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**The Application of Niobium Compounds as Catalysts
in Continuous Flow Reaction**

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for the degree of Doctor of Philosophy**

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“未来不迎，当下不杂，既往不恋”

— 曾国藩

Abstract

This Thesis describes the application of niobium oxide and niobium phosphate as solid acids for conducting continuous flow reactions, such as the Friedel-Crafts Reaction and the Skraup Reaction, and also as supports for photosensitiser immobilisation.

Chapter 1 introduces the concepts of green and sustainable chemistry, and give a review of niobium and niobium compounds, especially niobium oxide and niobium phosphate as well as their applications. A summary of flow chemistry is also presented. The continuous flow systems used to conduct the work of this Thesis are described in Chapter 2.

Chapter 3 introduces continuous alkylation of aniline with dimethyl carbonate or methanol over niobium solid acids. The synthesis process is automated by a self-optimisation system to search the best conditions for different products, including the NH_2 group methylation product monomethyl aniline and dimethyl aniline, and the Friedel-Crafts alkylation product N,N-Dimethyl-p-toluidine.

Chapter 4 describes the first exploration of the continuous Skraup synthesis of quinolines with heterogeneous catalyst niobium phosphate. A dissymmetric substituted quinoline compound, 4-(quinolin-6-yl methyl)aniline, was synthesized, and its crystal was grown and the structure was determined by crystallographic analysis for the first time.

Chapter 5 discussed the immobilisation of a photosensitiser meso-tetraphenylporphyrin on niobium solid acids, and the activity of these supported photocatalysts in continuous photo-oxidation, including the photo-oxidation of α -terpinene to ascaridole and the semi-synthesis of an antimalarial drug, artemisinin ART.

Finally, Chapter 6 summarises the work described in this Thesis and examines the success of the techniques and approaches discussed. A summary of potential routes for further study is also presented.

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Finally, to my loving and supportive family, your continued love and encouragements along the way are much appreciated.

Declaration

I declare that the work presented in this Thesis is a record of my own work for the period of November 2013 to May 2017. Where any work has been carried out in collaboration, the relevant researcher or researchers have been acknowledged. This Thesis has not been accepted in partial or complete fulfilment of any other degree or personal qualification.

Jing Jin, 31st of October 2017



31/10/2017

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Nomenclature

Amb	Amberlyst
AN	Aniline
ART	Artemisinin
BPR	Back Pressure Regulator
DHAA	Dihydroartemisinic acid
DMC	Dimethyl carbonate
ESI-MS	Electrospray ionisation mass spectrometer
EtOAc	Ethyl acetate
F-C reaction	Friedel-Crafts Reaction
GC	Gas chromatography
HOMO	Highest occupied molecular orbital
HPLC	High performance liquid chromatography
HPSL	High-pressure sample loop
ISC	Intersystem crossing
LED	Light-emitting diode
LUMO	Lowest unoccupied molecular orbital
MDA	4,4'-methylenedianiline 4l
MeOH	Methanol
NbO	Niobic acid

NbP	Niobium phosphate
NMR	Nuclear magnetic resonance spectroscopy
NMSIM	Modified simplex algorithm
$^1\text{O}_2$	Singlet oxygen
$^3\text{O}_2$	Triplet oxygen
OLEDs	Organic light-emitting diodes
PC	Photocatalyst
QUI	Quinoline
S_0	Ground state
S_1	The lowest excited singlet state
S_n	Singlet excited state
scCO ₂	Supercritical carbon dioxide
SEM	Scanning electron microscope
SOLK	Solketal
SMSIM	Super modified simplex algorithm
Sub	Substrate
T_1	Triplet excited state
TGA	Thermogravimetric analysis
TOF	Turnover frequency
Tol	Toluene
TPP	<i>meso</i> -tetraphenylporphyrin
UV	Ultraviolet
UV-vis	Ultraviolet-visible absorption
XPS	X-ray photoelectron spectroscopy

