. This new methodology was tested by manually changing the initial stock solution concentration of the reaction to mimic a fluctuation in the reaction stream that is common on industrial plants. The algorithm was able to detect a change in the response from the reaction with the new initial starting material



Scheme 11. Reduction of quinaldine with an Ir/carbon nanotube catalyst in the closed-loop self-optimising system with a ThalesNano H-Cube reported by Fabry *et al.*²⁴

concentration and explore the design space to find new optimal conditions. The group showed the successful implementation of this adaptive simplex optimisation on a number of reactions including the reduction of quinaldine shown in Scheme 11, where the stock solution was doubled from 0.1 to 0.2 M. The dynamic simplex algorithm re-optimised the reaction in 18 experiments increasing the yield from 40%, back up to 97%, comparable to that before the concentration was changed.

This new algorithm and methodology show promise for an application to address catalyst deactivation. As a catalyst deactivates, the original optimum conditions found from a self-optimisation will no longer be able to achieve the same response from the reaction due to the decrease in activity of the catalysts. The dynamic simplex algorithm reported by Fabry *et al.* could be used to track this change in the activity of the catalyst and adjust the reaction conditions to maintain the same reaction output. This would mean that the same yield of the reaction could be achieved for longer periods of time, which would extend the operational lifetime of the catalyst, and reduce precious metal waste as the bed could be used for a longer period of time before it is replaced.

5.2 Aims

This chapter aims to show the development of a way in which catalyst deactivation can be monitored and accounted for when performing a heterogeneously catalysed reaction in continuous flow. The dynamic simplex optimisation algorithm previously reported by Fabry *et al.* was used to monitor catalyst deactivation through repeat experiments and change the experimental conditions during an optimisation to maintain the same reaction output for an extended period of operating time. A reaction was first identified that demonstrates significant and permanent deactivation of the catalyst, and the catalyst amount was optimised to allow deactivation to be monitored over a 31 hour operating period. Modelling and simulation of the reaction design space

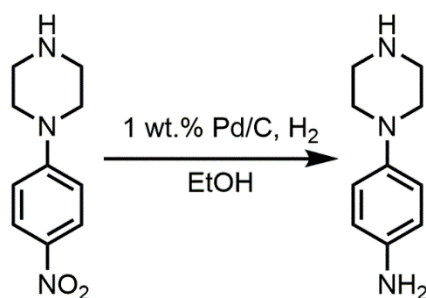
from experimental data is used to influence experimental design, to save on reaction costs and material waste.

5.3 Results

5.3.1 Initial deactivation studies

During all optimisations covered in chapters 2, 3, and 4, deactivation studies were performed to ensure that there was no change to the activity of the catalyst during the self-optimisation. Minimal deactivation was seen in all previous case studies, and the overnight shutdown column washing procedure was sufficient in reactivating the catalyst to the same activity as the start of the previous day, if any small decrease in activity was experienced during the optimisations. The same initial deactivation experiments were performed over two days to assess the stability of the 1 wt.% Pd/C JM pelleted catalyst in the reduction 1-(4-nitrophenyl) piperazine (Nitropip), shown in Scheme 12, before performing a self-optimisation. The reaction conditions were kept constant and the activity of the catalyst was monitored offline via GC analysis.

The results of the stability test are shown in Figure 95, demonstrating a slow decrease in the yield of the reaction over time, indicating the catalyst was becoming deactivated despite low liquid flow rates and high temperatures being tested. A lower liquid flow rate minimises the amount of material that is flowed over the catalyst over a period of time, leading to a lower rate of deactivation via fouling. High temperatures have been reported in the literature to limit the deactivation of the catalyst by increasing the desorption rate of the fouled material from the catalyst surface, with some reports showing that deactivation can be alleviated completely by using high temperatures.²⁵ Even at these favourable reaction conditions, deactivation of the catalyst was still



Scheme 12. The reduction of Nitropip.

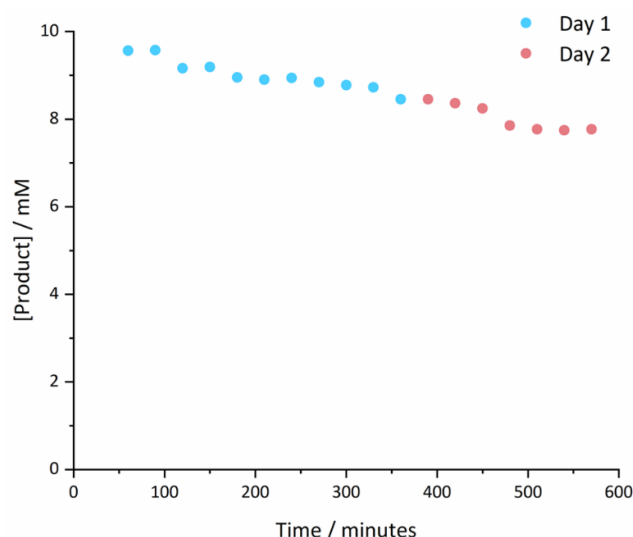


Figure 95. Concentration profile for the stability of the 1 wt.% Pd/C pellets (1 g) in the reduction of Nitropip. Fixed conditions: H_2 flow rate – 50 mL min^{-1} , liquid flow rate – 0.5 mL min^{-1} , pressure – 20 bar, concentration – 12 mM, and temperature – 85°C .

significant in this reaction. Despite this initial indication of the permanent deactivation of the catalyst, a self-optimisation was performed, to test the ability of the algorithm to find optimal conditions during deactivation.

5.3.2 Bayesian optimisation

The effect of catalyst deactivation on a self-optimisation was investigated with a BOAEI, previously described in chapter 2, initialised by LHC. The chosen reaction conditions and variable bounds were:

- Liquid flow rate – $0.5 - 3 \text{ mL min}^{-1}$.
- Concentration – $1.5 - 15 \text{ mM}$.
- Temperature – $40 - 85^\circ\text{C}$.

27 experiments were performed in total and the optimisation data is summarised in section 5.6.1 and Figure 96. It shows that the global optimum of the system was possibly missed by the algorithm due to the deactivation of the catalyst. The highest yielding experiment was found in the initial LHC, in experiment seven, at low concentrations, median temperatures and low liquid flow rates. However, due to significant deactivation of the catalyst, when reaction conditions at higher temperatures were explored, the yield of the reaction was much lower than expected. This caused the

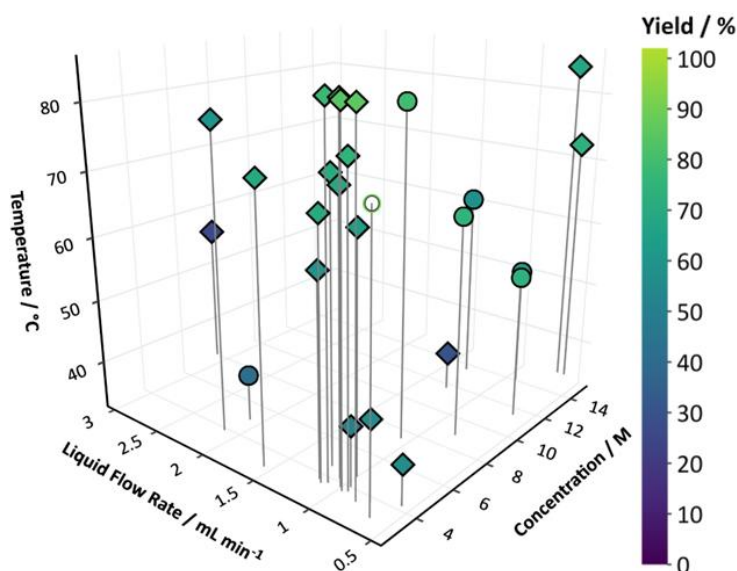


Figure 96. BOAEI optimisation results for the reduction of Nitropip, where ● – LHC experiments, ◇ – refinement experiments, and ○ – optimum conditions of the optimisation, found in experiment seven in the LHC. Fixed conditions: catalyst – 1 g, H₂ flow rate – 50 mL min⁻¹, and pressure – 20 bar.

optimisation algorithm to explore the design space more due to a poor repeatability, with many conditions across the design space being performed. When compared to BOAEI optimisations in previous chapters, where the algorithm efficiently explores the design space and found optimum conditions within a two/three refinement experiments, here it was seen that there was much more variation in the reaction conditions suggested by the algorithm. Repeat reactions were sampled offline to assess the activity of the catalyst during the optimisation and the results are shown in Figure 97. This shows that the catalyst was significantly deactivated during the optimisation, on day two and three (after experiment nine). The catalyst also continued to deactivate overnight despite the column being flushed with solvent and hydrogen for one hour in the shutdown procedure. As the catalyst could not be reactivated, an accurate self-optimisation of this system was not possible, and other options for this reaction were explored.

It has been reported that higher temperatures can be used in order to maintain catalyst stability, with Nambiar *et al.* reporting that a reactor temperature of 125 °C was required to limit deactivation in their heterogeneous hydrogenation of a nitro group.²⁵ However, heterogeneous hydrogenations can be highly exothermic, and if the reaction were to be scaled up, this may cause issues with process safety and controlling the exotherm in the reaction. Another way reported to limit deactivation of the catalyst, is

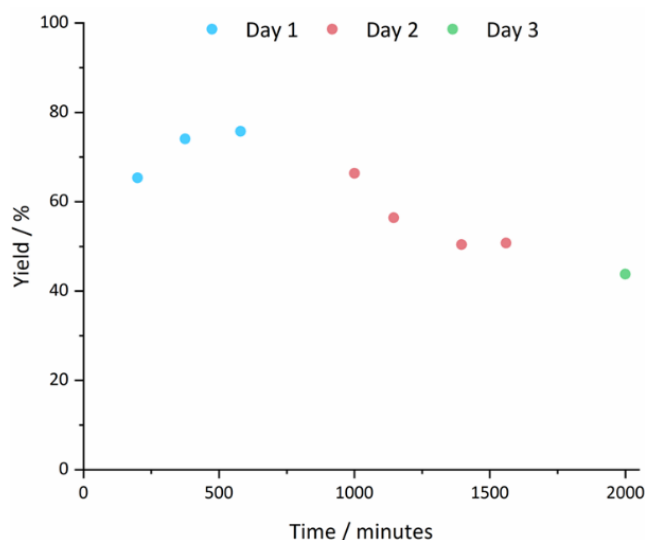


Figure 97. Repeat reactions sampled offline during the BOAEI optimisation. Repeat conditions: concentration – 0.015 M, temperature 70 °C, and liquid flow rate – 1 mL min⁻¹.

to introduce an additive to the stock reservoir of the nitro starting material.²⁶ This aims to limit permanent binding of the starting material or product to the surface of the catalyst. However, additives must be separated out of the reaction mixture at the end of the reaction, which has associated costs and solvent waste, decreasing the sustainability of the process. It could also cause problems downstream of the reactor if the reaction is part of a telescoped process, as the additives may react with other reagents in subsequent reaction steps.

As discussed in the introduction, the use of a dynamic simplex algorithm has been reported by Fabry *et al.* for monitoring changes of a design space when the input process conditions in a reaction change. This could be applied to monitor catalyst deactivation, although this was not demonstrated in the paper, as the dynamic simplex algorithm could detect small changes in the yield of a reaction (<5%) and adjust the reaction conditions to maintain the same reaction yield. Therefore, in an attempt to increase the productivity of the catalyst during permanent deactivation, and extend its operational lifetime, this method was explored.

5.3.3 Exploring catalyst loading to increase yield

From the initial self-optimisation outlined above, the optimum conditions for this reaction can be seen to lie in/near the corner of the design space that produce the

lowest throughput of product (at low concentrations, low liquid flow rates and high temperatures). Therefore, it would be beneficial to increase the yield of the reaction for the entire design space, to maximise yield and the distance from this corner for as long as possible to increase the reaction throughput. To demonstrate the use of the dynamic simplex algorithm to track catalyst deactivation over time, it was important that the design space explored was mostly 100% yielding and that the rate of deactivation was not too slow/too fast, to allow the algorithm to track the changes in the design space accurately. A DoE was used in order to assess the optimal catalyst amount which would show a design space that was mostly high yielding, to demonstrate the use of the dynamic simplex algorithm for detecting changes to the yield of the reaction in the reduction of Nitropip. The reaction conditions and results of these DoEs are summarised in 5.6.2 of the appendix.

The DoEs in Figure 98 show an increase in the yield of the reaction across the design space with an increasing catalyst mass, due to the increase in active sites available for catalysis. At the process conditions in the chosen design space, the 4.0 g

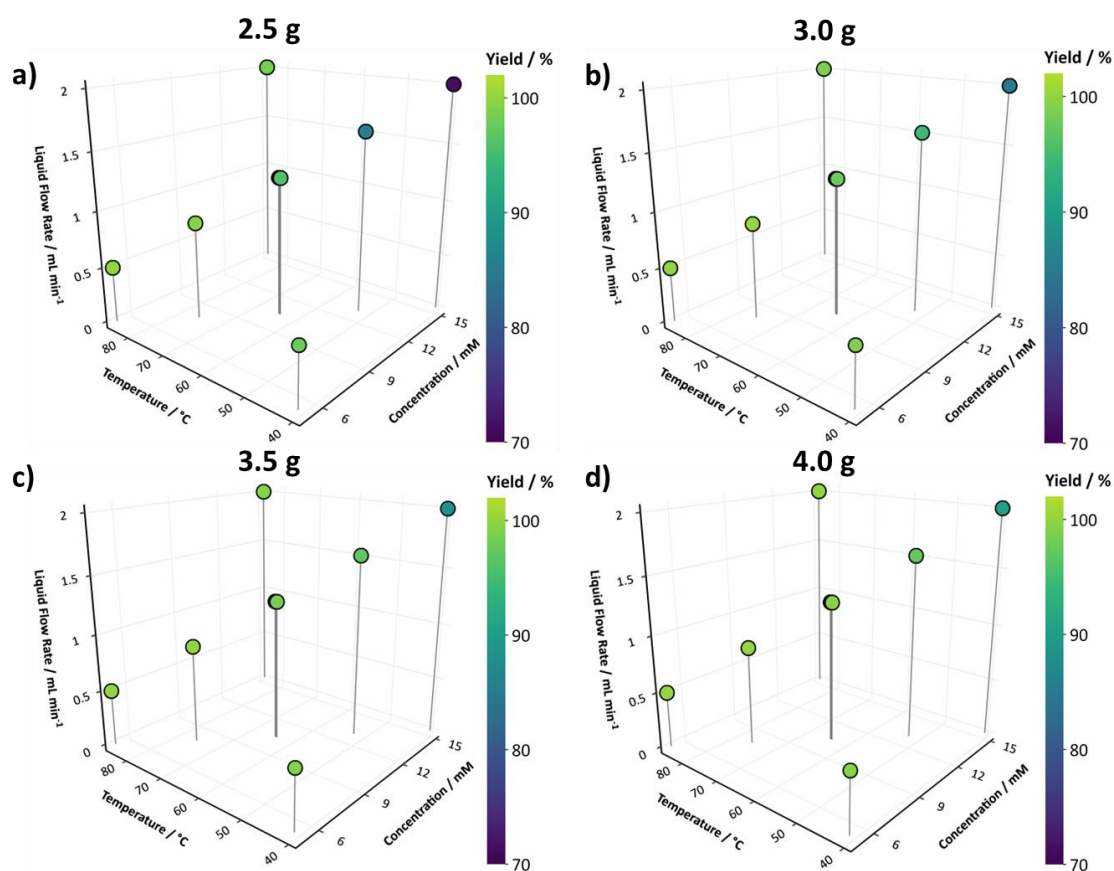


Figure 98. DoE data for the reduction of Nitropip at different catalyst loadings. **a)** 2.5 g, **b)** 3.0 g, **c)** 3.5 g, and **d)** 4.0 g. Fixed conditions: H₂ flow rate – 50 mL min⁻¹ and pressure – 20 bar.

catalyst loading would exhibit too slow of a deactivation rate to demonstrate the use of the dynamic simplex on an appropriate timescale, as all but one experiment showed yields of >97%. The 2.5 g catalyst design space shows that a yield of 100% could only be achieved at the optimal conditions in the corner of the design space. This would mean that as the catalyst deactivated, the simplex would find this area and have nowhere to explore as the yield was already below 100% at the boundaries of the design space. The DoEs for catalyst masses of 3.0 and 3.5 g showed promise with over half of the design space exhibiting high yields of greater than 99%.

To assess which catalyst amount would be best for the dynamic simplex, more tests were conducted to investigate the rate of deactivation over time from corner to corner of the design space. The rate at which the catalyst deactivated when moving towards the optimal corner was explored by performing a set of repeat experiments until the yield of the reaction was no longer 100%. For example, experiments **1, 2, 3, 1, 2, 3...** would be performed until experiment **3** was no longer 100% yielding (experiment locations shown in Figure 99a). Then experiments **2, 3, 4, 2, 3, 4...** would be performed until experiment **4** was no longer 100% yielding. This would provide information on how quickly the reaction would need to be explored by the simplex and could investigate if there was any reactivation of the catalyst at different reaction conditions in the design space (e.g. higher temperatures). Catalyst loadings of 3.0 and 3.5 g were chosen for this investigation as they seemed the most promising candidates from the initial DoE experiments. It can be seen from Figure 99b that after only one hour of use, the yield of experiment **3** had already decreased below 100% for the 3.0 g catalyst loading. When switching to experiments **2, 3**, and **4**, the yield of experiment **4** had already decreased below 100% too, showing a fast rate of deactivation at this catalyst loading. However, after performing experiment **4**, the yields of experiment **2** and **3** started to increase again, showing there was a reactivation of the catalyst with an increase in temperature. This was also seen when experiment **5** was performed. However, by day three, the higher temperatures were no longer having an impact on the yield of the reaction and the catalyst had started to deactivate again. This showed that although temporary reactivation was possible at higher temperatures, the catalyst would continue to permanently deactivate during a reaction. Figure 99c shows that with 3.5 g of the catalyst, deactivation at experiment **3** wasn't detected until day two of the reaction,

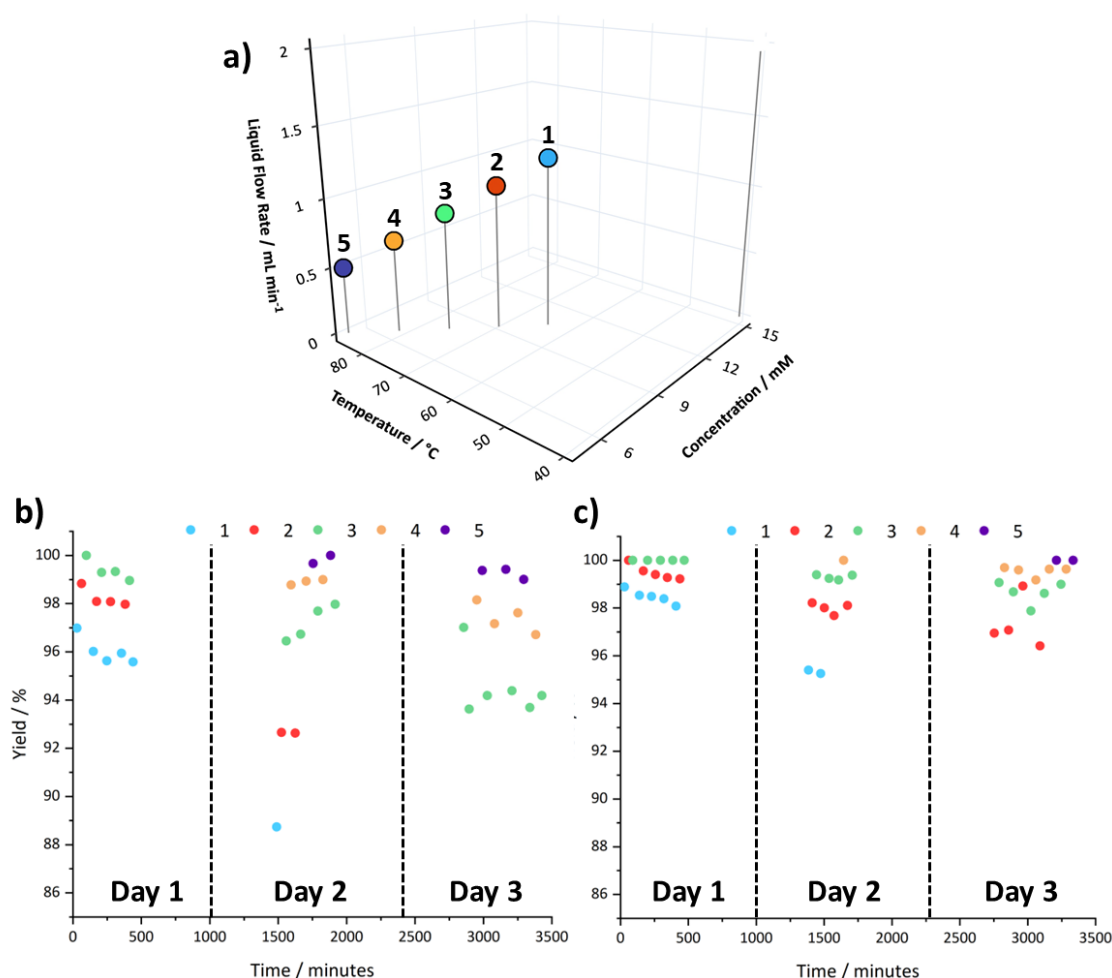


Figure 99. a) Experimental design space covered in the deactivation experiments, b) yield of the deactivation experiments over a three day operating period with 3.0 g Pd/C catalyst, and c) yield of the deactivation experiments over a three day operating period with 3.5 g Pd/C catalyst. Fixed conditions: H₂ flow rate – 50 mL min⁻¹ and pressure – 20 bar.

which was more favourable as it would mean that the simplex would have more time to investigate the design space and that more of the design space would be 100% yielding for longer, increasing the throughput of the reaction. Reactivation of the catalyst could also be seen at higher temperatures as when experiment **4** was performed there was a slight increase in the activity of the catalyst again. However, permanent deactivation at this catalyst loading was again detected, with a decrease in the yield of the reaction on day three.

The rate of deactivation of the 3.5 g catalyst was more favourable, however, in an attempt to decrease the steady state wait time of the reaction, the bounds for the liquid flow rate were increased, to decrease the residence time in the reactor. This would mean that the deactivation of the catalyst could be tracked with greater accuracy

as the steady state wait time would be smaller, meaning the reaction would be sampled more often. DoEs with the new process conditions (and a maximum steady state wait time of 24 minutes) with higher catalyst loadings were investigated (Figure 100). This showed that a 5.5 g loading of the catalyst was too high and there was very little variation in the yield of the reactions conducted in the investigated design space. With the higher liquid flow rates, 4.0 g of catalyst was seen to be a sufficient loading as most of the design space was 100% yielding, showing similar yields to the 3.5 g catalyst loading in Figure 98. Therefore, it was decided that the desired amount of catalyst to test the dynamic simplex methodology for extending the operational lifetime of the catalyst was 4.0 g with the variable bounds and conditions shown in appendix section 5.6.3.

The rate of deactivation was also tested for this reaction at the centre point of the DoE design space, and the results are shown in Figure 101. The reaction conditions were kept constant and sampled periodically to investigate the rate of decrease in the activity of the catalyst over 250 minutes of a reaction. The gradient of the line shown in the figure indicates the average decrease in the yield of the reaction and provides an estimation on how quickly the yield of the reaction would change across the entire design space. A decrease in yield of $0.0051\% \text{ min}^{-1}$ was found at the centre point conditions and was determined as a desirable rate of deactivation for the dynamic simplex testing. The rate of deactivation is slow enough that the catalyst would not deactivate too much while the algorithm was waiting for steady state and for the online analysis to be performed. However, the rate is not too slow, which would cause the

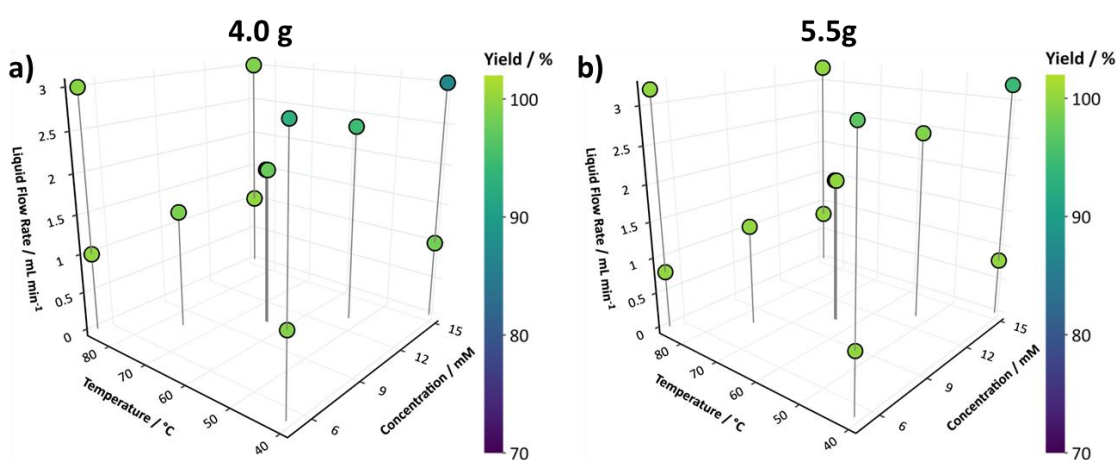


Figure 100. DoE data for the reduction of Nitropip at different catalyst loadings with higher liquid flow rates, a) 4.0 g, and b) 5.5 g. Fixed conditions: H_2 flow rate – 50 mL min^{-1} and pressure – 20 bar.

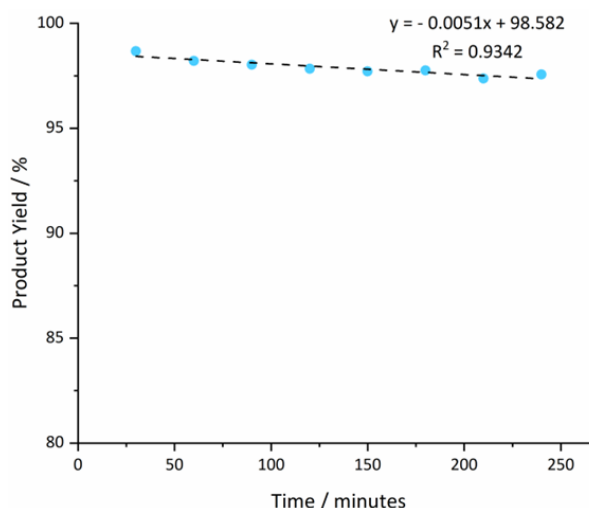


Figure 101. Deactivation profile using 4.0 g Pd/C catalyst at the centre point of the DoE in Figure 100.

deactivation to be undetectable by the algorithm and the dynamic simplex testing would take many days and use lots of resources.

5.3.4 Modelling deactivation data with 4g

To limit the unnecessary waste of reaction material and precious metal catalysts, the dynamic simplex optimisation was first investigated *in silico*. All modelling and simulation work was performed by Thomas Dixon, a PhD student at the University of Leeds. Simulated experiments would be performed in order to outline key input parameters required to perform the final dynamic simplex optimisation.

The 4.0g DoE data was fitted with a simple interactions model to visualise the entire design space, with the equation and fit of the data shown in Figure 102. The model showed a good fit for experimental data of this kind (equation 1), with a R^2 close to one and a small root mean square error (RMSE), which is a measure of how close the predicted and real data are from the linear regression. The interactions model allows interactions between variables to be observed and was a suitable model for a data set of only 14 experiments (from the DoE). Other models may have allowed better fitting of the data but would have required more laboratory experiments.

$$Yield / \% = 100.25 - 1.9C_{SM} - 0.6T - 7.4v_L + 3.1C_{SM}T - 2.7C_{SM}v_L + 8.2Tv_L \quad (1)$$

Where C_{SM} = concentration of starting material used in mol L^{-1} , T = Temperature in $^{\circ}\text{C}$, and v_L = liquid flow rate in mL min^{-1} .

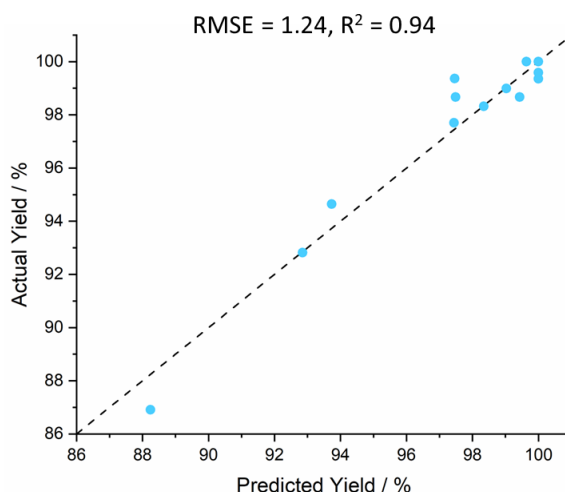


Figure 102. A comparison of the actual vs. predicted yields fitted with the interactions model, given by equation 1.

It can be seen from the relative coefficients for each variable in equation 1 that the liquid flow rate has the greatest impact on the overall yield of the reaction, with a four time larger number than the concentration term, and 12 times larger than the coefficient for temperature. The temperature and liquid flow rate interactions term also has a large positive coefficient suggesting a stronger interdependence.

To simulate how the yield of the reaction in the design space would change over time with catalyst deactivation, the gradient of the centre point deactivation data was used and it was assumed that the yield of the entire design space would decrease constantly by this value over the entire dynamic simplex experiment. This is a large assumption, as it is likely that different reaction conditions would cause different rates of deactivation. One example of these differences is that at higher temperatures, the rate of desorption from the surface of the catalyst is increased, often resulting in a slower rate of deactivation by fouling.⁴ As the simulations were used only to guide and help influence real experiments and not absolute models, this was deemed an acceptable assumption and would allow changes in the design space to be visualised over a period of time, without the need for more experiments. This has advantages in saving time for the experimentalist, reducing chemical use, and decreasing waste generation, which has both economic and environmental benefits. How the simulated design space changes over 1600 minutes is shown in Figure 103. To simulate this the DoE data was transformed, so that existing high yielding points at 100% were over extrapolated and increased in value by 10%. This would allow for a better fit for the

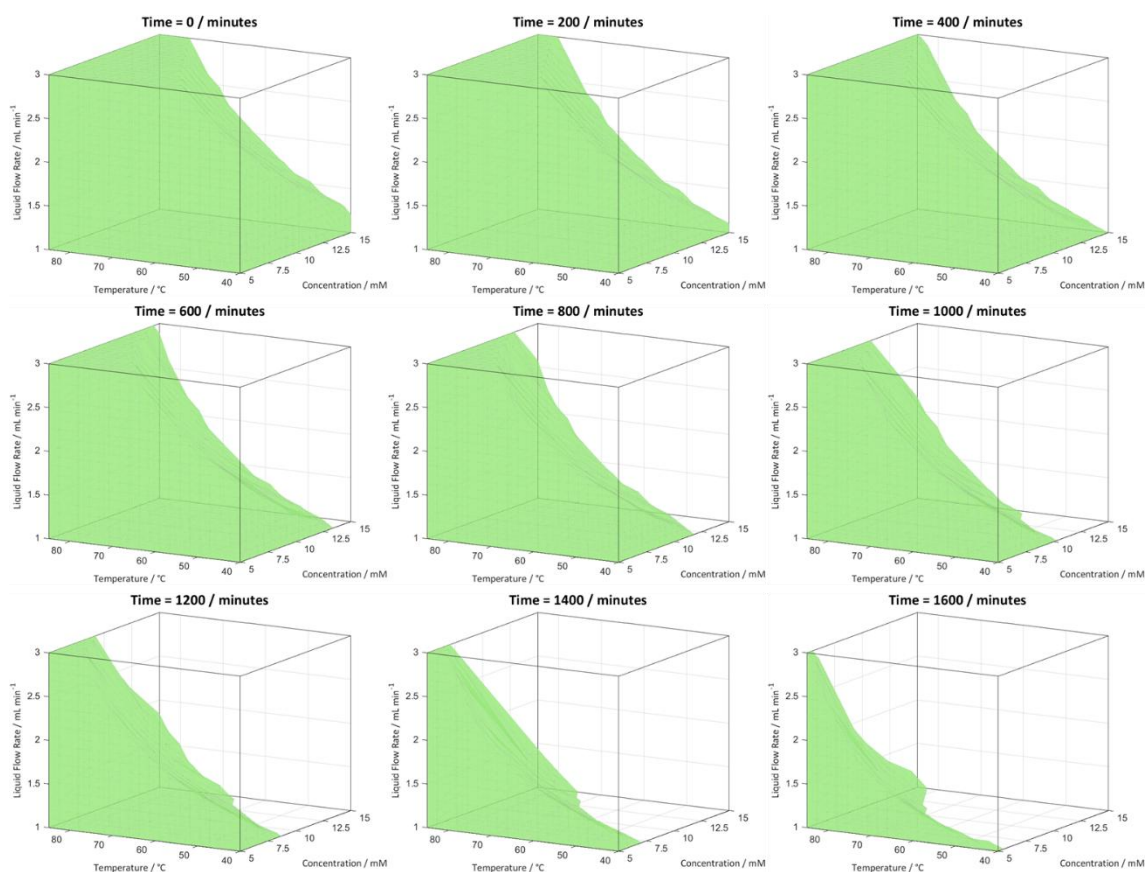


Figure 103. Modelled data for 4.0 g of catalyst with an interactions model over 1600 minutes, showing the area of the design space in green that was 100% yielding.

model and means that the yield could be subtracted from all points in the design space at the same rate but would remain above/close to 100% for a longer time period. This is because the model would remove the same value from every yield in the design space equally, however, areas that are 100% yielding would stay at those high yields for longer than the remainder of the design space. This was demonstrated to be realistic in reduction of Nitropip experiments previously, in Figure 99, where the yield closer to the optimum corner remained at 100% for multiple days, even as the catalyst deactivated. This model could then be used to simulate how the design space would change over time during the dynamic simplex optimisation and provided information on how the dynamic simplex algorithm would move through the design space as the catalyst deactivated and the reaction conditions were changed.

To demonstrate the capabilities of the dynamic simplex, the algorithm was initialised in an area of the design space that was lower yielding (with one of the vertices 10% into the design space from the corner with the best throughput conditions) to establish its ability to move towards areas with greater yields. During the dynamic

simplex, every other experiment performed is a repeat at the previously found optimum conditions, to check if there have been any changes to the yield in the design space. Starting in an area with a lower yield, with repeat reactions every other experiment, would mean that it would take much longer to identify the areas of the design space that were greater yielding and be wasteful of reactant materials. Therefore, it was decided that a basic simplex would be used initially, to explore the design space until an experiment of 98% yield was reached. Once reached, the dynamic simplex would then be initialised with the data from the basic simplex, with one of the starting simplex points being taken from the previous highest yielding experiment. This would mean that favourable conditions would be found on a smaller timescale, limiting material wastage and would also help minimise the level of human intervention needed in this adaptive optimisation.

As the optimum conditions were found to be in the corner of the design space, which exhibits the worst throughput for the reaction, it was important to remain as far away as possible from this corner, while still maintaining a high yield. Therefore, a weighted objective function (shown in equations 2 and 3) was required to maximise the normalised distance from the corner and the yield of the reaction simultaneously. However, the weightings of the two objectives would need to be investigated, to achieve an appropriate balance as to not favour one objective.

$$Response = (w_1 \cdot \log(yield)) + (w_2 \cdot Normalised Distance) \quad (2)$$

$$w_2 = 1 - w_1 \quad (3)$$

Where the response is the value read by the simplex algorithm from the analytics, w_1 and w_2 are values between 1 and 0, the yield is that of the product of the reaction, calculated from calibrations with an internal standard.

The normalised distance (between 0 and 1) is the distance of the experimental point to the corner of the design space where the optimum lies (high temperatures, low liquid flow rates and low concentrations). This distance is normalised and calculated with equation 4 and 5.

$$Distance = \sqrt{(x_{exp} - x_{opt})^2 + (y_{exp} + y_{opt})^2 + (z_{exp} + z_{opt})^2} \quad (4)$$

$$\text{Normalised Distance} = \frac{\text{Distance}}{\sqrt{3}} \quad (5)$$

A grid search, an optimisation technique that searches all possible combinations of variables, was performed to investigate how the following parameters affected the performance of the dynamic simplex adaptive optimisation:

- The size of the basic simplex.
- The size of the dynamic simplex.
- The weightings in the objective function.

A grid search was used to explore all possible values for these parameters to be used on the real reaction results from the 4.0 g Pd/C catalyst. To assess the results of the grid search, three objectives were investigated. An optimal simulated case would have a yield that remained close to 100% throughout the optimisation, the distance of the experimental point to the edge of the design space that was 100% yielding (the edge of the green area of the design spaces shown in Figure 103) would be small, and that the standard deviations of the experimental points from the edge of the design space in green would also be small. The results of the grid search could be compared and are shown in Figure 104.

When averaging these values for both the basic and dynamic simplex experimental points, Figure 104a, the average yield for all of the data points is lower than 100%, as the basic simplex is initialised in an area that has a lower yield. When only the experimental points from the dynamic simplex are investigated, Figure 104b, many points with an average yield of close to 100% could be seen as the switch to the dynamic algorithm only happens when the yield is >98%. However, many of these points were present at parameters with large simplex sizes and small weightings for w_2 , which meant that the experimental points were far apart and would explore a lot of the design space. This meant that they were therefore unable to track the deactivation closely (or track changes to the edge of the green 100% yielding area). An example of this case is demonstrated in the design space in Figure 105a and Figure 106a. As the simplex size was too large, the throughput of the reaction and the yield was affected, with 2.8 g made over the 20 hour dynamic simulation with an average yield of 99.1%. The design space in Figure 105b and Figure 106b shows a scenario where the simplex size was too small and the weighting for the normalised distance was too large. This showed that many

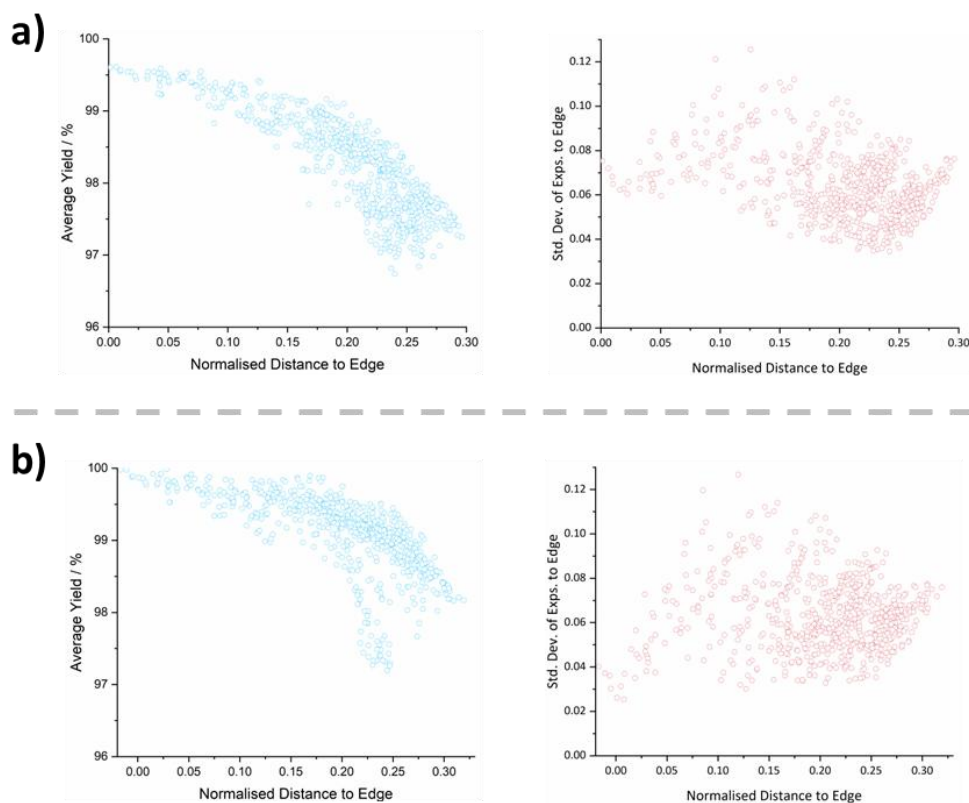


Figure 104. Grid search results showing a comparison between the average yield and normalised distance from the 100% yielding edge (blue), and a comparison of the standard deviation (std. dev.) of the points from the 100% yielding edge and the normalised distance to the edge (pink). a) accounts for all experiments in the basic and dynamic simplex experiments, and b) only accounts for the dynamic simplex experiments.

more basic simplex experiments were required at this simplex size to find the 98% yielding area of the design space, which took a simulated time of five hours. The small simplex size could not traverse quickly enough through the design space with this rate of deactivation to track the high yielding area, resulting in a lower average yield of 98% and a total mass of 3.6 g of product made over the 17 hour dynamic simplex portion of the simulation. This simulated optimisation led to a greater mass of product being produced than for the previous scenario, as the flow rate and concentrations remained higher for longer due to the small simplex size. However, the final product would contain more impurities in the form of leftover starting material as the deactivation is not followed closely (from a lower average yield). The ideal scenario found in the simulations is shown in Figure 105c and Figure 106c, where the deactivation was followed closely with a favourable simplex size for both the basic and dynamic simplex. The initial basic simplex size is large, which finds the 98% high yielding area of the design space quickly before significant deactivation of the catalyst happens. The following dynamic simplex

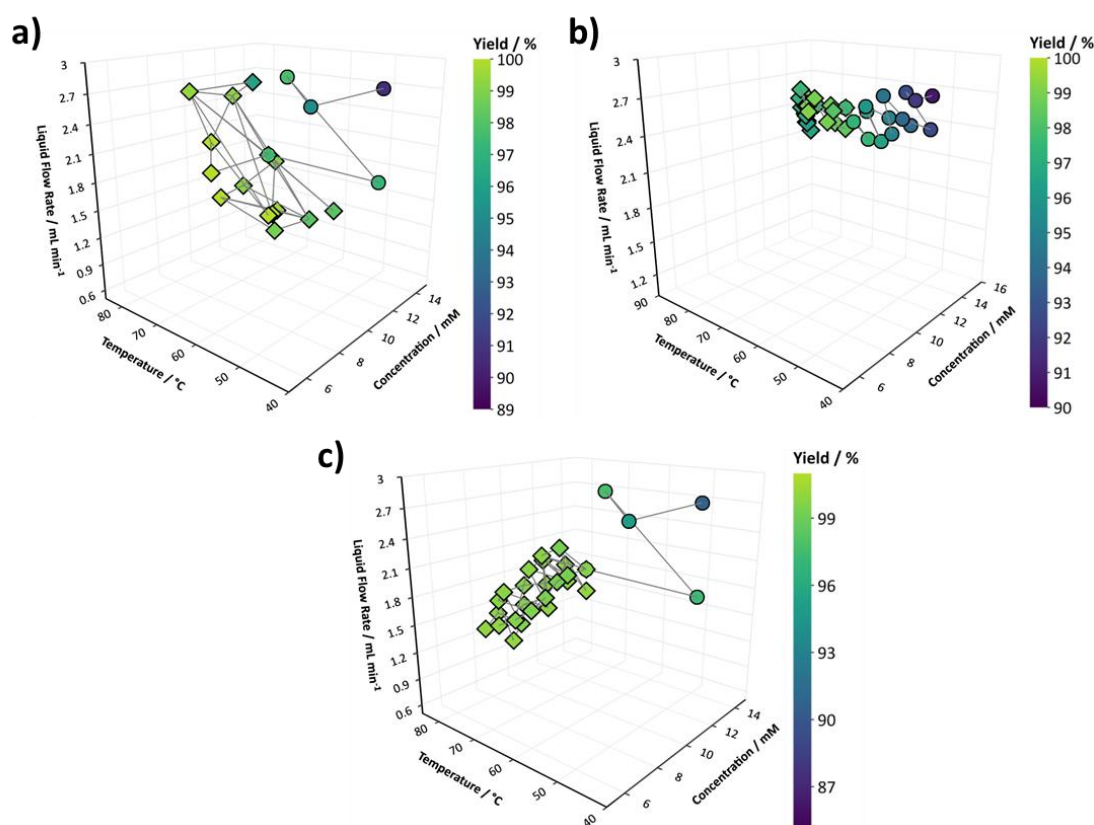


Figure 105. Design spaces covered in simulations in different scenarios, a) large simplex size, b) small simplex size, and c) ideal simplex sizes used in final simulation. Where ○ – basic simplex ◇ - dynamic simplex experiments.

size is small, which allows the edge of the high yielding area to be followed closely throughout the entire simulation. This leads to an average yield of 99.9% for the 20 hour dynamic simplex with 2.4 g of product formed. This resulted in a lower product mass than the other two scenarios shown, but the yield of the reaction achieved is greater, meaning the overall purity of the product would be improved. This is particularly important in the pharmaceutical sector where small impurities cannot be tolerated for safety standards. Therefore, the parameters found in this ‘ideal’ simulation were chosen for the final dynamic simplex experiment to be performed in the PBR platform. It would be near impossible to perform all experiments investigated here in this grid search if they hadn’t been performed *in silico*. If a smaller study was attempted experimentally, this would have likely resulted in the use of tens of grams of materials and catalysts, litres of solvent, and weeks/months of laboratory work.