List of compounds

Chapter 3

3a	<i>N</i> -mono-methyl aniline
3b	<i>N,N</i> -di-methyl aniline
3c	<i>p</i> -Methyl- <i>N,N</i> -dimethylaniline

Chapter 4

4a	Quinoline
4b	Glycerol
4c	Acrolein
4d	Solketal
4e	Acetone
4f	2,4-dimethylquinoline
4g	2,2,4- trimethyl-1,2-dihydroquinoline
4h	3-methylindole
4i	Hydroxyacetone
4j	2-hydroxy-1-propanal
4k	4-methoxyaniline
4k-1	6-methoxyquinoline
4k-2	4-methoxy- <i>N</i> -methylaniline

4k-3	N-ethyl-4-methoxyaniline
4l	4,4'-methylenedianiline
4l-1	4-(quinoline-6-yl methyl)aniline
4l-2	Di(quinolin-6-yl)methane

Chapter 1. Introduction

The concept of green and sustainable chemistry focusses on the development of chemistry, which seeks to minimise the effect on the environment and health, and to maximise the societal and economic benefits of the chemical manufacturing process (Figure 1.1.1).¹⁻⁴

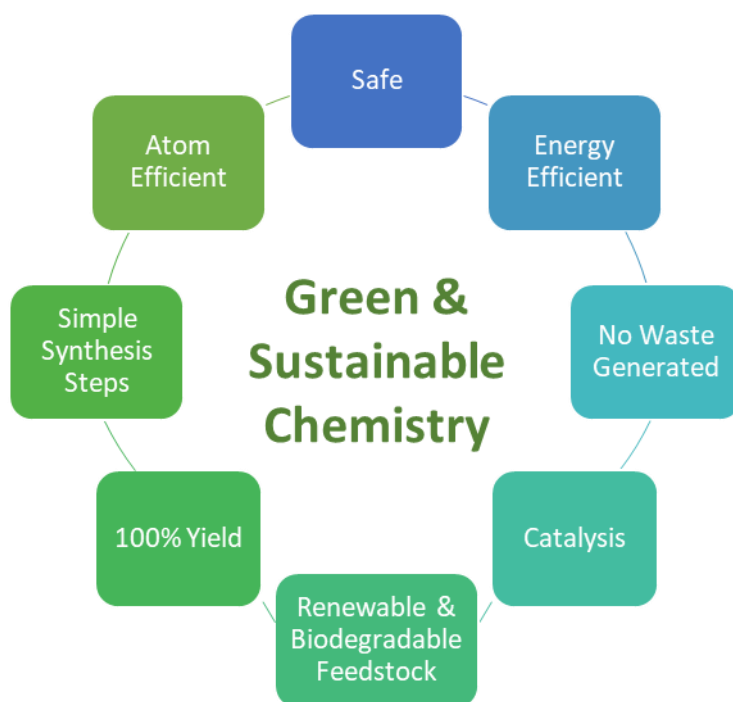


Figure 1.1.1. The goal of Green and Sustainable Chemistry.

The development of solid acid catalysts can meet these targets for green catalysis. Though most fine and pharmaceutical chemical production processes are under homogenous conditions, and hence do not use solid acid. Some of them have been developed over hundred years and optimised to be green processes that have high yield and low impact on environment. However, there are still chemical manufacturing processes, which generate substantial quantities of waste during the product separation step, an area which needs to be improved.

More than 90% of all commercial chemicals are produced through at least one catalytic process.⁵⁻⁷ Moreover, the most common acid that is used in the chemical industry is sulfuric acid. Every year more than 15 million tons of sulfuric acid are consumed, which brings about the significant cost of separating the product from homogeneous reaction mixtures and results in a negative impact on the environment.⁸

⁹ The application of solid acids offers a new way to address these issues.

Compared to conventional mineral acids, such as hydrofluoric acid and sulfuric acid, solid acids are environment-friendly catalysts with several of advantages. More specifically, reaction processes which involve liquid acids are typically associated with issues such as high toxicity, corrosion of the equipment, chemical waste, and difficulty in product separation and recovery.^{6, 10} By contrast, solid acids are environmentally friendly catalysts which have advantages with respect to lower toxicity, reduced corrosiveness, less waste, recyclability of the catalyst and ease of product separation.¹¹ Given this, solid acids are clearly a desirable replacement for liquid acids both in chemical research and the wider chemical industry.