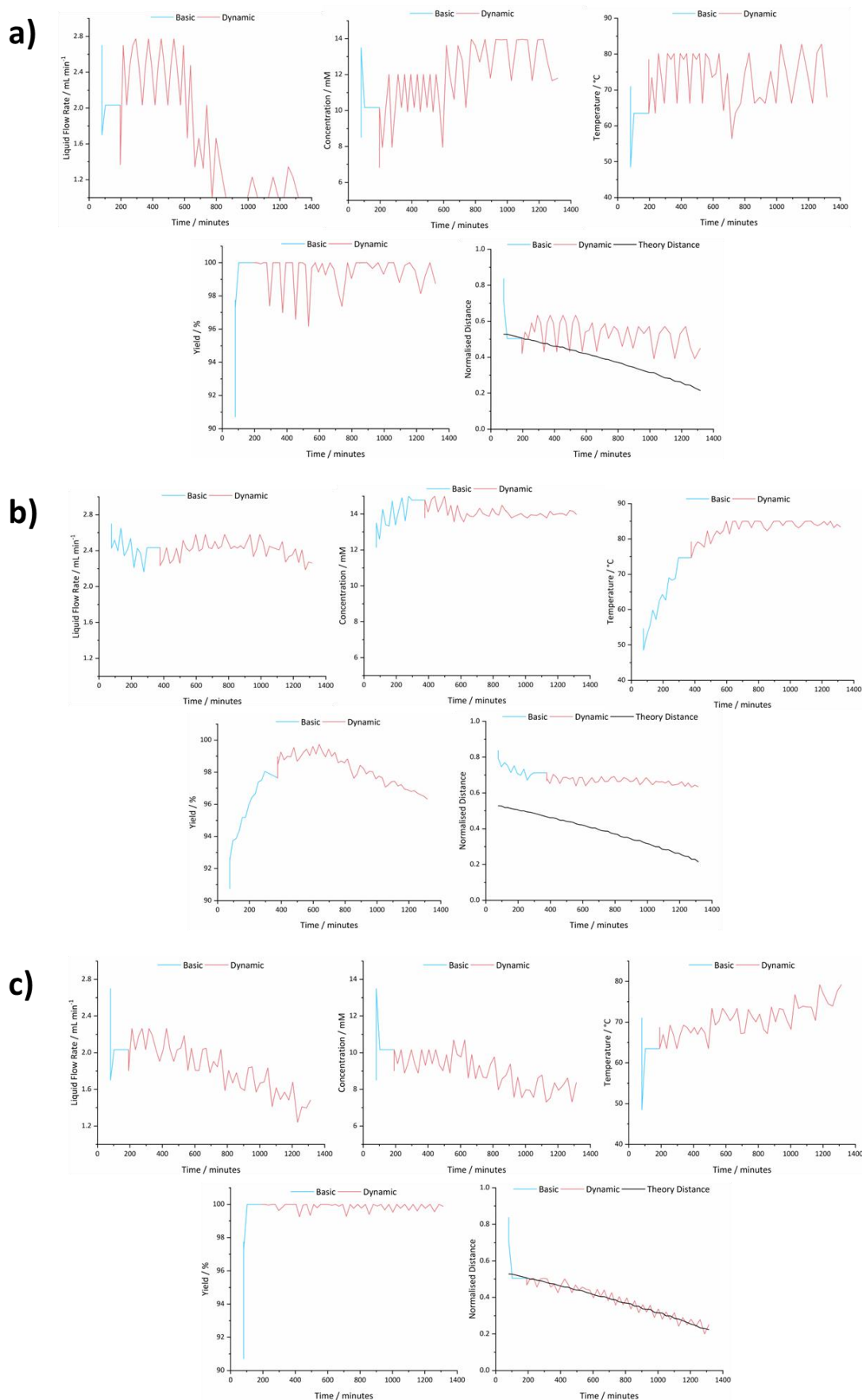


Figure 106. Changes to the variables with basic (blue) and dynamic simplexes (pink) in simulations a) large simplex sizes, b) small simplex sizes, and c) ideal simplex sizes that were use in the final real life testing.

5.3.5 Dynamic Simplex

With both simplex sizes and weightings for the objective function determined from *in silico* simulations, the final dynamic simplex adaptive optimisation could be performed. Due to the low concentrations of this reaction, from solubility limits in ethanol, the reaction was sampled offline at steady state (after eight residence times) and analysed by GC, as the online HPLC peaks, even with the largest 500 nL Vici sampling valve size, were too small for accurate yield measurements. The GC samples were analysed manually and the resulting yield of the reaction was inputted into the algorithm, which would then suggest the next experimental condition and change pump flow rates and the temperature of the reactor autonomously. The total reaction time investigated was 31 hours, with 50 experiments performed in both the basic and dynamic simplex. The results of the dynamic simplex adaptive optimisation are shown in Figure 107, which appears to be very similar to the previous 'ideal' simulation shown in Figure 105c. This shows that the simulations and modelling of the design space were sufficiently accurate and could describe the design space well to influence the real life experiments. However, the yield of the reaction found here was lower than that was seen in the 'ideal' scenario simulation (shown in Figure 108). This may have been due to the difference in the rate of deactivation of the catalyst in different areas of the design space (at different reaction conditions). In the simulated experiments, the rate of

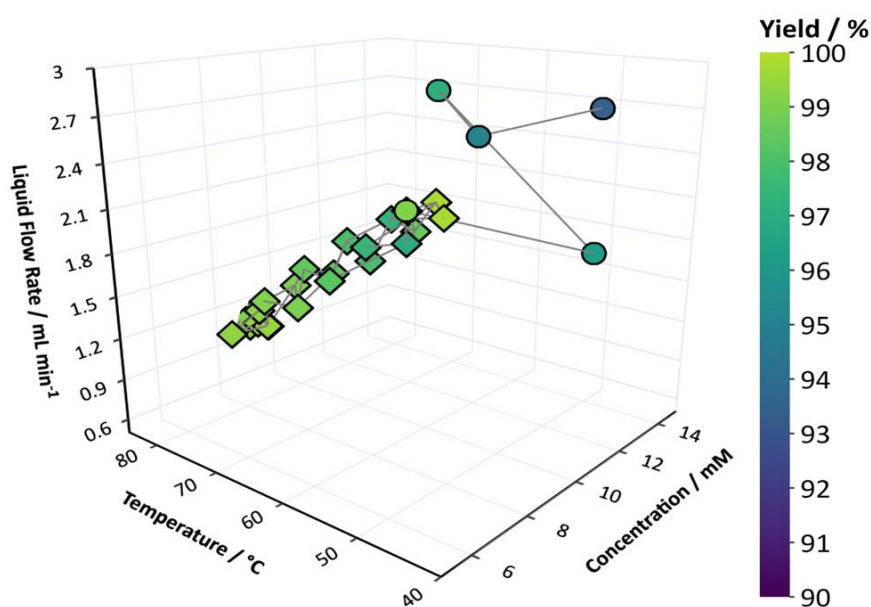


Figure 107. The resulting design space for final dynamic simplex adaptive optimisation with 4.0 g catalyst over 31 hours. Where ○ – basic simplex ◇ - dynamic simplex experiments. Fixed conditions: catalyst – 4.0g, H₂ flow rate – 50 mL min⁻¹, and pressure – 20 bar.

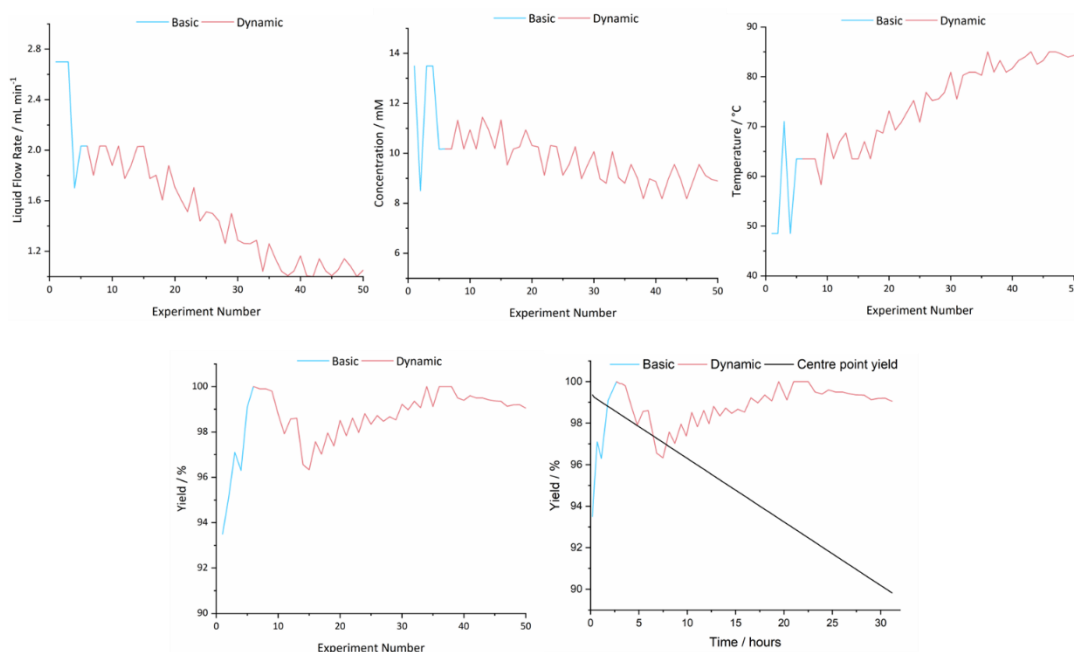


Figure 108. Changes made to the variables in the real reaction during the basic (blue) and dynamic (pink) simplex optimisations over time (top three graphs). A comparison of the centre point yield with linear deactivation and the real yield of the dynamic simplex is shown in the bottom right graph.

deactivation was modelled from data taken only at the centre point in the design space. However, in the real dynamic simplex adaptive optimisation, the deactivation rate would be affected by a range of reaction conditions in the different areas of the design space that the catalyst was subjected to.

Figure 108 shows a comparison of the yield of the dynamic simplex experiments compared to the linear deactivation seen at the centre point in the design space. This shows that there would be a 10% decrease in the yield of the reaction if the reaction conditions remained unchanged over the 31 hour experiment (at the centre point). When using the dynamic simplex algorithm, the average yield of the reaction is much higher, meaning a greater purity in the resulting product solution. If the conditions remained unchanged for 31 hours (in the centre of the design space) it was calculated that 3.3 g of product could be made (with a 94% average yield). 2.5 g of the product could be made in the dynamic simplex adaptive optimisation (with a 99% average yield). This is due to the simplex algorithm decreasing the liquid flow rate and concentration of starting material during the optimisation to maintain a higher output yield over the 31 hours. Although the centre of the design space could produce more product, the resulting solution was less pure, decreasing its quality. If the reaction conditions were held in the optimal corner of the design space throughout the 31 hour experiment, the

product yield would be 100%, but would only produce 0.9 g of product, which is a significant decrease. When scaled up, this would have an even greater effect on the overall process throughput. Due to the low solubility of the reagents in the solvent for this reaction, a maximum concentration of 0.015 M was investigated in this work. In an ideal process, a more concentrated solution would be used to increase the throughput of the reaction to a kg day^{-1} scale, which would make this reaction more pharmaceutically relevant. Further work into the deactivation mechanism of the catalyst during the reaction would be beneficial to aid limiting deactivation of the catalyst, but this was not within the scope of this project. Overall, using the dynamic simplex optimisation, a higher average purity and yield of product could be produced when compared to keeping the conditions the same throughout the operating period.

Other catalytic reactions and protocols could be investigated using this methodology for exploring deactivation. An extension of this work could be to introduce additional columns packed with catalyst. When the deactivation of the catalyst causes the throughput or yield of the reaction to fall below a pre-defined threshold, the catalyst bed could be exchanged for a fresh one and the dynamic optimisation could continue. This would demonstrate the applicability of this method for long process times and show what could be achieved on plant in a real process.

Another interesting problem that could be investigated would be the production of side products at different process conditions, which lead to deactivation of the catalyst. A typical multi-objective approach to optimise both the maximisation of the yield and minimisation of the side product formation would likely not be achievable if there was catalyst deactivation at different reaction conditions. Different reaction conditions can lead to a change in the amount of impurities or byproducts that are made during a reaction. If these side products cause deactivation of the catalyst via poisoning, it would be beneficial to investigate the boundary at which the side products are made and how the impurities change the rate of deactivation of the catalyst.²⁷

5.4 Conclusion

In this chapter, an investigation into catalyst deactivation was reported. Initial studies into the optimisation for the reduction of Nitropip were conducted, finding the

optimum conditions for the reaction could not be determined due to significant deactivation of the catalyst. A method to limit the effect of deactivation was proposed as an alternative to the use of additives or higher temperatures and was applied to this reaction. Initial catalyst studies were performed to define the appropriate mass of catalyst that should be used to test the proposed approach. Using real experimental data, modelling and simulations of the reaction were performed to limit reactant and catalyst waste. A final dynamic simplex adaptive optimisation was shown to monitor and adjust the reaction conditions to account for catalyst deactivation. With the proposed method, a higher yield was achieved over a 31 hour operating period, showing significant advantages over a system that maintains the same reaction conditions throughout.

5.5 Experimental

5.5.1 Chemicals

1-(4-Nitrophenyl)piperazine (97%, Fluorochem), 4-(1-piperazinyl)aniline (97%, Thermo scientific), biphenyl (99.5%, Sigma Aldrich), ethanol (>99.8%, Sigma Aldrich) hydrogen gas (99.99% BOC Gas), nitrogen gas (99.998%, BOC Gas) and extrudate Pd/carbon pellets (product code:113784, 1 wt.% Pd, JM) were purchased from suppliers and used without further purification.

5.5.2 PBR platform

The platform, typical procedure and column packing used for all reactions was the same as reported in Chapter 2. Samples were taken and analysed offline by an Agilent Technologies 7890B GC-FID system fitted with a HP-5 column, with a temperature range of -60 – 325 °C, 30 m in length, a diameter 0.32 m, and a film thickness 0.25 µm. The same GC method was used as described in Chapter 2.

Example GC chromatogram

Samples taken were diluted down to an appropriate concentration (1 mg mL⁻¹) with ethanol and analysed by GC.

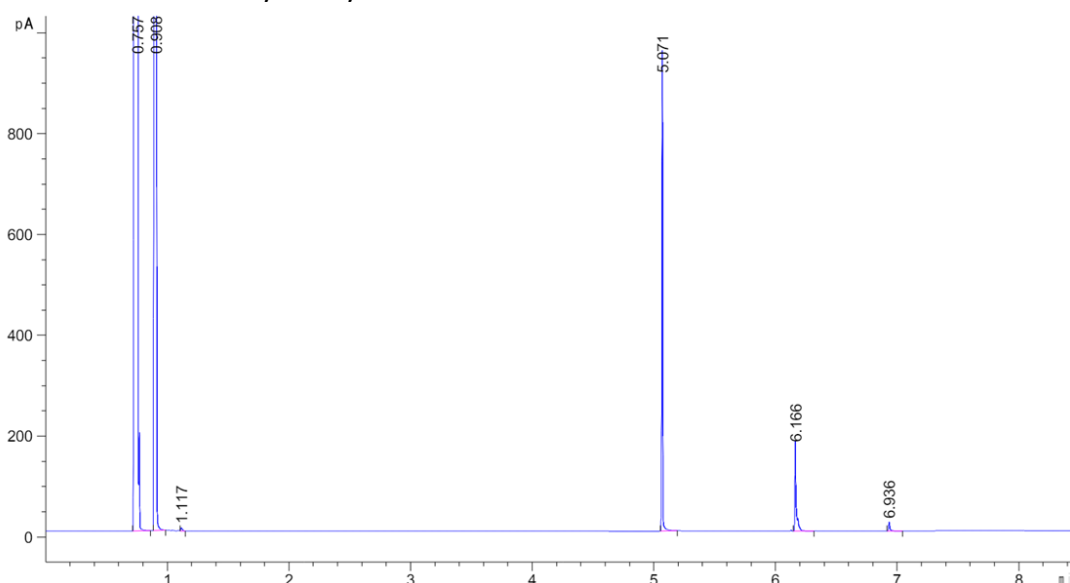


Figure 109. Example GC chromatogram for the reduction of Nitropip.

Table 35. Assignment for example GC in Figure 109 for the internal standard (IS), product (P) and starting material (SM).

Peak / min	Assignment
0.75-1.1	Solvent (ethanol)
5.071	Biphenyl (IS)
6.166	4-(1-piperazinyl)aniline (P)
6.936	Nitropip (SM)

5.6 Appendix

5.6.1 BOAEI optimisation data

Table 36. Optimisation data for Nitropip reduction with BOAEI algorithm.

Exp. No.	Exp. Type	Variables			Flow Rate / mL min ⁻¹		Objective
		Liq. Flow Rate / mL min ⁻¹	Temp. / °C	Conc. / mM	Nitro. Pip.	EtOH	Yield / %
1	Initial	0.73	66.80	8.34	0.406	0.324	75.14
2	Initial	2.00	41.26	4.52	0.603	1.396	41.00
3	Initial	0.85	52.47	13.41	0.758	0.090	62.59
4	Initial	1.25	63.15	12.91	1.072	0.174	57.64
5	Initial	0.57	55.90	10.89	0.412	0.156	73.37
6	Initial	1.00	82.32	6.95	0.461	0.534	79.54
7	Initial	0.58	74.35	2.67	0.103	0.475	89.77
8	Refinement	0.59	72.21	15.00	0.594	0.000	73.07
9	Refinement	1.19	40.00	11.07	0.878	0.308	29.99
10	Refinement	1.48	74.24	2.65	0.266	1.210	69.11
11	Refinement	0.50	40.00	3.77	0.127	0.375	56.63
12	Refinement	1.13	74.91	4.10	0.309	0.822	70.43
13	Refinement	0.89	84.76	3.21	0.191	0.702	84.20
14	Refinement	2.03	79.54	3.43	0.460	1.570	59.45
15	Refinement	3.01	56.00	7.48	1.504	1.504	25.42
16	Refinement	0.88	42.92	3.56	0.211	0.668	51.45

17	Refinement	1.06	70.93	3.13	0.218	0.838	69.96
18	Refinement	0.68	45.83	3.31	0.150	0.530	56.55
19	Refinement	0.93	84.94	3.35	0.210	0.718	82.52
20	Refinement	1.09	63.37	3.27	0.241	0.853	59.74
21	Refinement	0.99	74.14	3.70	0.245	0.749	68.87
22	Refinement	0.86	78.35	3.32	0.189	0.671	74.44
23	Refinement	1.02	84.95	3.28	0.225	0.798	77.52
24	Refinement	0.75	84.97	3.04	0.150	0.600	85.35
25	Refinement	0.92	68.71	4.13	0.255	0.670	64.59
26	Refinement	0.65	83.81	15.00	0.652	0.000	67.82

5.6.2 DoE data – Different weights of 1 wt.% Pd/C catalyst

Table 37. Experimental conditions and results for DoE of Nitropip reduction with different amounts of catalyst.

Exp. No.	Variables			Flow Rate / mL min ⁻¹		Yield with different catalyst loadings / %			
	Liq. Flow Rate / mL min ⁻¹	Temp. / °C	Conc. / mM	Nitro. Pip.	EtOH	2.5 g	3.0 g	3.5 g	4.0 g
1	2.000	40.0	15.0	2.000	0.000	71.39	84.66	88.33	90.60
2	1.625	51.3	12.5	1.354	0.271	85.32	94.51	96.93	97.26
3	1.250	62.5	10.0	0.833	0.417	94.52	99.15	99.32	100.00
4	0.875	73.8	7.5	0.438	0.438	99.30	100.00	100.00	100.00
5	0.500	85.0	5.0	0.167	0.333	100.00	100.00	100.00	100.00
6	1.250	62.7	10.0	0.833	0.417	95.19	98.09	98.48	100.00
7	0.500	40.0	5.0	0.167	0.333	97.63	98.99	99.08	99.47
8	2.000	85.0	15.0	2.000	0.000	98.50	98.84	99.47	100.00
9	1.250	62.3	10.0	0.833	0.417	96.02	97.74	98.53	99.42

5.6.3 DoE data – Shorter residence times with 4.0 and 5.5 g 1wt.% Pd/C catalyst

Table 38. Experimental conditions and results for DoE of Nitropip reduction with shorter residence times.

Exp. No.	Variables			Flow Rate / mL min ⁻¹		Yield with diff. catalyst loadings / %	
	Liq. Flow Rate / mL min ⁻¹	Temp. / °C	Conc. / mM	Nitro. Pip.	EtOH	4.0 g	5.5 g
1	40.0	15.0	3.000	3.000	0.000	86.91	94.48
2	40.0	5.0	3.000	1.000	2.000	92.82	96.72
3	40.0	15.0	1.000	1.000	0.000	98.32	100.00
4	40.0	5.0	1.000	0.333	0.667	99.36	100.00
5	62.5	10.0	2.000	1.333	0.667	99.36	100.00
6	51.3	12.5	2.500	2.083	0.417	94.64	99.10
7	73.8	7.5	1.500	0.750	0.750	98.67	100.00
8	62.5	10.0	2.000	1.333	0.667	98.67	100.00
9	85.0	5.0	1.000	0.333	0.667	100.00	100.00
10	85.0	15.0	3.000	3.000	0.000	98.99	100.00
11	62.5	10.0	2.000	1.333	0.667	97.70	100.00
12	85.0	5.0	3.000	1.000	2.000	99.59	100.00
13	85.0	15.0	1.000	1.000	0.000	100.00	100.00
14	62.5	10.0	2.000	1.333	0.667	97.71	100.00

5.6.4 Dynamic simplex optimisation

Table 39. Experimental data and conditions used in the final dynamic simplex adaptive optimisation with 4.0 g of catalyst.

Exp. No.	Simplex Type	Variables			Flow Rate / mL min ⁻¹		Objective
		Liq. Flow Rate / mL min ⁻¹	Temp. / °C	Conc. / mM	Nitro. Pip.	EtOH	Yield / %
1	Basic	2.700	48.5	13.5	2.430	0.270	93.50
2	Basic	2.700	48.5	8.5	1.530	1.170	95.10
3	Basic	2.700	71.0	13.5	2.430	0.270	97.10
4	Basic	1.700	48.5	13.5	1.530	0.170	96.30
5	Basic	2.033	63.5	10.2	1.378	0.655	99.10
6	Dynamic	2.033	63.5	10.2	1.378	0.655	100.00
7	Dynamic	1.802	63.5	10.2	1.222	0.580	99.90
8	Dynamic	2.033	63.5	11.3	1.535	0.498	99.90
9	Dynamic	2.033	58.3	10.2	1.378	0.655	99.80
10	Dynamic	1.879	68.7	10.9	1.370	0.509	98.79
11	Dynamic	2.033	63.5	10.2	1.378	0.655	97.92
12	Dynamic	1.777	67.0	11.5	1.356	0.420	98.57
13	Dynamic	1.879	68.7	10.9	1.370	0.509	98.61
14	Dynamic	2.029	63.5	10.2	1.378	0.650	96.56
15	Dynamic	2.031	63.5	11.3	1.535	0.496	96.33
16	Dynamic	1.777	67.0	9.5	1.129	0.648	97.58
17	Dynamic	1.802	63.5	10.2	1.222	0.580	97.02
18	Dynamic	1.605	69.3	10.3	1.097	0.508	97.96
19	Dynamic	1.879	68.7	10.9	1.370	0.509	97.38

20	Dynamic	1.705	73.1	10.3	1.172	0.533	98.52
21	Dynamic	1.606	69.3	10.3	1.098	0.508	97.83
22	Dynamic	1.513	70.9	9.1	0.920	0.592	98.61
23	Dynamic	1.705	73.1	10.3	1.172	0.533	97.97
24	Dynamic	1.439	75.2	10.3	0.985	0.454	98.81
25	Dynamic	1.513	70.9	9.1	0.920	0.592	98.34
26	Dynamic	1.499	76.9	9.5	0.954	0.545	98.72
27	Dynamic	1.439	75.2	10.3	0.985	0.454	98.47
28	Dynamic	1.262	75.5	9.0	0.756	0.506	98.67
29	Dynamic	1.499	76.9	9.5	0.954	0.545	98.53
30	Dynamic	1.288	80.9	10.1	0.864	0.423	99.22
31	Dynamic	1.262	75.5	9.0	0.756	0.506	98.97
32	Dynamic	1.260	80.3	8.8	0.739	0.521	99.36
33	Dynamic	1.288	80.9	10.1	0.864	0.423	99.07
34	Dynamic	1.041	80.9	9.0	0.626	0.415	100.00
35	Dynamic	1.260	80.3	8.8	0.739	0.521	99.12
36	Dynamic	1.141	85.0	9.6	0.727	0.414	100.00
37	Dynamic	1.041	80.9	9.0	0.626	0.415	100.00
38	Dynamic	1.007	83.3	8.2	0.549	0.458	100.00
39	Dynamic	1.045	80.9	9.0	0.626	0.419	99.50
40	Dynamic	1.163	81.7	8.9	0.688	0.475	99.40
41	Dynamic	1.007	83.3	8.2	0.549	0.458	99.60
42	Dynamic	1.000	83.9	9.0	0.597	0.403	99.50
43	Dynamic	1.141	85.0	9.6	0.727	0.414	99.50
44	Dynamic	1.045	82.5	9.0	0.624	0.421	99.42

45	Dynamic	1.007	83.3	8.2	0.549	0.458	99.36
46	Dynamic	1.052	85.0	8.9	0.622	0.430	99.35
47	Dynamic	1.141	85.0	9.6	0.727	0.414	99.13
48	Dynamic	1.080	84.5	9.1	0.656	0.424	99.19
49	Dynamic	1.000	83.9	9.0	0.597	0.403	99.20
50	Dynamic	1.050	84.3	8.9	0.622	0.427	99.05

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Chapter 6 : Catalyst Formulation and Screening Platform Development

6.1 Introduction

The development of novel, active, stable catalysts is imperative to this growing area of research, which has led to the enhancement of new and existing processes, with the aim to maximise yields, minimise waste, and use fewer raw materials.¹ Most of the applied catalysis that is performed industrially, homo- and heterogeneous, uses precious metals due to their activity and selectivity for key reaction steps.^{2,3} In heterogeneous catalysis, these metal catalysts are immobilised on a support which enhances the stability and recyclability of the catalyst. It allows the catalysts to be separated easily, avoiding lengthy and costly recycling procedures that are usually required to separate homogeneous catalysts from the final reaction mixture. This is particularly important in the pharmaceutical sector, where the purity of the final API is of the utmost importance, due to the strict safety regulations required to keep patients safe.

The transfer of catalysts from batch to continuous flow systems can be challenging and is known to cause significant problems, including metal leaching and crushing of the catalyst support at high pressures, leading to blockages, reducing the processes efficiency. Therefore catalysts need to be immobilised on an appropriate effective support to benefit fully from the transfer to continuous flow. Successful support materials have large active surface areas, and maintain chemical and physical stability, while limiting the pressure drop across the reactor bed.

6.1.1 Carbon based supports

Carbon is a common catalyst and support material used in heterogeneous catalysis due to its versatility.⁴ It possesses properties such as chemical inertness towards side reactions, high electrical conductivity, and the ability for the user to easily modify factors such as porosity and surface area, meaning the shape of the catalyst can be optimised for specific process requirements.^{5,6} Common forms of carbon that are used as supports for catalysts include graphite, glassy carbon, fullerenes, carbon nanofibers, polymer-based carbon, and activated carbon (AC).⁷ These materials can come in many

different forms depending on the chemical application (e.g. pellets, powders, beads, and fibres).^{8,9} Larger catalyst supports lead to lower pressure drops across PBRs, but often have smaller surface area to volume ratios and can cause inhomogeneity in the flow path of reagents through a catalyst bed, decreasing the efficiency of the catalyst. However, smaller supports such as powders can have detrimental effects to flow systems as they can compress under high pressures, causing blockages and large pressure drops.¹⁰ Pressure drops in PBRs at different flow regimes were modelled by Hickman *et al.* in 2016, and the group suggested a guideline of a maximum pressure drop of 20% of the reactor inlet pressure was acceptable for successful operation.¹¹

6.1.1.1 Carbon pellets, fibres, and powders

Commercial carbon-support based catalysts formed by extrusion and pelleting produces (carbon pellets and granules) are uniform in size and have a high mechanical strengths (Figure 110).¹² JM,¹³ Evonik,¹⁴ and Strem Chemicals^{15,16} are among many companies that produce a wide range of carbon-supported transition metal catalysts. AC is a common powdered catalyst which has been used as both a catalyst and a support, often to remove toxic gases and metals from gas or liquid mixtures, making it highly important in the environmental and sustainability sector.¹⁷ AC has been traditionally made from the carbonization (at temperatures <800 °C) and activation (950-1000 °C) of

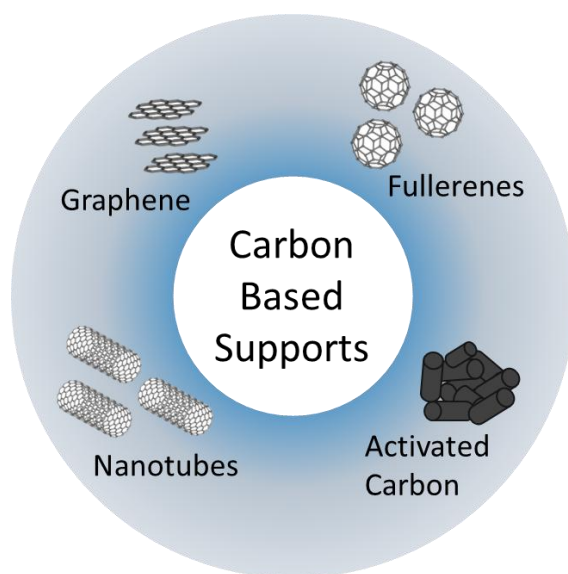


Figure 110. Different carbon based support types including CNTs, graphene, fullerenes, and activated carbon pellets.

naturally occurring products such as coconut shells, wood, and coal. However, due to the variance in the quality of these starting materials, the properties such as pore size and structure can be inconsistent and cause poor reproducibility.¹⁸ Aumo *et al.* reported AC as a Pt-support for hydrogenation reactions, where it was compared to a Pt supported woven active carbon cloth for the hydrogenation of citral.¹⁹ It was shown that the powdered AC catalyst had a productivity of over ten times that of the woven catalyst, due to the advantage of having a large active surface area. However, it creates a significant pressure drop across PBRs, making it unfeasible for use in continuous flow, particularly in pilot scale reactions where the pressure drop is intensified.¹⁰

Many groups have researched the use of different carbon supports, including graphitised nanofibers (GNFs) and carbon nanotubes (CNTs) due to their highly active surface area, improving their activity and selectivities in many reactions.²⁰⁻²⁴ Amorim *et al.* investigated the structural and chemical differences between palladium nanoparticles (PdNPs) deposited on AC, graphite, and GNFs, with their findings summarised in Table 40.²⁵ Transmission electron microscopy (TEM) showed the PdNPs/AC had a 'globular' structure which indicated little particle-support interactions, while the PdNPs deposited on the GNFs were more 'evenly' distributed in a thin coating on the support surface, indicating a strong metal-support interaction. This is an important parameter to consider when making heterogeneous catalysts, as they must be stable for extended periods of operation. In this work the group showed the efficiency of GNFs as a catalyst support over other carbons based materials, reporting no metal leaching from the three supports (during testing in the hydrodechlorination of chlorobenzene) despite their structural differences. However, their particle size means

Table 40. Summary of the chemical and physical properties of the three catalysts, Pd/AC, Pd/Graphite and Pd/GNFs reported by Amorim *et al.*²⁵

Property	Pd/AC	Pd/Graphite	Pd/GNF
BET Surface Area / m ² g ⁻¹	875	11	74
Total Pore Volume / cm ³ g ⁻¹	0.47	0.04	0.08
Average Pore Radius / nm	3.2	9.2	4.8
Pd Content / wt. %	7.8	8.5	8.7
H ₂ Uptake / cm ³ g _{Pd} ⁻¹	1.0	2.2	1.7
Average Pd Diameter from XRD Line Broadening / nm	20	25	23
Number Average Pd Diameter from TEM Analysis / nm	10	8	13

that they are an unsuitable support to be used alone for continuous flow operations.

Producing the optimal size and shape of the catalyst support is essential, as the ratio between particle size and the internal column diameter of a reactor largely affects reactions and their associated pressure drop.¹¹

6.1.1.2 Spherical carbon beads

Spherical carbon beads possess high surface areas due to the presence of internal pore structures within the larger particle size and have also been shown to have high mechanical strengths. This is another essential property for catalysts used in PBRs, to avoid crushing of the support and the blockage of filters, which leads to over pressurisation of the system.¹⁸ Spherical activated carbon (SAC) can be formed from precursors such as, pitch, carbohydrate, phenolic resins and sulphonated polystyrene resins.¹⁷ Yang *et al.* described the synthesis of carbon spheres by a one-step hydrothermal carbonization of glucose.²⁶ The process involves heating glucose in deionised water with a metal chloride such as NaCl, MgCl₂ or FeCl₂ for four hours at 180 °C. Yang *et al.* noted that increasing the reaction time gave an increase in the size of the spheres from the nanoscale to the microscale. By changing the metal salt that was used in the process, the size of the carbon spheres could also be adjusted. It was found that a larger atomic radius of the metal ion promoted the growth process of the carbon sphere and also made the spheres more uniform in size, with FeCl₃ producing the largest

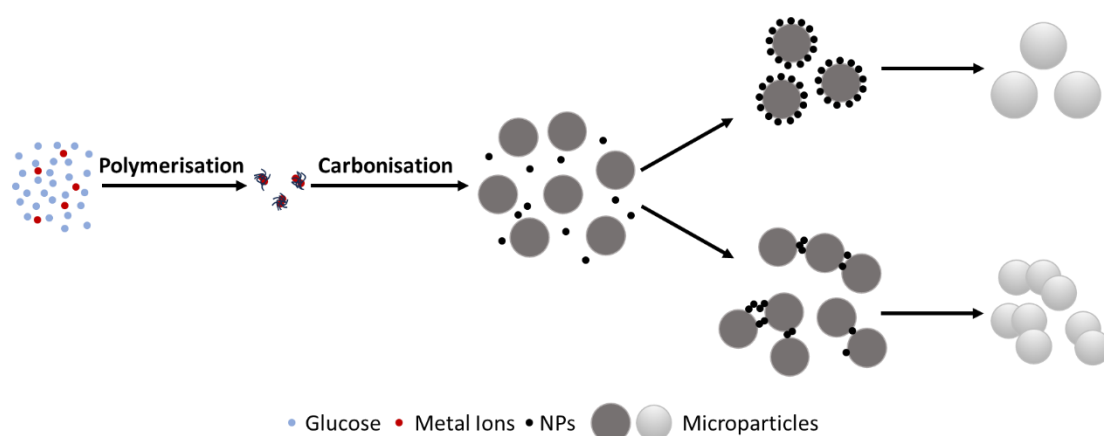


Figure 111. The growth mechanism suggested for the formation of spherical carbon spheres produced from a one-pot hydrothermal carbonisation of glucose by Yang *et al.*²⁶

and most uniform particles. The group suggested a growth mechanism, shown in Figure

111, where the metal ions interacted with the glucose catalytically through electrostatic or chelating forces. This helped to increase the reaction speed and facilitate the polymerisation of the glucose to form a colloid/aggregate which would then grow and form microparticles. Uniformity in catalyst size is beneficial in PBRs as it allows for more consistent packing of the columns, which affects the flow path inside the reactor, aiding the reproducibility of reactions.²⁷

Polymer-based spherical activated carbon (PBSAC) beads are derived from well-defined polymer precursors, alleviating issues in the variation in the support's pores and shapes. An internal pore structure is established during the carbonisation stage of their synthesis and can be extended into the activation stage. Blucher GmbH have produced commercially available SARATECH PBSAC that have a high mechanical strength, high purity, and a narrow and well-defined particle size distribution, with customisable pore sizes (micro, meso, macro).²⁸ Their performance in a continuous flow system has been demonstrated by GSK to assess their suitability to be used in both lab and pilot scale reactions. Their physical properties, including their mechanical strength, particle size distribution, activity, and the stability of the catalyst in both batch and flow reactions were tested (Figure 112).¹⁰

GSK pre-defined the minimum performance features they would accept from the catalysts before taking them forward for scale up in a pilot-plant trickle bed reactor. One feature stated that the maximum pressure drop allowed by each catalyst particle was 5 bar at a flow rate of 10 mL min⁻¹. In all four catalysts tested, a pressure drop of less than

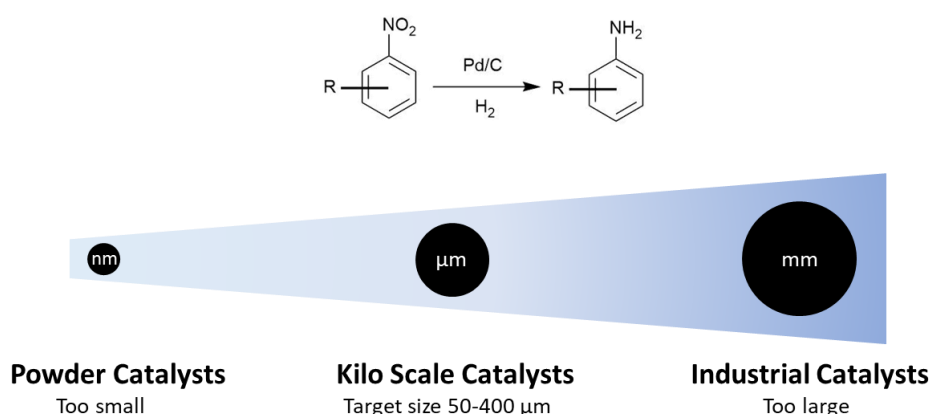


Figure 112. Scheme for nitro reductions commonly used in pharmaceutical synthesis and images showing the ideal particle size of SARATECH PBSAC catalyst for kilo scale applications.¹⁰

2 bar was recorded at this flow rate, the lowest occurring with the largest support size

of 200 μm with 5% Pd loading. The catalysts were also tested in batch and in flow in model reduction reactions of nitro compounds, such as the reduction of 1-methoxy-4-nitrobenzene, to assess their catalytic activity. The extent of deactivation was investigated for this reaction and GSK found that there was minimal or no catalyst deactivation at the optimum reactor temperature of 75 $^{\circ}\text{C}$ and 10 bar pressure over a six hour continuous operation. This example demonstrates the real-life useability of commercial PBSAC support materials.

Dispersion of the active catalyst over the support is also a significant parameter to consider when developing novel heterogeneous catalysts, as it directly related to size of the active surface area and affects the stability of catalyst NPs.

6.1.2 NP deposition techniques

The NP deposition technique used when forming immobilised catalysts is important when producing a highly active catalyst material, as the selectivity and activity of the catalyst for different reactant molecules is largely dependent on the morphology and dispersion of the NPs on the support.²⁸ In heterogeneous catalysis, the binding of

Table 41. Examples of some NP deposition techniques.²⁹⁻³¹

Technique	Type	Description	References
Co-precipitation	Chemical	The precursors for the support and NPs are simultaneously precipitated.	32,33
Impregnation	Chemical	Impregnation involves the 'wetting' of the support with the metal precursor solution. The metal is dissolved in a minimum amount of solvent.	34
Microemulsions	Chemical	A solid support is impregnated with a dissolved metal salt precursor in a microemulsion. The support-metal interaction is improved by increasing the supports hydrophobicity.	35,36
Sonochemical	Physical	Sonic waves are introduced to the reaction mixture to deposit and reduce the NPs on the support, avoiding the need for a heating step in the process.	37,38
Pulsed Laser Ablation (PLA)	Physical	PLA uses a laser to vaporise the metal precursor in order to control the deposition of the metals on the support.	39
Deposition-precipitation	Chemical	The dissolution of the metal precursor in solvent, followed by a pH adjustment to precipitate the metal hydroxide fully before the hydroxide is deposited on the support.	40

the metal NPs to the support is also a significant parameter as this helps to avoid catalyst deactivation by metal leaching. The metal NPs can first be synthesised before being applied to the support, or they can be formed *in situ* from a precursor species. Some common physical and chemical deposition techniques are outlined in Table 41, however, there are many other deposition techniques reported in the literature for a range of different catalyst support materials.²⁹⁻³¹

The influence of the NP deposition techniques on the structure and catalytic performance of PdNPs/GNFs composites was investigated by Cornelio *et al.*⁴¹ Five Pd@GNF were synthesised using different deposition techniques and their catalytic activities were tested in a Suzuki-Miyaura cross-coupling. It was found that the Pd@GNF formed via impregnation of the Pd salt into the GNF followed by a gas phase reduction, could achieve high conversions of 98% and selectivities of 95% for the nitrobenzene product. The oxidative addition step of the catalytic cycle happened at the GNF step-edge, showing the influence of nanoscale confinement on the reaction steps. Different NP deposition techniques such as the ones described by Cornelio *et al.* will be explored in this project and their effect on the catalyst activity will be tested in a reduction reaction in continuous flow.

Aygün *et al.* reported the use of different deposition techniques of transition metals supported on to GNFs to produce magnetically recyclable carbon nanoreactors.³² Two deposition methods were investigated: physical vapour deposition (PVD) to produce PdGNF-1, produced NPs located only on the inside of the GNF at the step edges; and impregnation deposition produced Pd-GNF-2, where the PdNPs were mostly attached on the inside of the GNFs, with some present on the outside. The different techniques resulted in a change to the NP sizes present in both supported catalysts, with

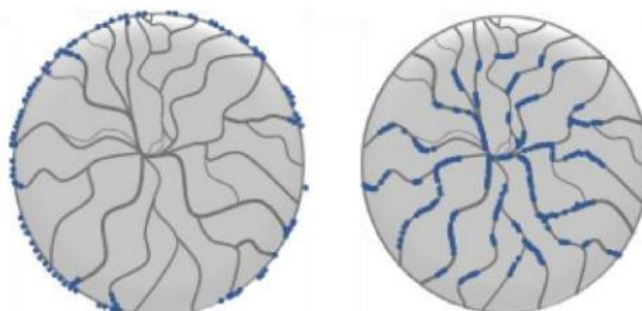


Figure 113. A comparison of where the NPs are located with different deposition methods, left – NPs are restricted to the surface of the support, right - NPs can enter the inner pore network.

PdGNF-2 exhibiting much smaller NPs (2.3 ± 0.6 nm), and this contributed to their higher activity and selectivity. When different NP deposition methods are explored, the NP catalysts may show different characteristics and morphologies, as well as be present at different locations on the catalyst supports. Gaseous reagents are more likely to be able to infiltrate micro and meso-sized pore networks within supports materials, which could enhance the stabilisation of the NPs due to the large energy barrier that would need to be overcome to remove them (Figure 113). This will aid in preventing catalyst deactivation via metal leaching. However, NPs isolated only to the inner pore network of a support may lead to a lower activity of the catalyst as the reactants may not be able to reach the catalyst NPs. PVD and impregnation techniques for NP deposition will be investigated here with the aim of creating different NP characteristics, to understand their influence on a chemical reaction.

6.2 Aims

This chapter aims to evaluate PBSAC supports for their use in continuous flow and PBRs and investigate how the method of PdNP deposition affects their catalytic activity for a well-known, model reduction reaction. They will be benchmarked against a commercial pelleted catalyst to ensure their activity is comparable to existing catalysts. Additionally, the stability of the catalysts formulated will also be monitored and characterised, in order to assess their ability to be used for extended periods of time, demonstrating their use for industrial applications. The catalysts will be fully characterised, which will aid in explaining their physical and catalytic properties and provide a comparison between the different methods of deposition.

6.3 Catalyst formulation

Two methods for PdNP deposition were investigated in this work on commercial carbon beads, solution-phase deposition (impregnation) and gas phase deposition (sublimation-deposition) at a range of different theoretical loadings (1-5 wt.% Pd). The catalysts were formulated using the methods described in experimental section 6.10.2, based on work previously reported by Aygün *et al* on GNFs.³¹ These two methods were

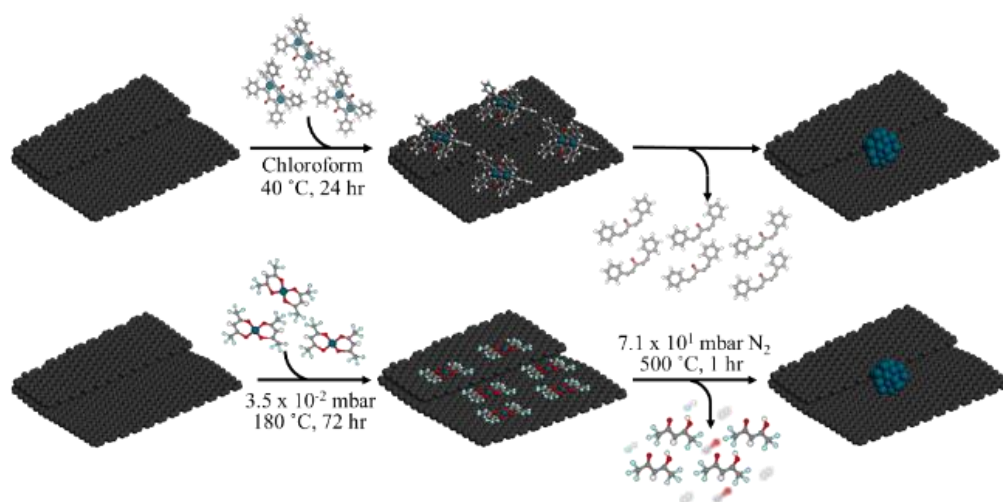


Figure 114. Deposition techniques used to form PdNPs on to the surface of carbon beads. a) Solution phase, dissociative adsorption of $\text{Pd}_2(\text{dba})_3$ from CHCl_3 , and b) gas phase deposition of $\text{Pd}(\text{HFAC})_2$ under reduced pressure, followed by thermal decomposition.

chosen with the aim to produce different catalytic properties so that their performance, activity, and stability could be investigated. A visual overview of the two techniques is summarised in Figure 114.

6.4 Catalyst characterisation

Once formulated, the catalysts were characterised using a number of techniques, in order to fully understand their catalytic properties when used in a model reduction reaction. The catalysts for ease of identification are labelled **1a-e** (solution phase deposition) and **2a-e** (gas phase deposition), where **a** is the lowest Pd loading and **e** is the highest.

The Pd content of each catalyst was investigated and quantified using inductively-coupled-plasma-mass-spectrometry (ICP-MS), and samples were prepared using the method outlined in experimental section 6.10.3.1. The expected and actual loadings for all catalysts are shown in Figure 115. Gas phase deposition catalysts, **2a-e**, showed a greater Pd loading than those made via solution phase deposition, however both sets of catalysts exhibited Pd loadings much lower than their theorised amount. When forming catalysts **2a-e**, the heated ampule, containing the carbon bead support and gaseous Pd precursor, is rapidly cooled to deposit the Pd onto the support before forming the PdNPs. This means that the precursor is deposited where it is located in the

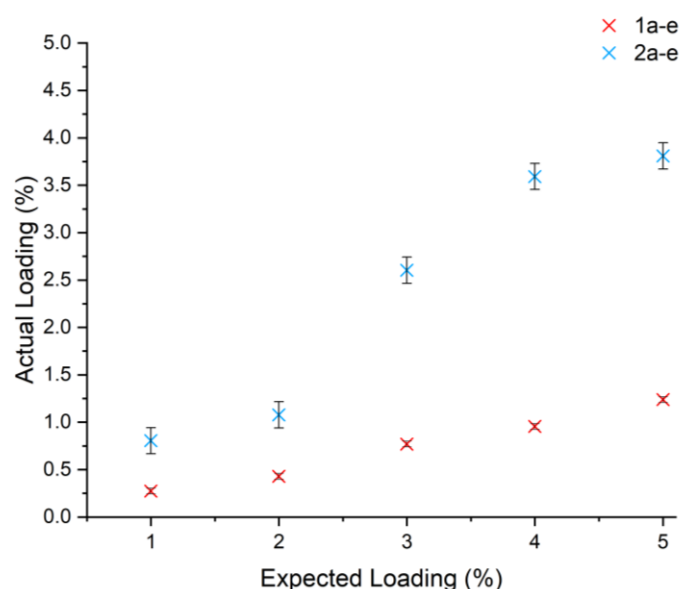


Figure 115. ICP-MS data showing the actual vs. the expected PdNP loadings for the different deposition techniques, blue = **1a-e**, and red = **2a-e**.

ampule at that time, including on the walls of the glass ampule (Figure 116 shows white coating on the inner walls of the ampule). This can be seen in the image below where the inner walls of the ampule are coated in the metal precursor after being cooled in an ice bath. To decrease this effect (for the future optimisation of the process) smaller ampules could be used to decrease the internal surface area available for deposition.

Catalysts **1a-e** had a Pd loading much lower than was expected, which is possibly due to the low affinity of the Pd precursor to this carbon bead support. However, this is not well documented in the literature and no further optimisation of either of the Pd deposition techniques was performed in this work. To increase the Pd loadings for

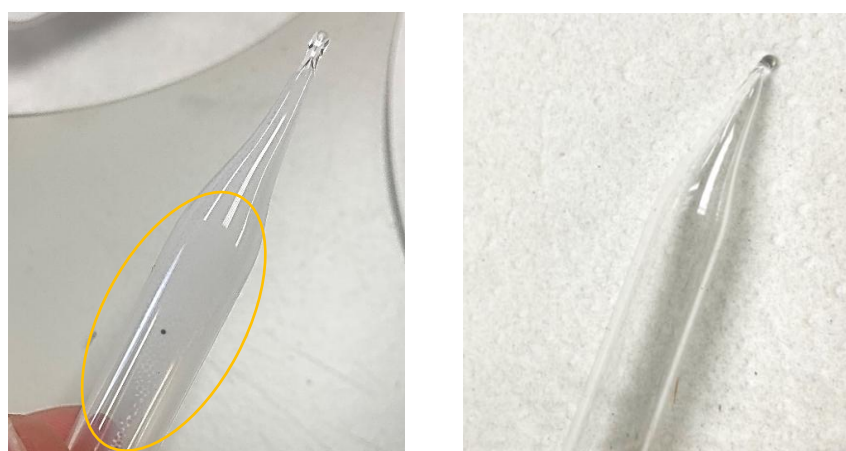


Figure 116. Images of ampules before (right) and after (left) they were used for gas phase NP deposition.

Table 42. Summary of catalyst characteristics for unfunctionalized carbon supports and supported Pd metal catalysts. ^a SSA = specific surface area.

Catalyst	Average Particle Size (μm)	Pore Volume ($\text{cm}^3 \text{g}^{-1}$)	SSA ($\text{m}^2 \text{g}^{-1}$) ^a	Average Pore Diameter (nm)	Crush Strength (N)
1 wt.% Pd/C pellets ⁴³	Length – 307, Diameter – 165	0.16	1102	3.9	1.12 ± 0.55
Carbon pellets ⁴³	Length – 307 Diameter – 165	0.09	954	4.4	/
PBSAC beads	465	0.66	1582	12.8	0.69 ± 0.27
1e	465	0.57	1136	17.3	0.79 ± 0.33
2e	465	0.62	1275	20.7	1.09 ± 0.34

solution phase deposition the temperature and the amount and type of solvent could be investigated.

N₂ adsorption/desorption was used to investigate the pore structure, pore volume and surface area of the unfunctionalized carbon beads, commercial carbon extrudates, supported PBSAC PdNP catalysts, and commercial 1 wt.% Pd/C extrudate catalysts. Samples were prepared using the procedure outlined in the experimental section 6.10.3.2 and a full summary of all data is shown in appendix section 6.11.1. Key characteristics of the catalysts are outlined in Table 42 showing a higher surface area, average pore size, and pore volume for both the unfunctionalized beads and PBSAC supported catalysts than the commercial carbon pellets. This could offer a larger surface area (including the inner pore network of the carbon bead) for the deposition of PdNPs, increasing the potential for more catalytically active sites. A larger pore diameter could allow PdNPs to deposit inside the pores of the support, possibly offering stabilisation,

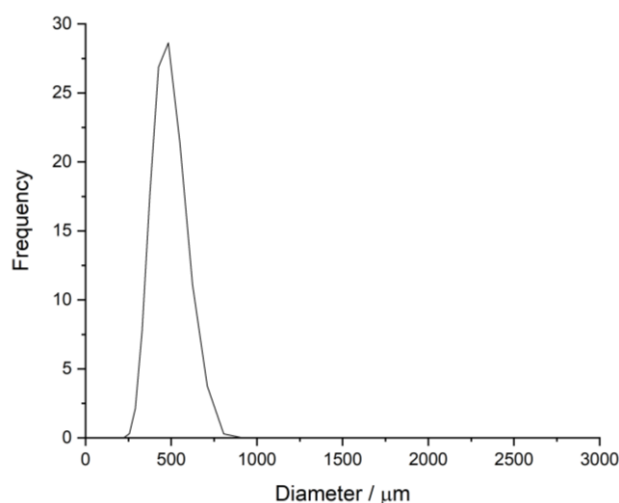


Figure 117. Mastersizer data showing the average size distribution of the unfunctionalized carbon beads.

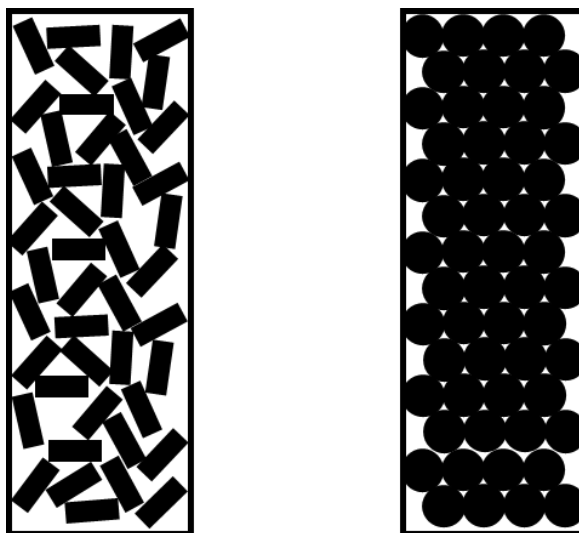


Figure 118. Packing of pellets (left) and spherical beads (right) in a column.

and in turn reducing the possibility for metal leaching. With deposition of the PdNPs on to the beads, the specific surface area of the samples decreased, likely due to the blockage of some of the smaller internal micropores by PdNPs within the carbon bead. This could also explain the increase in the average pore diameter of the supported catalysts, as some of the smaller pores were closed off after the deposition of the metal NPs. When compared to other PBSAC supported catalysts in the literature, both the unfunctionalized supports, and Pd loaded catalysts were comparable to those reported ($1160\text{--}1946\text{ m}^2\text{ g}^{-1}$).^{44,45} They also exhibit higher surface areas than other alternative carbon supports, such as AC and CNT supports (890 and $531\text{ m}^2\text{ g}^{-1}$ respectively).⁴⁶ The size of the PBSAC support was measured using a Mastersizer and the distribution is shown in Figure 117, exhibiting a narrow size distribution. This is essential for the intended use in a PBR, which requires reproducible, uniform packing of the catalyst particles. Pellets/extrudates have less uniform packing, as their orientation could be in any direction when the bed is packed, resulting in a less reproducible bed and changes to the flow path of reagents through the bed (i.e. channelling or liquid holdup). Spherical beads pack more uniformly, which should result in more reproducible results between reactions, demonstrated in Figure 118. The crush strengths of the catalysts were also tested to probe their applicability for a high pressure reactor platform and whether the deposition techniques had caused the catalyst supports mechanical strength to change (experimental procedure outlined in section 6.10.3.3). The data shows that all four materials tested showed similar values (within the experimental error calculated from standard deviations of the 50 samples). There was very little differences in crush

strengths upon deposition of the PdNPs onto the support, showing that both techniques did not cause any change to the support itself, making them suitable candidates for catalytic tests.

6.4.1 NP characterisation

Scanning electron microscopy (SEM) was used to evaluate the topography of the outer surface and inner pore network of the carbon supports (Figure 119). Cracks could be seen on the surface of the carbon beads. These are created during the manufacture of the commercial carbon beads and can offer beneficial binding sites for the PdNPs during deposition. A bead was crushed and SEM was used to highlight the porosity of this material, as intricate pore networks can be seen throughout the entire bead.

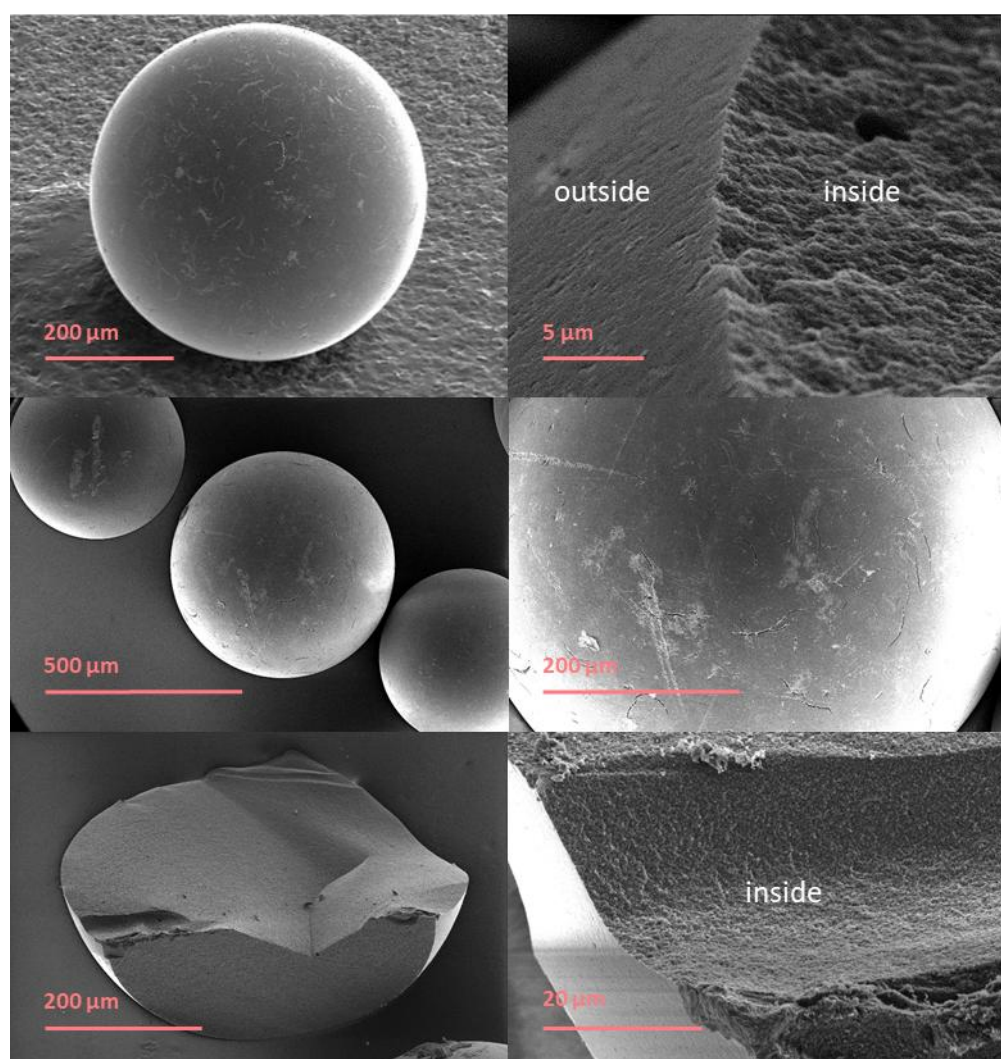


Figure 119. SEM images of unfunctionalized PBSAC beads.

An energy dispersive X-ray spectrometry (EDS) map of the outer surface of the functionalised catalysts (**1e** and **2e**) was taken to investigate the PdNP dispersity across the beads surface, Figure 120. The maps show that both deposition techniques achieved a homogeneous distribution of Pd across the surface of the carbon bead, but more Pd was concentrated in the defects (i.e. cracks) of the beads. The cracks can offer beneficial sites for the nucleation and growth of the NPs as they can bind strongly at these defects.⁴⁷ This may increase the stability of the NPs too and limit the deactivation of them by metal leaching due to enhanced binding to the carbon surface. However, the cracks may have a negative effect on the mechanical strength of the support. Many groups have documented this in the literature and the extent of cracks in the beads

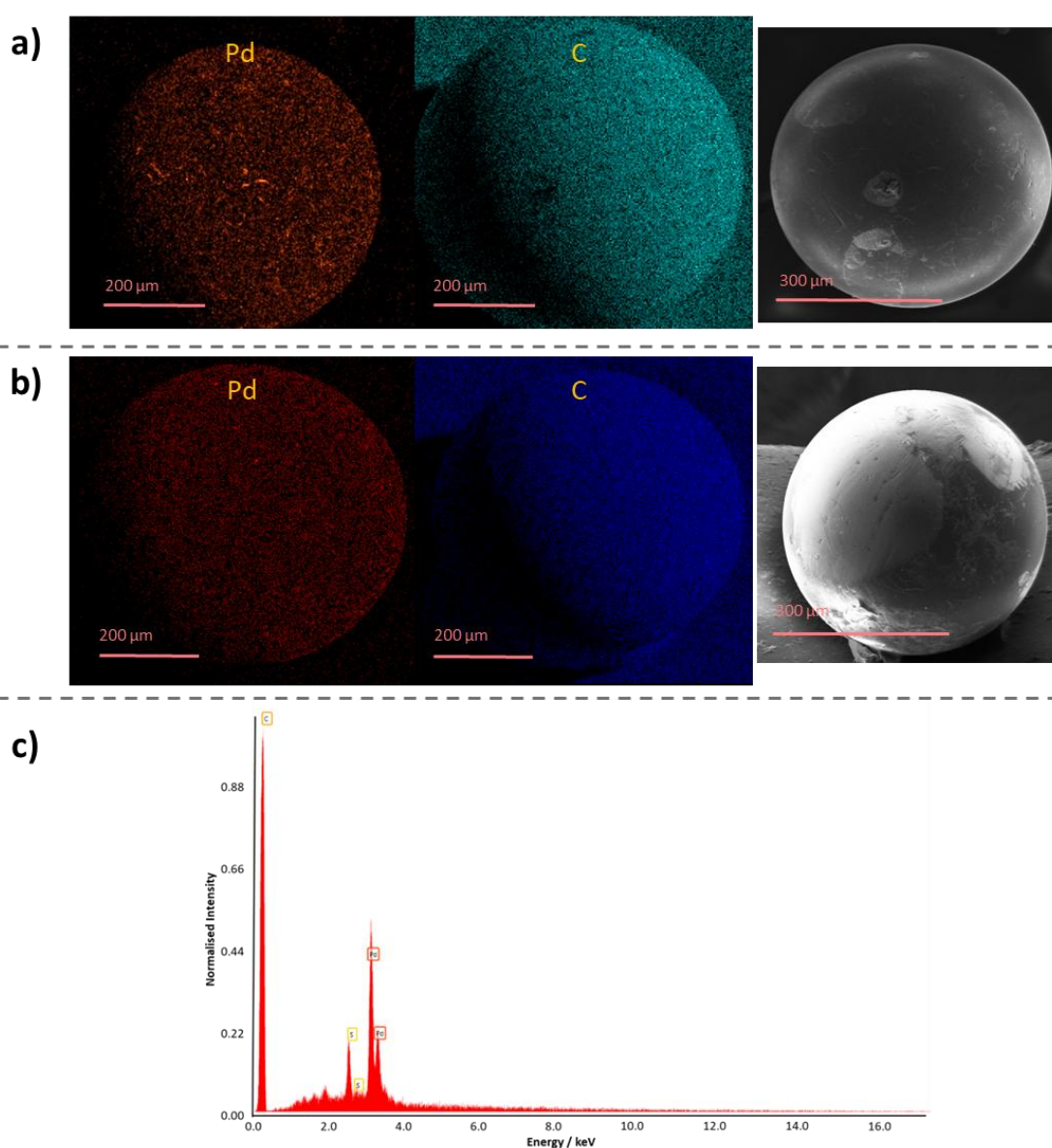


Figure 120. EDS maps and SEM images of catalyst a) **1a**, b) **2a**, where Pd – red, carbon – blue. c) An example EDS spectra of the functionalised Pd/PBSAC beads.

surface can be controlled during the manufacture of the carbon spheres. For example Singh *et al.* developed a method for producing activated carbon spheres with resole-type cross-linked phenolic beads, and investigated the effects of burn-off on surface cracks.⁴⁸ They showed the correlation of an increase in burn-off producing an increase to the number of surface cracks on the beads, and noted that this had a detrimental effect on the carbon spheres mechanical strength (decreasing from 120 to 3 N mm⁻² when increasing burn-off and surface cracks). This demonstrates the importance of investigating this characteristic when designing catalyst supports.

A number of techniques were used to investigate where the PdNPs were located inside the functionalised carbon bead catalysts. The beads can be crushed, but this creates small fragments and it is difficult to determine where these fragments are from in the original bead. In an attempt to have better control over this, the beads were immobilised in resin, cured, ground and wet polished to produce a cross-section of the inside of the beads. This was first done on unfunctionalized PBSAC beads to develop a polishing procedure without wasting the precious metal catalysts. The immobilised beads in resin are shown in Figure 121. SEM was used to investigate the surface of the beads after they had been polished to see if EDS mapping could be performed on the sample (Figure 122). Unfortunately, the polishing material produced large scratches and indents in the cross-sections of the beads. Significant amounts of the polishing material could also be seen remaining embedded in the samples. This would mean that the EDS map would be disrupted as the polishing material completely covered the entire cross-section of the bead, and the small Pd peaks could not be mapped accurately. It would also be difficult using this technique to know how deep the beads had been polished back to as the beads did not uniformly disperse in the resin and there is a small

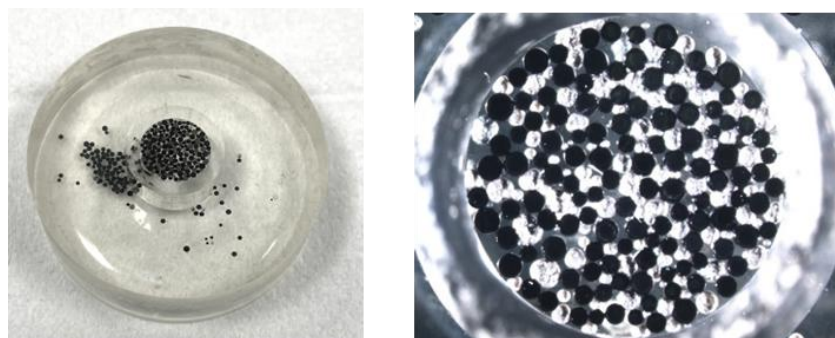


Figure 121. Left – Image of whole resin block with beads immobilised. Right – Microscope image of beads immobilised in resin, showing carbon beads (black spheres) and gas bubbles in the resin (white spheres).

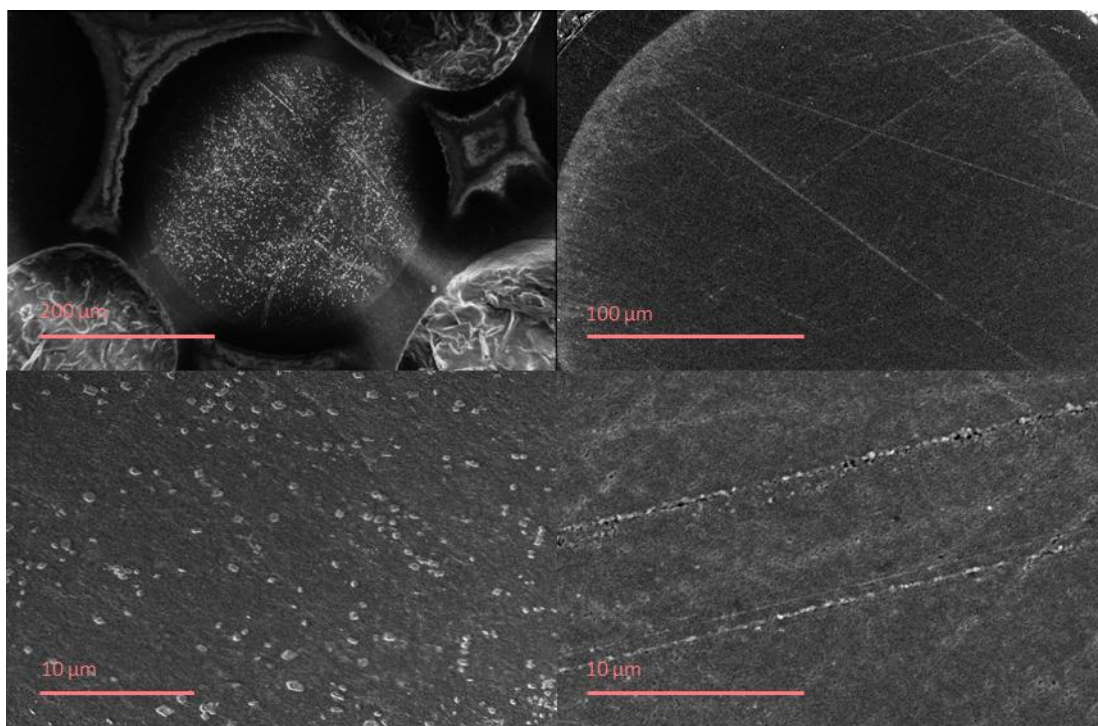


Figure 122. SEM images of polished cross-sections of carbon beads in a resin block, showing scratches in the beads created by the polishing materials.

variation in the carbon bead sizes, as seen in the size distribution measure by the Mastersizer.

Plasma-focussed-ion-beam-SEM-EDS (PFIB-SEM-EDS) was therefore used to probe the location of PdNPs in a more controlled way. Using a plasma beam allows the depth investigated into the bead to be controlled accurately and it can also be used to probe deeper into the sample than traditional FIB lasers. This provided more information about how far the PdNPs can penetrate into the pores of the beads. Catalysts **1e** and **2e** were analysed (samples were prepared as described in experimental section 6.10.3.6) as they contained the highest Pd content for each deposition type, which would improve the Pd signal seen on the EDS map. Figure 123 shows the results of the PFIB-SEM-EDS analysis, showing the Pd concentration of the beads up to 100 μm depth into the carbon bead. Both **1e** and **2e** show the concentration of Pd remains mostly unchanged throughout the cross-section of the bead investigated. This shows the PdNPs were able to penetrate the inner pore network of the bead to a depth of 100 μm (radius of entire bead is 232 μm) using both deposition techniques. SEM-EDS was also performed on the commercial JM 1 wt.% Pd/C pellets by White *et al.*, where they

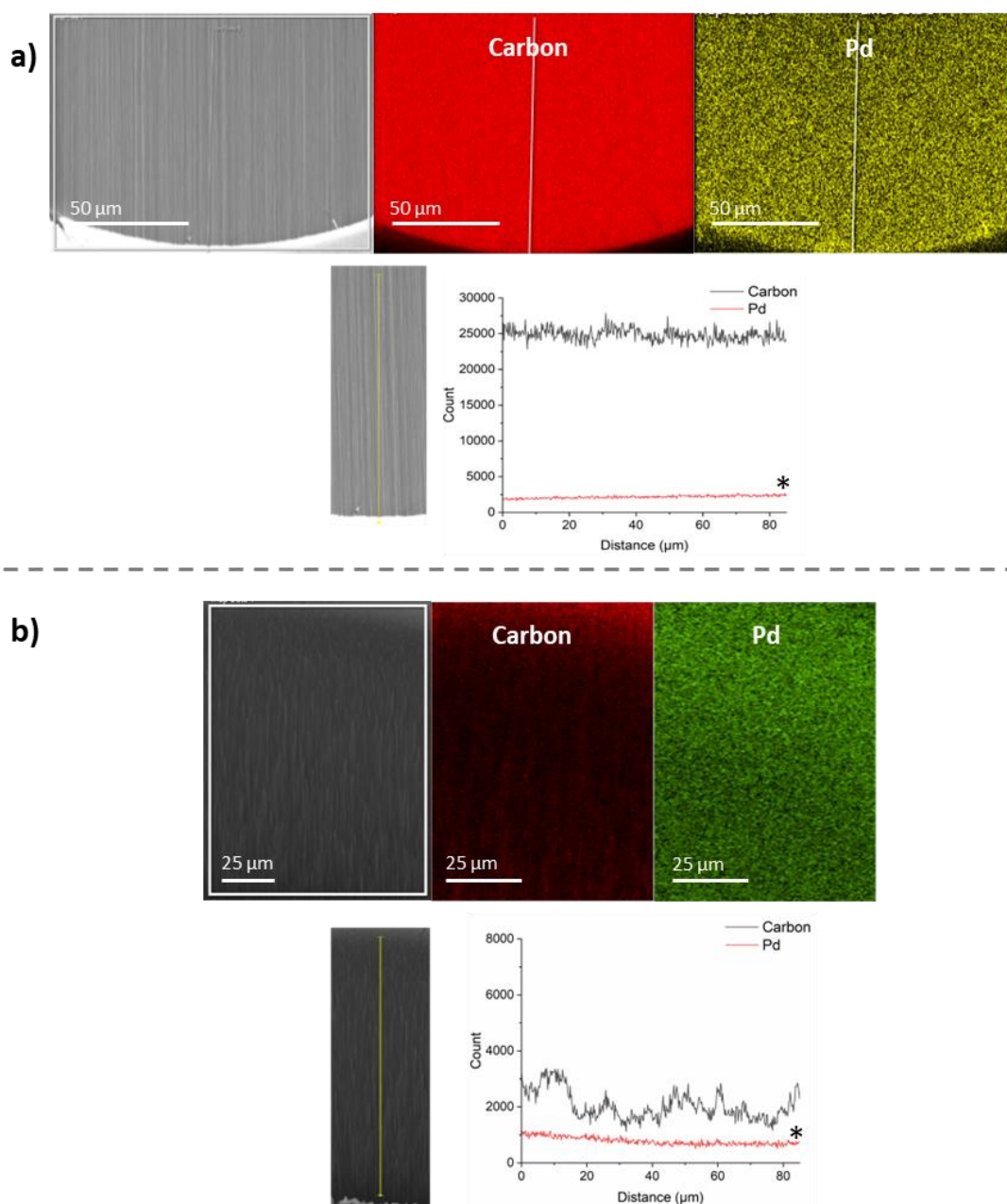


Figure 123. SEM image, EDS maps and EDS line scans for carbon and palladium elemental content for catalysts a) **1e** and b) **2e** from PFIB-SEM-EDS analysis. * = surface of the bead.

reported that the Pd is limited to the top 6 μm of the catalyst support, showing an enriched shell of Pd on the outer surface of the carbon pellet.⁴³

TEM and scanning transmission electron microscopy (STEM) were used to investigate the size and size distribution of the PdNPs produced from both deposition techniques (sample preparation detailed in experimental section 6.10.3.5). TEM/STEM images for each catalyst are shown in Figure 124. The difference in size of the NPs for the two different deposition techniques can be clearly visualised here, with the scale bar of catalysts **1a-e** being 20 and 50 nm, whereas the images of catalysts **2a-e** are all scaled

to 200 nm. It is also clear from the images that the size of the NPs increases with increasing Pd loading for both deposition techniques. 200 NPs were sized for each catalyst and a summary of their sizes and distributions are shown in Figure 125. This highlights the significant difference in size of the NPs made via solution phase deposition (**1a-e**) than gas phase deposition (**2a-e**). The distribution of sizes is also much greater in catalysts **2a-e** and shows an increase with increasing loading. This suggests that any increase in Pd content of these catalysts, preferentially promotes the growth of existing NPs rather than the nucleation of new ones. This trend in NP size was also reported by Aygün *et al* (using the same deposition techniques), who described a much larger NP size for gas phase deposition vs. solution phase deposition of their PdNPs on GNFs.³² This suggests that the size of the NPs has little to do with the support used but is down

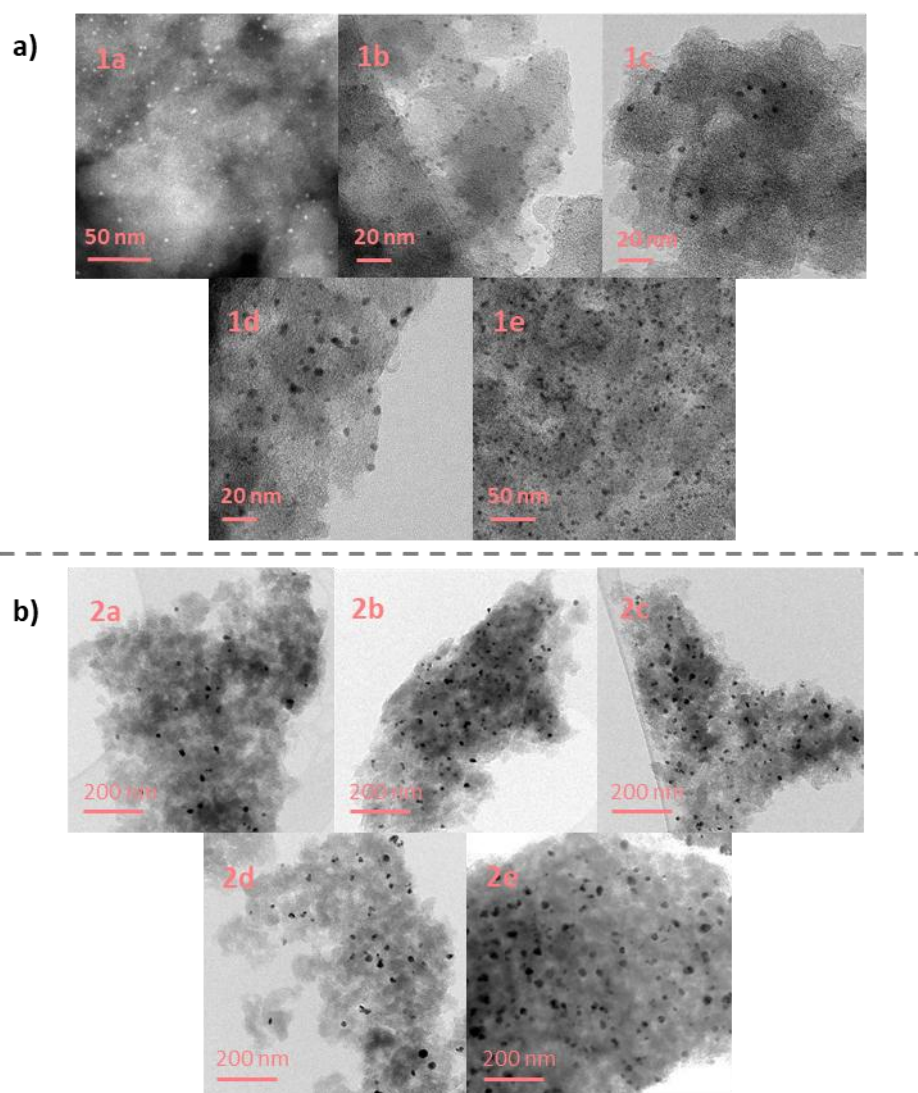


Figure 124. TEM images showing the size of the NPs made via the two deposition techniques, showing the smaller NPs of catalyst a) **1a-e**, than b) **2a-e**.

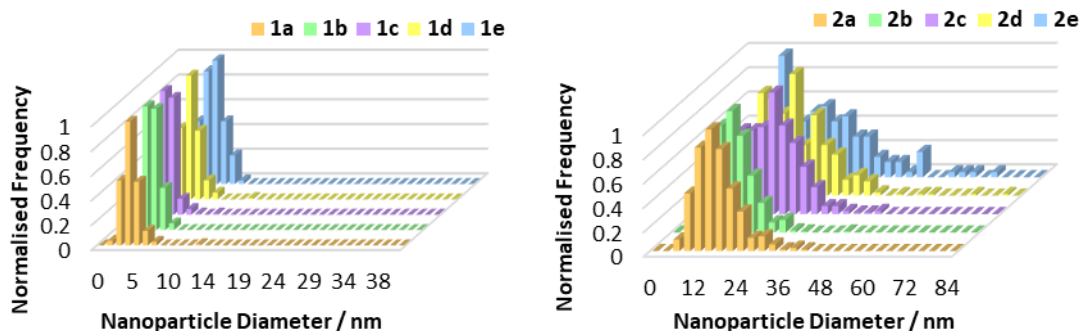


Figure 125. TEM data showing the size of PdNPs for different Pd wt.% loadings for **1a-e** (left) and **2a-e** (right) showing the increase in the average size and size distribution of the PdNPs made via the two deposition techniques.

to the deposition technique itself. With the catalysts fully characterised, their catalytic performance could now be tested, and their activity and stability in a model reaction compared to commercial 1 wt.% Pd/C catalysts.

6.5 Development of the recirculating batch platform

A small scale screening platform was designed in order to evaluate the catalysts performance and compare them to a commercial pelleted catalysts. An initial setup was designed to use a peristaltic pump to recirculate the liquid reagents through the system (Figure 126) and initial testing using a model nitrobenzene reduction and the commercial pelletised catalysts was carried out.

The system did not contain a BPR, due to the peristaltic pumps lack of ability to flow reagents under pressure. However, the PBR containing glass beads and catalyst pellets created too large of a back pressure, resulting in no liquid phase entering the

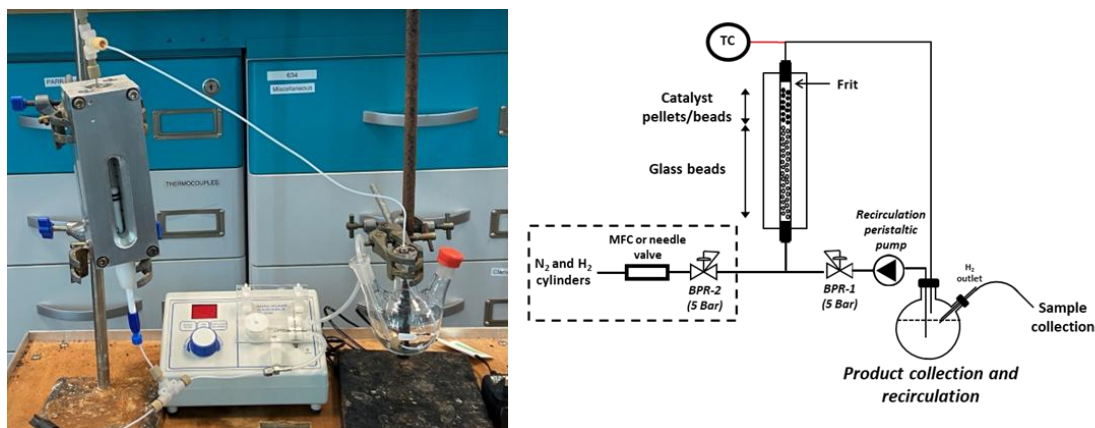


Figure 126. Image and P&ID of recirculating batch system setup with peristaltic pump.

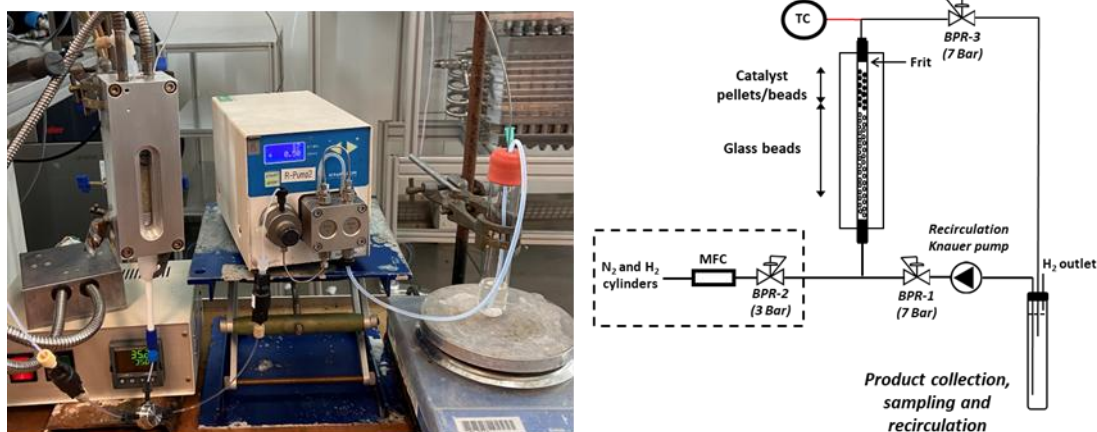


Figure 127. Image and P&ID of the improved recirculating batch system with a dual piston pump.

reactor. Therefore, the peristaltic pump was exchanged for a Knauer HPLC dual piston pump, which contains internal check valves, allowing it to pump against pressure, and a BPR was placed on the outlet of the catalyst bed to pressurise the system (Figure 127). The setup benefits from having accurate control of the gas flow rates via a mass flow controller, and liquid flow rates from the piston pump, connected to a computer. It also contains a Eurotherm temperature controller which provides accurate heating of the catalyst bed to the desired temperature via a thermocouple placed in the reaction stream at a t-piece on the outlet of the packed bed. Therefore, key reaction parameters can be controlled in a continuous recirculating system that still maintains the versatility of operation in batch. It benefits from the ease of sampling at ambient temperature and pressure and can be used to screen small amounts of catalysts as it allows the reactant solution to pass over the bed multiple times in a controlled manner. The system, instrumentation and column packing are explained in more detail in section 6.10.4.2. The reactor column contains a hydrogen pre-saturation section of only glass beads, to increase mixing of the gaseous and liquid reactants, and therefore increase the mass transfer between the two phases, before it reaches the catalyst.

To ensure that the catalyst supports were useable in the system, pressure drop data was collected for both the PBSAC and pelleted commercial catalysts (Figure 128). It is an important factor to monitor as it largely affects hydrogen solubility and reaction rate, and thus affects the yields and selectivities of reactions.⁴⁹ The figure shows that the pressure drop data for both commercial pelleted catalysts and the carbon supports gave comparable pressure drops of 0.1 bar (5% difference between inlet and outlet pressures). As outlined by Hickman *et al.*, pressure drops of <20% are the maximum

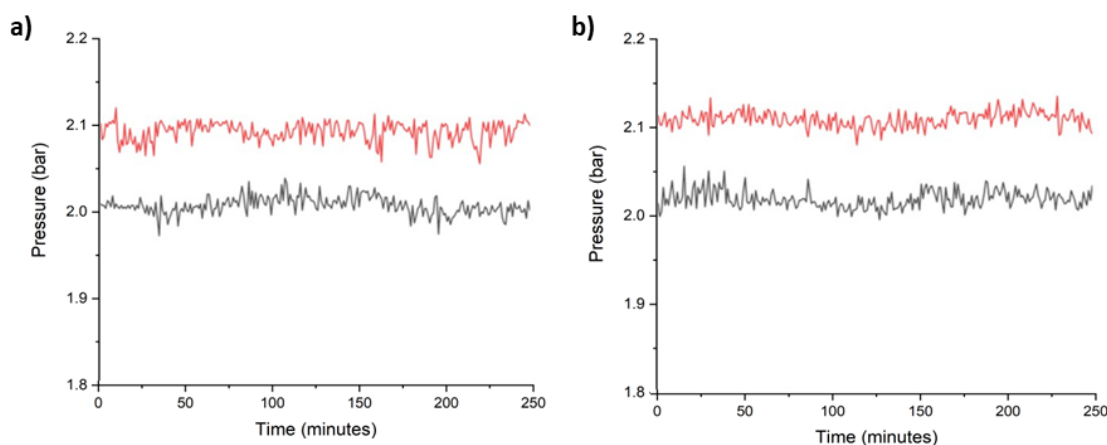


Figure 128. Pressure drop data, where red = top pressure transducer, black = bottom pressure transducer, a) pellets, b) carbon beads.

recommended for PBR systems.¹¹ The pressure drops measured here are well below the maximum allowed value, demonstrating their applicability to be used in this system and for scale up.

6.6 Activity comparison in model nitrobenzene reduction

With a screening system in place, the catalysts could now be tested for their activity in a model nitrobenzene reduction reaction. This reaction was chosen, as it is known, well understood, and reported heavily in the literature, with well-defined side products that are easy to identify and quantify. A typical reaction procedure is outlined

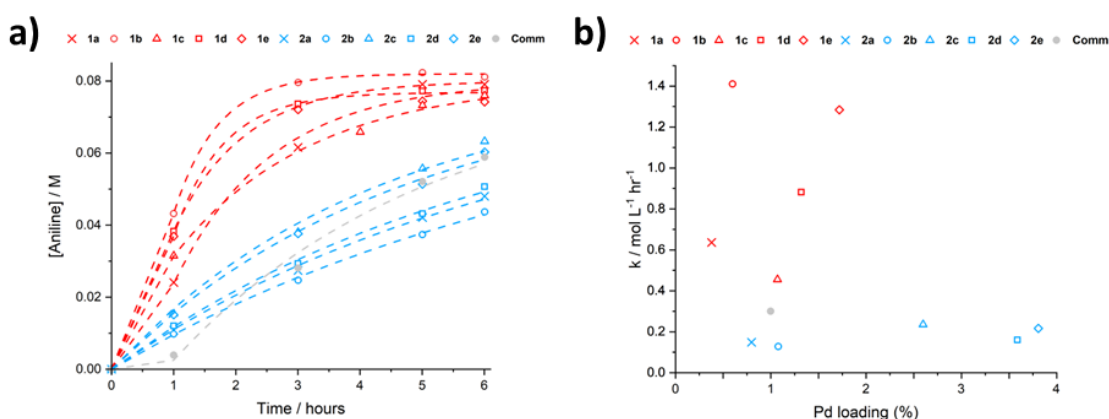


Figure 129. a) A comparison of the activities of the catalysts **1a-e** (red) **2a-e** (blue) and the commercial catalyst pellets (grey). b) Relationship between the observed rate constants and the Pd loading % on each catalyst, with solution phase catalysts **1a-e** in red, gas phase catalysts **2a-e** in blue, and the commercial pellets in grey. Reaction conditions – 7 bar pressure, 35 °C, 1 mL min⁻¹ liquid flow rate (0.08 M), 20 mL min⁻¹ hydrogen flow rate, Pd/C catalyst (20 mg).

in section 6.10.4.2. Catalysts **1a-e**, **2a-e** and commercial 1% Pd/C pellets were tested out in the recirculating batch platform and the results were analysed by offline GC measurements (example spectra shown in 6.10.4.4).

The data from each reaction was then fitted with a two component model (Figure 129a): the initial linear period of 0 – 60 minutes incorporates a hydrogen limited regime, $K_{\text{obs}}t$, where k_{obs} is the observed rate constant; the final five hours were fitted with a pseudo first order reaction model. The pseudo first order rate equation was rearranged to model for the final five hours, shown in equations 1-6 below.

$$[NB]_t = [NB]_0 e^{-k't} \quad (1)$$

$$[Ani]_t = [NB]_0 - [NB]_t \quad (2)$$

$$[NB]_t = [NB]_0 - [Ani]_t \quad (3)$$

$$[NB]_0 - [Ani]_t = [NB]_0 e^{-k't} \quad (4)$$

$$[Ani]_t = [NB]_0 - [NB]_0 e^{-k't} \quad (5)$$

$$[Ani]_t = [NB]_0 (1 - e^{-k't}) \quad (6)$$

Where $[NB]_0$ = initial concentration of nitrobenzene / M, $[NB]_t$ = concentration nitrobenzene at time t / M, k' = pseudo first order rate constant / $\text{mol L}^{-1} \text{hr}^{-1}$, t = time / hr, and $[Ani]_t$ = aniline concentration at time t / M.

Reactions with catalysts **1a-e** all reached completion after five hours, showing a high activity for this transformation. This is likely due to the small NP size of those synthesised using solution phase deposition, which has shown to be directly related to catalyst activity.⁵⁰ Typically, the smaller the NP size, the larger the surface area: volume, which increases the number of catalytic sites available. The larger sized NPs present in catalysts **2a-e** would have a smaller active surface area, which is mirrored in their lower activity for the reduction of nitrobenzene. This can be seen as all of the reactions with **2a-e** catalysts failed to reach completion after the six hour experiment. As there was no difference in the location of the PdNPs within the catalyst supports for both deposition types, the differences in activity must primarily be a result of the NP sizes. From the fitted models rate constants could be calculated for each catalyst and compared to their catalyst loadings (Figure 129b). This shows that even at similar loadings, the solution

phase deposition catalysts ($K_{\text{obs}} = 0.46\text{-}1.41 \text{ mol L}^{-1} \text{ hr}^{-1}$) outperformed all of the gas phase deposition catalysts ($K_{\text{obs}} = 0.13\text{-}0.24 \text{ mol L}^{-1} \text{ hr}^{-1}$).

The results from the commercial JM 1 wt.% Pd/C catalysts were also fitted with the same models and could be compared to the synthesised catalysts. They showed a very similar activity to catalysts **2a-e**, however, their average PdNP size is comparable to catalysts **1a-e**. This shows that their difference in activity must be due to the different catalyst supports and the location of the PdNPs on the pellets. Brunauer-Emmet-Teller (BET) analysis of the pelleted support showed a smaller surface area, pore volume and pore diameter than the carbon bead supports, which could result in a loss of sites available for catalysis. In the JM catalysts, the PdNPs are limited to the top 6 μm of the support, whereas the carbon beads catalysts showed that the PdNPs were distributed throughout the support. This may indicate that the pores of the carbon bead support are accessible and may offer beneficial sites for catalysis during the reaction.

TON and turnover frequencies (TOF) were calculated for each catalyst, allowing for a direct comparison of the catalysts at different Pd loadings for each deposition techniques.

$$TON = \frac{\text{moles of aniline produced in six hours}}{\text{moles of Pd used in reaction}} \quad (7)$$

$$TOF = \frac{TON}{\text{number of hours of reaction (hr)}} \quad (8)$$

An increase in Pd loading results in a decrease in the TON for each catalyst, with catalyst **1a** exhibiting the largest TON of 2246 and TOF of 374.3 hr^{-1} after the six hour reaction. All kinetic and characterisation data for each catalyst is summarised in appendix section 6.11.3. This could be compared to similar catalysts in the literature for the reduction of nitrobenzene (summarised in appendix section 6.11.4). Wang *et al.* reported a TOF of 108.8 hr^{-1} for a Pd/AC catalyst, which is three times smaller than catalyst **1a** reported here, but greater than all gas phase deposition catalysts (which displayed a TOF of $78.5 - 21 \text{ hr}^{-1}$ for catalysts **2a-e** respectively).⁵¹ The data also shows that the commercial pelletised catalysts had TONs that were much lower than catalysts **1a-c**, reflecting a lower activity. Catalysts **1a-c** showed a greater activity with a decrease in the amount of Pd loading, which would lead to a reduction in the use of limited precious metal resources.

6.7 Stability of catalysts

It is not only important for the catalysts to be active, but they must also be stable for extended periods of time in order to make them industrially useful, and to minimise the waste of precious metals. The stability of the PBSAC catalysts were tested in the same small scale screening platform, however, the outlet of the reactor was now removed from the reservoir, so that the reaction mixture could only pass over the catalyst bed once (shown in Figure 130a). Catalysts **1e** and **2e** were chosen for stability testing and the reaction was sampled for 11 hours (results shown in Figure 130b). The data shows there was no significant decrease in the activity of catalyst **1e** during the 11-hour experiment as the yield of aniline remained constant. However, a decrease in activity over time could be seen with catalyst **2e**, indicative of the slow deactivation of the catalyst.

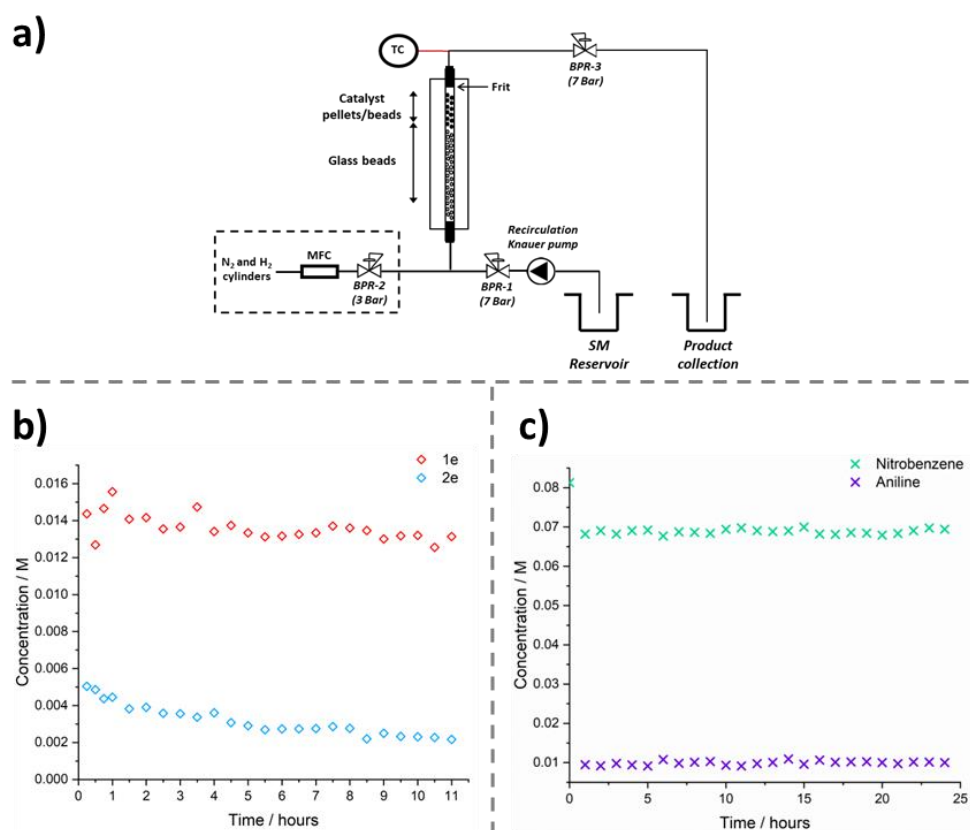


Figure 130. a) Small scale continuous flow PBR for stability testing of small amounts of catalysts. b) Comparison of the stability of the two different deposition catalysts showing aniline concentration over 11 hours for **1e** and **2e** sampled every 30 minutes, and c) concentration of nitrobenzene and aniline over 24 hours using catalyst **1e** sampled every hour. Reaction conditions – 7 bar pressure, 35 °C, 1 mL min⁻¹ liquid flow rate (0.08 M), 20 mL min⁻¹ hydrogen flow rate, Pd/C catalysts (20 mg).

In order to investigate the mechanism of the deactivation of the catalysts, X-ray photoelectron spectroscopy (XPS) analysis was conducted to determine the oxidation states of the PdNPs before and after they had been used in a reaction (shown in Figure 131). XPS analysis and interpretation was performed by Andrew Britton and Alexander Massey (respectively). Samples **1e** and **2e** were chosen for XPS analysis to ensure that

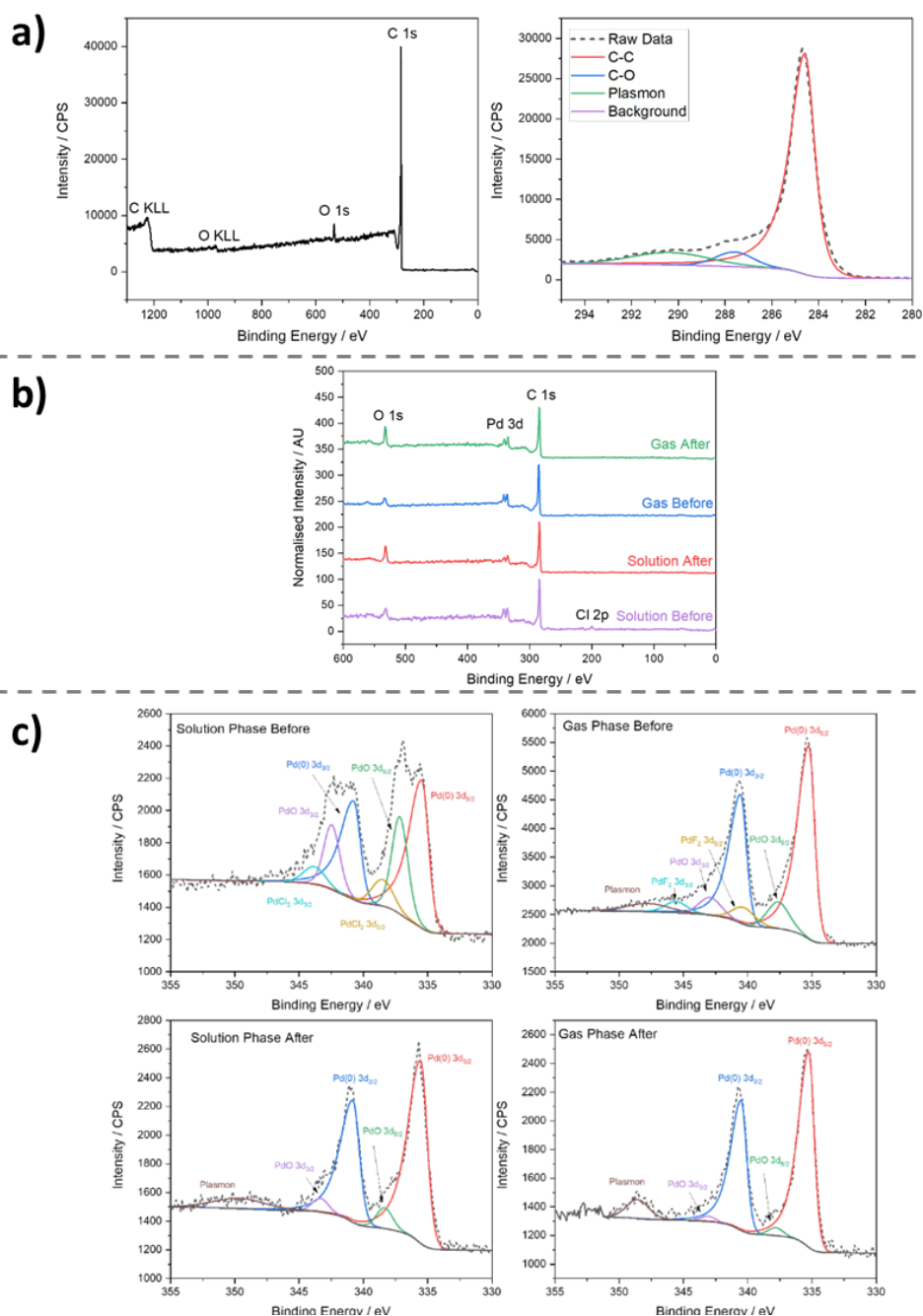


Figure 131. a) Survey and high-resolution C 1s spectra for unfunctionalized PBSAC. b) Survey spectra of **1e** (solution) and **2e** (gas) prepared by different synthetic approaches, before and after they were used to catalyse the reduction of nitrobenzene. c) High-res Pd 3d spectra for the **1e** (solution) and **2e** (gas) before and after catalysis.

the signal to noise ratio was high enough to achieve good fitting of the data. In all samples, the most abundant form of Pd was Pd(0), evidenced via the observation of large peaks at 335.4 eV and 340.7 eV in Figure 131c, which corresponds to the characteristic binding energies of Pd(0) $3d_{5/2}$ and $3d_{3/2}$ respectively.⁵² Catalyst **1e** shows a relatively large peak for Pd(II), shown in the deconvoluted peaks at higher binding energies. This is most likely in the form of PdO; due to the small size of the NPs, their surface is prone to oxidation.^{53,54} In contrast, the high-resolution spectrum for catalyst **2e** exhibits much lower amounts of Pd(II). The Pd $3d_{3/2}$ peak also has a long tail compared to catalyst **1e**, which is proposed to be the result of PdF₂ from the Pd(HFAC)₂ precursor and the presence of a plasmon loss peak.⁵² After its use in the catalytic reaction, the total concentration of Pd(II) in this sample decreases similar to that of **1e**. This shows there was no significant change to the oxidation state of the NPs in catalyst **2e**, showing the presence of mostly Pd(0) (characteristic of PdNPs) both before and after the reaction.⁵⁵ However, upon using catalyst **1e** in the reaction, the concentration of Pd(II) decreases significantly, as it is reduced via the catalytic mechanism with H₂. This can be seen in the increase in the peak area of the Pd(0) species.

As there was no significant change in the oxidation state of the PdNPs on catalyst **2e**, XPS could not provide an explanation for the catalyst deactivation. Therefore, ICP-MS was used to investigate if the deactivation was caused by metal leaching of the PdNPs from the support. Catalyst **1e** showed no change in the Pd content, however, there was a significant decrease in the metal loading seen for catalyst **2e** (from 3.8 to 1.5 wt.% Pd). This showed that the deactivation method for this catalyst was likely due to metal leaching, suggesting that the binding of these NPs to the carbon support was weak. This would be a significant problem if these catalysts were used in a process, as not only would the yield of the reaction decrease over time, the Pd would also contaminate the product, making it unlikely to pass quality control. The Pd would need to be separated from the desired product and recycled to limit the waste of precious metals, which can be costly and time consuming.

Due to the positive outcome of the initial stability tests, catalyst **1e** was taken forward and monitored for 24 hours, using the same reaction procedures as detailed previously. Figure 130c shows that there was no decrease in the concentration of aniline

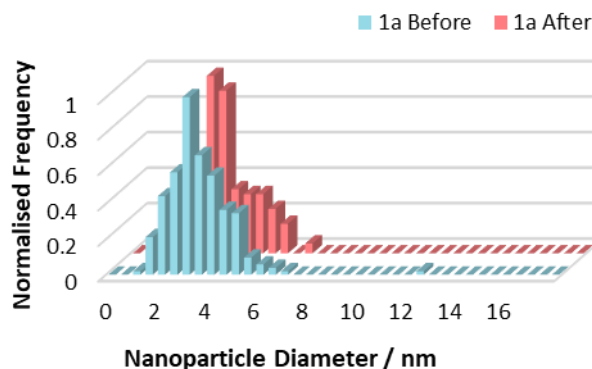


Figure 132. TEM data showing there was no difference in size of the **1a** catalyst PdNPs before and after an 11-hour stability test.

produced over the 24-hour reaction under the mild reaction conditions (relatively low process temperatures and pressures) with no reactivation of the catalyst or human intervention required. The 24-hour reaction was able to produce 1.33 g of product at low concentrations, mild reaction conditions and with only 20 mg of catalyst. To assess the stability further TEM analysis of the PdNPs before and after the reaction was performed to investigate if there was any change to the size or size distribution. The results of this, Figure 132, showed there was no change to either the average size or size distribution of the NPs, with the average size remaining at 3.1 ± 1.2 nm.

6.8 Scale up

The activity of the catalysts could then be tested in a larger scale automated PBR, outlined in Chapter 2, on the scale of 0.5 – 1 g of catalyst. This was used to demonstrate their applicability on a scale that is similar to that used in industry, capable of producing kgs day^{-1} of products.⁵⁶ Catalyst **1a** was chosen as the most appealing candidate, as it possessed the lowest Pd loading, while still maintaining a good activity, exhibiting the largest TON and TOF of all the catalysts synthesised. The activity could then be compared to the commercial JM pellets in the reduction of nitrobenzene.

The scale up results are shown in Figure 133, showing catalyst **1a** was stable at harsher process conditions (higher temperatures and pressures) over a two day operating period. When compared to the commercial pellets, **1a** had a much higher activity, with yields of 96% seen for this catalyst, compared to only 52% with the same

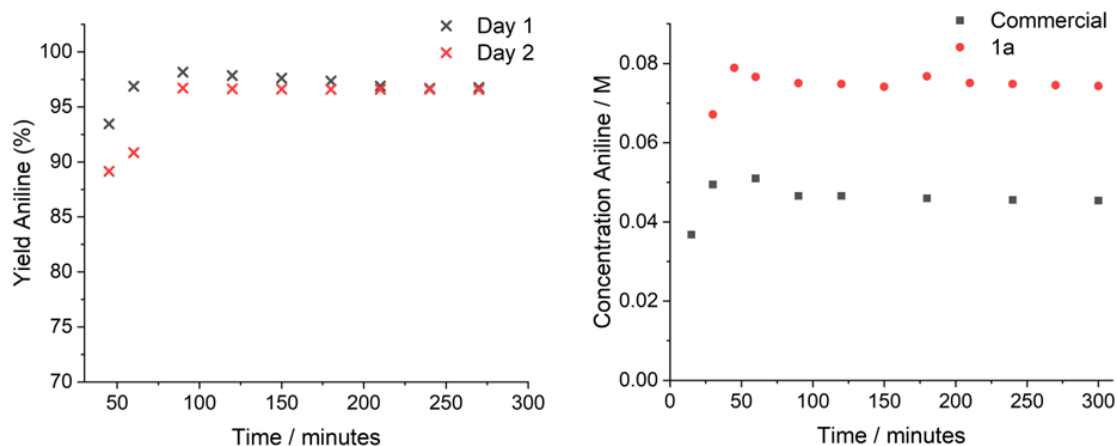


Figure 133. Left - Yield of aniline produced in PBR platform with **1a** showing the stability of the catalyst over two days, sampled every 30 minutes. Right - Comparison of yield of aniline produced using commercial 1 wt.% Pd/C and **1a**. Reaction conditions – 40 bar pressure, 50 °C, 1 mL min⁻¹ liquid flow rate (0.08 M), 50 mL min⁻¹ H₂ flow rate, Pd/C catalysts (500 mg).

mass of the commercial pellets. The calculated TOF for the scaled up reaction was 261 hr⁻¹ which is slightly lower than that achieved in the recirculating batch platform. This may be due to scale up factors such as a change in the process conditions (temperatures, pressures, or hydrogen flow rate), or due to a change in the reactor dimensions which would affect mass transfer rates. However, the TOF achieved in the scale up experiments is a significant improvement over the commercial catalyst pellets, which only achieved a TOF of 59 hr⁻¹. ICP-MS analysis was performed on samples from the resulting reaction solutions of the experiments conducted in the larger scale PBR platform on both the commercial pellets and catalyst **1a**. The analysis showed that there were no detectable amounts of Pd in the samples, therefore demonstrating their stability to deactivation by loss of active catalyst under these process conditions.

Over the 10 hours of processing, the system was able to make 4.6 g of product (with the capability of 11 g day⁻¹) under these reaction conditions. This could be increased by increasing the flow rate and concentration of the reaction to increase the throughput of product. However, no optimisation of this reaction was performed with these catalysts in this chapter, and reaction conditions were kept constant throughout the process to enable differences in reaction performances, relating to the catalysts used, to be determined.

6.9 Conclusion

Pd-PBSAC catalysts were made via two different deposition techniques of varying Pd loadings and were compared to a commercial 1 wt.% Pd/C catalyst extrudate from JM. All catalysts and unfunctionalized supports were characterised and their activities were evaluated in a bespoke recirculating batch platform that was capable of small scale screening. Catalysts **1a-e**, prepared by solution phase deposition, had a greater activity than those made via gas phase deposition (**2a-e**), due to their smaller PdNP sizes (e.g. **1e** – $d_{\text{NP}} = 5.0 \pm 1.4$ nm and **2e** – $d_{\text{NP}} = 22.8 \pm 13.1$ nm). This led to a higher TON, TOF and observed rate constant for their use in a model test reaction, and they were shown to outperform commercial pelletised Pd/C catalysts, even at a lower Pd loading. Catalyst **1a** also showed its stability under both mild (7 bar pressure and 35 °C) and harsher conditions (40 bar pressure and 50 °C) and demonstrates their potential to be used industrially. This is in trend with the paradigm shift towards the implementation of large-scale continuous manufacturing in the pharmaceutical sector.

6.10 Experimental

6.10.1 Chemicals and materials

Unfunctionalized PBSAC beads (IBUtec, Germany), tris(dibenzylideneacetone) dipalladium(0) (Sigma-Aldrich), palladium(II) hexafluoroacetylacetonate (Sigma-Aldrich), methanol (>99%, Sigma-Aldrich), water (99.99%, Sigma-Aldrich), biphenyl (99.5%, Sigma Aldrich), isopropyl alcohol (99.9%, Sigma-Aldrich), nitrobenzene (99.5%, Acros Organics), aniline (99.5%, Acros Organics), hydrogen gas (99.99%, BOC Gas), nitrogen gas (99.998%, BOC Gas), palladium standard for ICP (TraceCERT, 1 g L⁻¹, Supelco), and extrudate Pd/carbon pellets (product code: 113784, 1 wt.% Pd, Johnson Matthey) were purchased from suppliers and used without further purification.

6.10.2 Catalyst preparation

Two methods for PdNP deposition were tested in this chapter, solution phase deposition and gas phase deposition. These procedures are detailed below.

6.10.2.1 Solution phase deposition

IBUtec PBSAC beads were heated in a furnace using the heating protocol shown in Figure 134 to remove any water from the pores of the beads and cooled to room temperature. A portion of the beads (100 mg) was then sealed in a round bottom flask (50 mL) with chloroform (1 mL) and stirred at room temperature. Pd₂(dba)₃ (4.35 mg,

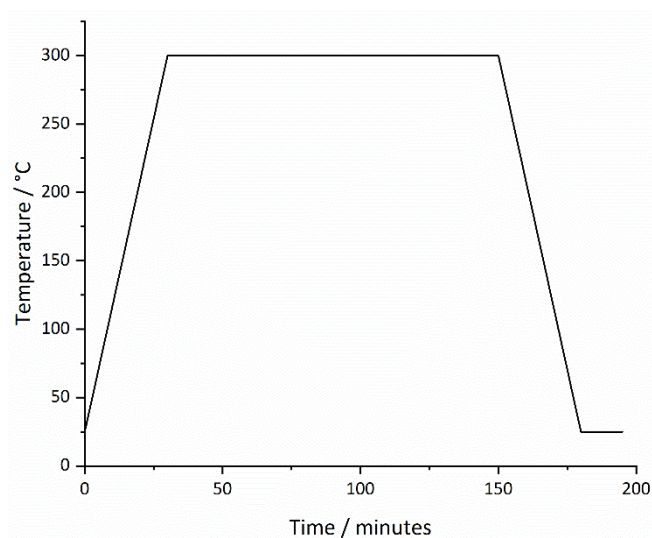


Figure 134. Heating protocol used to remove water from unfunctionalized carbon beads.

9.49 μmol , 1 wt.%) was dissolved in chloroform (9 mL) and added dropwise to the flask containing the PBSAC beads over ten minutes. The flask was heated to 40 °C and stirred for 24 hours. The beads were then filtered, washed thoroughly with chloroform, and dried under reduced pressure in a flask for 24 hours. This yielded catalyst **1a**, and this procedure was repeated for theoretical loadings of 2-5 wt.% Pd for catalyst **1b-e**. The Pd added for each catalyst loading is summarised in Table 43. Scaled up catalyst synthesis of 500 mg catalysts for **1a** were made using the same procedure.

Table 43. Mass of $\text{Pd}_2(\text{dba})_3$ precursor used to produce different Pd wt.% loadings.

Sample	$\text{Pd}_2(\text{dba})_3$ Mass / mg	Theoretical Loading / %
1a	4.35	1
1b	8.78	2
1c	13.31	3
1d	17.93	4
1e	22.64	5

6.10.2.2 Gas phase deposition

IBUtec PBSAC beads were heated in a furnace using the heating protocol shown in Figure 134. The beads (75 mg) were cooled to room temperature and sealed with $\text{Pd}(\text{HFAC})_2$ (3.71 mg, 7.12 μmol , 1 wt.%) in a glass ampule under reduced pressure (3.5×10^{-2} mbar) using the high vacuum equipment shown in Figure 135.³² The ampule was heated to 180 °C in an oil bath for 72 hours. The ampule was removed and cooled rapidly in an ice bath. The ampule was opened and the resulting material was transferred to a fresh ampule and placed under a reduced nitrogen atmosphere

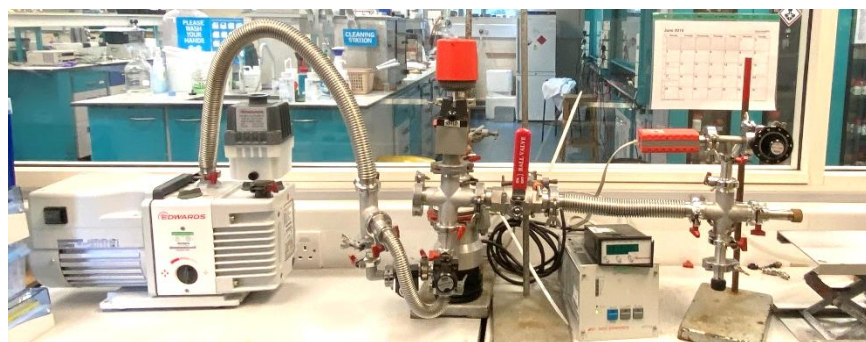


Figure 135. High vacuum setup used to form ampules under reduced pressure for the gas phase deposition catalysts.

(7.1×10^1 mbar). The ampule was heated in a furnace to 500 °C for one hour to yield catalyst **2a**. This procedure was repeated for theoretical catalyst loadings of 2-5 wt.% Pd to yield catalysts **2b-e**.

Table 44. Mass of Pd(HFAC)₂ precursor used to produce different Pd wt.% loadings.

Sample	Pd(HFAC) ₂ Mass / mg	Theoretical Loading / %
2a	3.71	1
2b	7.49	2
2c	11.35	3
2d	15.28	4
2e	19.31	5

6.10.3 Catalyst characterisation

The resulting catalysts were characterised using a number of materials characterisation techniques.

6.10.3.1 ICP-MS

ICP-MS analysis was conducted in a Perkin-Elmer DRC-e ICP-MS instrument for all catalysts synthesised and commercial 1 wt.% Pd/C JM pellets and was used to investigate Pd loadings. Samples (5 mg) were heated to 600 °C in a muffle furnace for two hours to remove the carbon support from the sample, to leave only the Pd. The remaining samples were then dissolved in aqua regia (5 mL, HCL 35%: HNO₃ 65%, in a 3:1 ratio) and diluted to an appropriate concentration with water (45 mL). Calibration solutions were made up from Pd ICP standard (2, 4, 6, 8, and 10 mg L⁻¹).

6.10.3.2 BET

BET was performed on all Pd catalyst samples, unfunctionalized carbon beads and unfunctionalized carbon pellets, using a Micrometrics Tristar at -77 K. Samples were first dried under nitrogen at 100 °C for six hours. Samples were then cooled and analysed on the Tristar instrument.

6.10.3.3 Mastersizer

The unfunctionalized bead size distribution was analysed on a Mastersizer 3000. Beads (1 g) were suspended in water and stirred using a hydro MV at 3500 rpm, before being pumped through the Mastersizer for analysis.

6.10.3.4 SEM

SEM was performed using a Nova NanoSEM 450 instrument. Samples were immobilised using carbon tape on an SEM specimen stub.

6.10.3.5 TEM and STEM

TEM and STEM were performed on a FEI Titan3 Themis 300 microscope. Catalyst samples were prepared by first grinding them into a powder. The samples were then dispersed in IPA and drop cast onto a 200-mesh holey carbon supported copper TEM grid. The grids were allowed to dry before being placed in the spectrometer. 200 NPs were sized for each sample using ImageJ.

6.10.3.6 PFIB-SEM-EDS

An AmberX Xe plasma focussed ion beam from Tescan with an Oxford instruments 170 mm² XMAX EDS detector and a ToFwerk time-of-flight secondary ion mass spectrometer was used to perform PFIB-SEM-EDS on catalyst samples. The beads were first immobilised in carbon paint on an SEM specimen stub and placed in the instrument. Data was analysed using Oxford Instruments Aztec software.

6.10.3.7 XPS

XPS was performed on a SPECS EnviroESCA system with an Ar cluster source, charge neutralisation and sample heating and cooling. Samples were immobilised on carbon tape on a SEM specimen stub, placed in the instrument and put under 3 mbar of nitrogen pressure. Data was processed using CasaXPS software, and all spectra were calibrated against the C 1s peak, which was set to a binding energy of 284.8 eV. The angular distribution correction was set to 54.7 °, and survey quantification was performed using the CasaXPS quantify tool. Shirley-type backgrounds were applied to elemental peaks and subsequent integration of the peaks enabled quantification of the atomic concentrations at the surface of the sample. Default RSF values for each element contained within the CasaXPS software were used to scale the peak areas of interest. A

Shirley background was also defined for the high-resolution spectra. When deconvolving the Pd 3d high-res spectra, the Pd(0) contributions were assigned an asymmetric LA(1.9, 7, 2) line shape and all other peaks were then fitted with GL(30) line shapes. The area of the Pd $3d_{\frac{3}{2}}$ peaks were constrained to two-thirds the area of the Pd $3d_{\frac{5}{2}}$ peaks. The position of the Pd $3d_{\frac{3}{2}}$ peaks was constrained to +5.3 eV of the corresponding Pd $3d_{\frac{5}{2}}$ peaks.

6.10.3.8 Crush testing

The mechanical strength of the unfunctionalized samples was tested using an Instron-5566 using a modified version of the ASTM D-4179 standard testing protocol.⁵⁷ The samples were heated to 250 °C under vacuum for three hours, then cooled and stored under nitrogen in a desiccator. When performing the measurements, an increasing force of 0.05 N s⁻¹ was used on the sample until the sample was crushed. The crush strength of the sample was then recorded and this was performed for 50 particles for each sample. For the unfunctionalized extrudates, the samples were crushed in a radial orientation.

6.10.4 Catalyst testing

The catalysts catalytic performance was tested and compared to the commercial JM 1 wt.% Pd/C pellets.

6.10.4.1 Recirculating batch platform

A Knauer Azura P4.1S dual piston pump with a ceramic pump head (1-10 mL min⁻¹) was used to recirculate the liquid reactants through the platform. Gas flow rates were maintained by a Brooks SLA 5800 series mass flow controller (1-300 mL min⁻¹), and controlled via the bespoke optimisation program using MATLAB, as outlined in Chapter 2. The reactor column was heated using a Eurotherm temperature controller connected to heating cartridges in an aluminium heating block (25-250 °C). IDEX BPR P-761 (40 PSI) and P-763 (100 PSI) cartridges were used to maintain pressure in the system.

6.10.4.2 Typical procedure

1. The column was packed with the catalyst, as per the packing procedure outlined in section 6.10.4.3, and sealed.
2. It was placed in the aluminium heating block and connected to the rest of the recirculating batch platform.
3. The system was flushed with N₂ gas (20 mL min⁻¹) to remove air from the system for 15 minutes.
4. The system was flushed with H₂ gas (20 mL min⁻¹) and heated to 35 °C for 90 minutes at 7 bar pressure.
5. A flask of nitrobenzene (150 mg, 0.08 M) and biphenyl (75 mg, 0.03 M) in methanol (15 mL) was prepared under stirring at ambient conditions.
6. The reaction solution was then recirculated through the system (along with the H₂ gas) at 1 mL min⁻¹ for six hours.
7. The reaction was sampled at one, three, five and six hours and analysed using an Agilent Technologies 7890B GC-FID system.

6.10.4.3 Column packing

The Diba Omnifit EZ column (6.6 mm ID, 100 mm in length) was packed with 2 mm diameter glass beads (Supelco), followed by a layer of 0.5 mm diameter glass beads (Sigma-Aldrich) to ensure the catalyst beads (of the same size) do not fall down the column and stay in a separate band. The catalyst sample (20 mg) was then placed on top of this glass layer, followed by another layer of 0.5 mm diameter glass beads to fill the remainder of the column (packing shown in Figure 136).

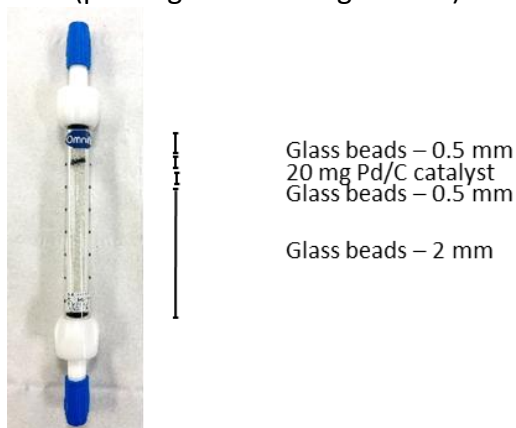


Figure 136. Packing of the Omnifit column with PBSAC catalyst (20 mg).

6.10.4.4 Example GC chromatogram

The GC column used was a HP-5 with a temperature range of -60 – 325 °C, 30 m in length, had a diameter 0.32 mm, and a film thickness 0.25 µm. A typical GC chromatogram is shown in Figure 138.

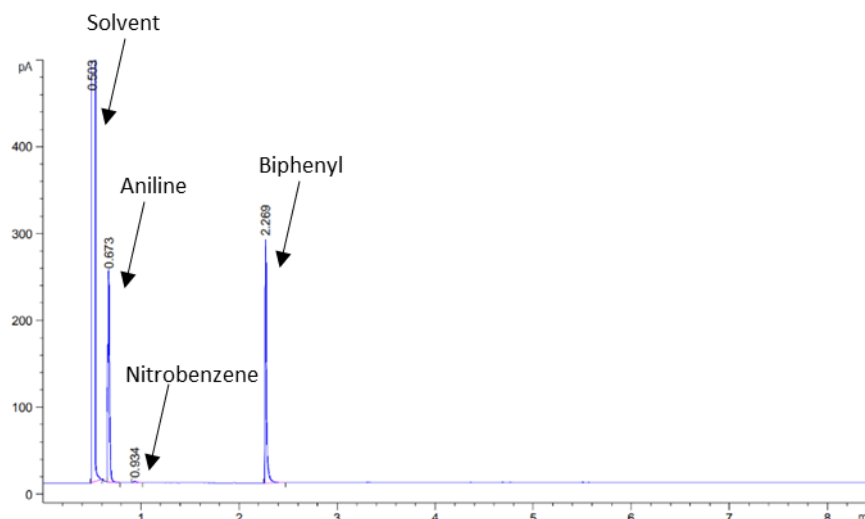


Figure 138. Example GC chromatogram for the recirculating batch platform catalyst tests with the reduction of nitrobenzene (starting material) to aniline (product) with biphenyl as an internal standard.

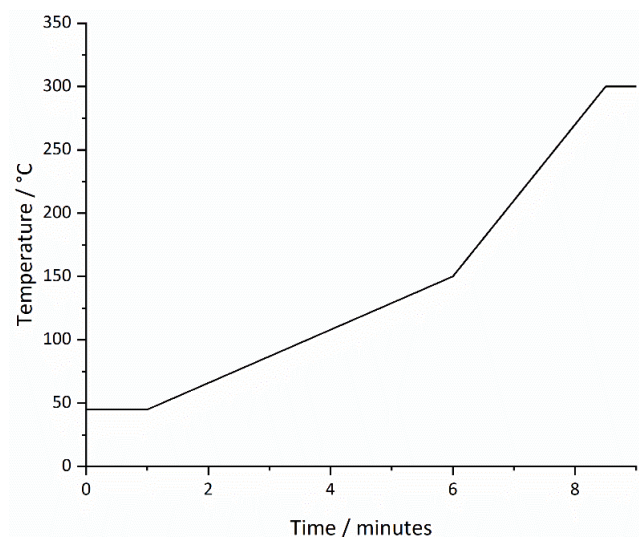


Figure 137. Temperature protocol for GC analysis.

6.10.4.5 Packed bed reactor

The PBR platform that was used to perform catalyst scale up reactions and typical procedure are outlined in Chapter 2.

6.11 Appendix

6.11.1 Summary of BET data

Table 45. Summary of the BET data for all unfunctionalized supports and catalysts.

Catalyst	BJH Ads Pore Volume / $\text{cm}^3 \text{g}^{-1}$	BET Surface Area / $\text{m}^2 \text{g}^{-1}$	BJH Ads Average Pore Diameter / nm
1a	0.57	1269.9	16.69
1b	0.74	1295.2	19.61
1c	0.62	1144.1	18.37
1d	0.54	1129.7	16.12
1e	0.60	1136.2	17.30
2a	0.62	1529.9	15.18
2b	0.58	1418.8	16.34
2c	0.56	1242.7	18.86
2d	0.53	1208.7	16.33
2e	0.68	1275.4	20.66
PBSAC beads	0.66	1563.3	15.15
1% Pd/C pellets	0.16	1102.1	3.92
Carbon pellets	0.09	954.4	4.40

6.11.2 TEM – NP size distribution

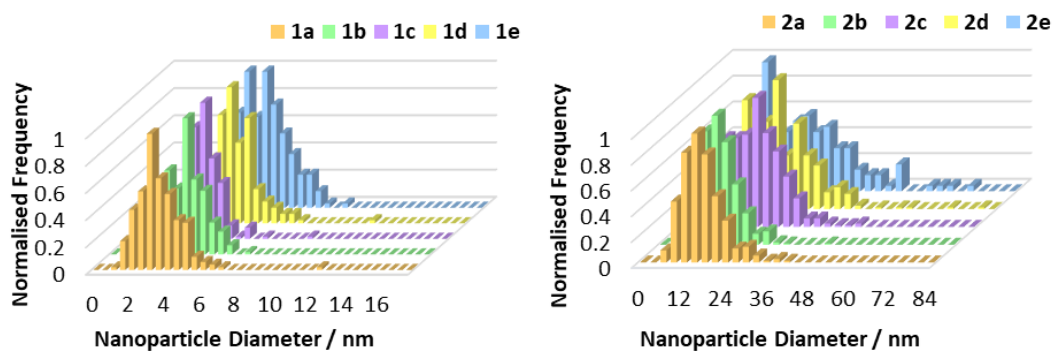


Figure 139. TEM data showing the size of PdNPs for different Pd wt.% loadings for **1a-e** (left) and **2a-e** (right) showing the increase in the average size and size distribution of the PdNPs made via the two deposition techniques (different scales for NP diameter are used to show the details in more depth).

6.11.3 Summary of kinetic and characterisation data

Table 46. Summary of kinetic and characterisation data for catalysts **1a-e**, **2a-e**, and the commercial (comm.) pelletized JM catalysts.

Catalyst	Theoretical loading / %	Actual Loading / %	Average NP Diameter (nm)	K_{obs} (mol L ⁻¹ hr ⁻¹)	TON	TOF (hr ⁻¹)
1a	1	0.38	3.2 ± 1.2	0.65	2246	374
1b	2	0.60	3.8 ± 1.0	1.41	1553	259
1c	3	1.07	3.7 ± 1.0	0.46	569	95
1d	4	1.32	4.4 ± 1.3	0.88	467	78
1e	5	1.72	5.0 ± 1.4	1.28	346	58
2a	1	0.80	15.3 ± 6.0	0.15	471	79
2b	2	1.08	15.0 ± 5.3	0.13	324	54
2c	3	2.60	18.9 ± 7.8	0.24	194	32
2d	4	3.59	20.7 ± 12.8	0.16	113	19
2e	5	3.81	22.8 ± 13.1	0.22	126	21
Comm.	1	1	6.0 ± 2.0	0.30	470	78

6.11.4 Literature rate data

Table 47. Rate and TON data collected from the literature.

Catalyst Type	Rate Constant/TON	Reactor Type
10% Pd/carbon paste ⁵⁸	TON - 2392	Miniature cascade CSTRs – fReactors – 1.7 mL reactors
Pd-Pt/carbon black ⁵⁹	$K = 5.5 \times 10^{-3} \text{ s}^{-1}$	STR - Büchi Uster Picoclave reactor – 200 mL
Pd/glassy carbon foam ⁶⁰	$K = 5.7 \times 10^{-4} \text{ s}^{-1}$	STR - Büchi Uster Picoclave reactor – 200 mL
Pd-maghemite ⁶¹	$K = 4.09 \times 10^{-2} \text{ s}^{-1}$	STR - Büchi Uster Picoclave reactor – 200 mL
Pd/powdered activated carbon ⁶²	TOF – 0.26 s^{-1}	STR – Büchi autoclave reactor
Pd nanosheets/layered double hydroxide ⁵¹	TOF = 108.8 hr^{-1}	STR – Autoclave reactor – 7 mL
Au/Zirconia ⁶³	TOF – 1.58 s^{-1}	STR – Parr autoclave reactor
Immobilised Pt/C coated on capillary tubing ⁶⁴	TOF – 1200 h^{-1}	Micro continuous flow reactor
3% Pd/powdered activated carbon ⁶⁵	$K = 4.5 \text{ mol l}^{-1} \text{ min}^{-1}$	STR – Parr autoclave reactor – 300 mL

6.11.5 XPS data

Table 48. XPS Pd species peak areas and calculated Pd(0):PdO ratios.

Sample	Pd Species	Peak Area / %	Pd(0):PdO
1e Before	Pd (0)	61.3	2.1
	PdO	29.8	
	PdCl ₂	8.9	
1e After	Pd (0)	93.5	14.3
	PdO	6.5	
	PdCl ₂	0	
2e Before	Pd (0)	79.7	6.4
	PdO	12.4	
	PdF ₂	7.9	
2e After	Pd (0)	96.8	30.3
	PdO	3.2	
	PdF ₂	0	

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Chapter 7 : Conclusions and Future Work

The work shown in this thesis has focused on the transfer of heterogeneously catalysed reactions to continuous flow in a custom built automated packed bed reactor platform. The work aimed to improve upon existing applications of optimisation algorithms, by applying self-optimisation approaches to multiphase systems that are currently underreported in the field.

Chapter 2 focused on the construction of a bespoke automated packed bed reactor platform that could perform the self-optimisations of industrially important reaction steps. Initial characterisation of the platform showed that the automated system could be used to vary reaction conditions and achieve reproducible results. The integration of an inline tube-in-tube gas-liquid separator allowed for the use of online HPLC analysis, creating closed-loop feedback control via a computer. The application of both SNOBFIT and Bayesian optimisation algorithms were successfully applied to two case studies, showing that this optimisation approach could afford the optimal conditions for maximising the yield of reactions in a minimum number of experiments. To further this work, more complicated chemistries and discrete variables could be investigated in the developed platform. The use of other gases such as air, oxygen, or carbon monoxide could be used safely in continuous flow at scale due to the enhanced process control achieved in this system. Modifications would be required to dilute the gas outlet with nitrogen when using oxygen, however, nitrogen gas is already available in the reactor system, so this would be trivial.

The work in Chapter 3 aimed to translate an important API reaction step into a continuous flow process (the reduction of osimertinib nitrodiamine - the sixth step in the production of AZ9291). This process has been historically performed in batch; however, the reaction step offers a great opportunity for translation to continuous flow. An appropriate selective catalyst was chosen from screenings conducted in small scale batch reactions, and an OVAT approach to reaction optimisation was performed to determine relevant kinetic information (rate constants and activation energies). The reaction was transferred to continuous flow, where both a DoE and self-optimisations were conducted to find optimal reaction conditions to maximise the yield of the reaction. The data from these optimisations found improvements to the originally OVAT

optimised process conditions reported by AstraZeneca. These improvements resulted in an increased productivity and a decreased catalyst use for the reduction reaction, resulting in less waste and a more efficient process capable of producing over 4 kg L⁻¹ day⁻¹. Further improvements to this process could be found by investigating discrete variables and employing multi-objective optimisation algorithms, to identify the trade-offs between the explored process metrics (STY, RME, TON) and identify the most appropriate catalyst loading, to avoid the waste of precious metals. Deactivation studies on the catalysts would also be important to assess the operational lifetime of the chosen catalyst loading, in the interest of scale up.

The work detailed in Chapter 4 demonstrated the development of a two-step telescoped process for the production of Paracetamol. Continuous flow offers the possibility for fast on-demand product synthesis, which is crucial for drugs such as Paracetamol, that are found on the WHO list of essential medicines. Telescoping reactions improves their sustainability by reducing the number of purifications, solvent use, and transportation costs in the production of the desired products. Self-optimisations for both the single step and telescoped processes were performed, and showed a reduced number of experiments were required when both reaction steps were optimised simultaneously. Benefits in reduced solvent use were also mirrored in a decrease in the PMI of the telescoped process, showing significant improvements to the reaction's sustainability metrics. To accurately assess the effect of the reaction conditions on green metrics such as PMI or STY, a multi-objective optimisation would be useful in future. However, deactivation of the catalyst may cause problems with the increased number of experiments that would be required.

The deactivation of heterogeneous catalysts was addressed in Chapter 5, in an example reaction that caused permanent deactivation of a commercial catalyst. Deactivation of heterogeneous catalysts is one of the main disadvantages of transitioning homogeneous processes to this reaction type. It results in the waste of precious metals, the interruption of plant processes, and increased process costs to replace spent catalysts. Deactivation is also a major concern when performing the self-optimisation of heterogeneously catalysed processes and affects the accuracy of the results. An adaptive simplex optimisation protocol was developed to extend the operational lifetime of catalysts in the packed bed reactor. Modelling and simulations

were performed using real experimental data to limit the consumption of materials and influence the final dynamic simplex optimisation. The proposed protocol showed improvements to product quality, with higher yields and throughputs produced when compared to maintaining the same reaction conditions throughout the experiment. Future work would involve introducing multiple columns to the system, to extend the operational lifetime further. The influence of byproducts would also be an important parameter to investigate in catalyst deactivation and could result in the improvement to many existing processes.

Chapter 6 aimed to address problems with the availability of appropriate catalysts for packed bed reactors. PBSAC bead supports have been shown to be a promising candidate for packed bed reactors, due their high mechanical stability, large active surface area, and low pressure drops. Different NP deposition techniques were investigated, to assess how this affected their activity and physical properties. A bespoke recirculating batch platform was developed in order to perform small scale screening of the catalysts prior to scale up in the automated packed bed reactor platform (developed in Chapter 2). An active, stable Pd/PBSAC bead supported catalyst was developed using a solution phase deposition method, which showed a great activity in a model reduction reaction. The novel catalyst outperformed a commercial pelleted catalyst at both the lab and pilot scale, demonstrating its potential for industrial use. Further work in evaluating the catalysts activity toward other functional groups/industrially important reactions would be critical for supporting its implementation at scale.

In summary, the transfer of heterogeneous catalysts and multiphase hydrogenations to continuous flow has significant benefits. Self-optimisation of these processes can result in the rapid identification of their optimal reaction conditions. The application of optimisation algorithms to multiphase reactions was demonstrated with great success for a range of different problems: API production; the telescoping of reactions; and problems caused by deactivation. There is still many problems that require improvement in this field, including the exploration of multi-objective algorithms with multiphase systems. The investigation of discrete variables such as the catalyst and loading in the reactor would lead to significant progress and allow the relationship between continuous and discrete variables to be better understood.