Since the middle of the twentieth century, over three hundred different solid acids have been discovered and investigated. According to a review by Tanabe,¹² till now, there are now more than 180 industrial processes using solid acid catalysts in a

variety of chemical reactions, for instance alkylation, isomerization, dehydration, condensation, cracking and etherification, most of which are carried out in the gas phase. The large number of catalysts investigated include zeolites, clays, metal oxides and ion-exchange resins. It is noteworthy that zeolites and bases are the most widely used catalysts, with more than 41% of industrial processes employing zeolite catalysts, because of their excellent thermal and chemical stability, acid properties and shape selectivity.¹²

Using water as a solvent gave an additional environmental benefit, since it is low cost, non-flammable, non-toxic and safe. However, a significant number of acid-catalysed reactions, such as Friedel-Crafts reactions, esterification, hydration, and hydrolysis, are still catalysed by homogeneous acids such as hydrofluoric acid and sulfuric acid.^{13, 14} This is due to the fact that most solid acids are highly sensitive to water which can poison acid sites. In fact, most solid acids lose their catalytic activity in aqueous solutions.¹⁵

Development of new, water-tolerant, solid acids to replace liquid acids would have a major impact in industrial applications. According to a review by Okuhara,¹¹ solid acids which can be used in water include zeolites, heteropoly compounds, polymer resin-silica composites, metal oxides (such as niobic acid), mixed metal oxides (such as $\text{MoO}_3\text{-ZrO}_2$), and phosphates (such as niobium phosphate). Among these solid acids, niobic catalysts exhibit superior catalytic activity and long lifetimes when reactions are performed in water. This will be discussed in next section.

1.1. Niobium and Niobium Containing Compounds

1.1.1. Niobium

Niobium, the 41st element, is in group 5 of the periodic table. It is a soft, grey, ductile transition metal (Picture 1.1.1.1).¹⁶ It was first discovered by the English chemist Charles Hatchett in 1801 and was named originally columbium. As the physical and chemical properties of niobium are similar to its neighbour tantalum in the periodic table, it was very difficult to separate the two metals in the early 19th century. By 1846, the German chemist Heinrich Rose had proved that there is a second element in tantalum ores and he named it niobium. The name niobium was officially adopted by IUPAC in 1950.^{16, 17}



Picture 1.1.1.1 Pure niobium metal produced by Brazilian mining company CBMM, Companhia Brasileira de Metalurgia e Mineração, which is the world largest producer of niobium. (Author's photo taken in CBMM, Araxá, Brazil)

Historically, the majority of known niobium reserves are found in Brazil and Canada, and recently it has also been found in some geopolitically sensitive areas, such as southern Afghanistan and the Democratic Republic of the Congo.^{18, 19} However,

according to geologists' Theorize, there may be lots of niobium 'missing' which may be contained in deep silicate reservoirs in the planet's core.²⁰



Picture 1.1.1.2 The car - body steel structures using different niobium micro-alloyed steels. The coloured parts represent the niobium containing steels made in different strengths. (Author's photo taken in CBMM, Araxá, Brazil)

The major consumer of niobium is the steel industry. Every year about 90% of the niobium produced is used to make micro-alloyed steels. Niobium does not alter the structure of the iron when it is used as a micro-alloying element in steel.^{21, 22} Instead it combines with the carbon, nitrogen, and sulphur, changing the microstructure of steel. Adding only 0.001% - 0.1% of niobium is enough to change the mechanical properties of steel. For example, when adding 0.1% of the alloying element, the increase in the strength of steel is: 118 MPa for niobium; 71.5 MPa for vanadium; 40 MPa for molybdenum; 17.6 MPa for manganese; and 0 for titanium. In fact, adding as little as 0.03% - 0.05% niobium, will increase steel strength by more than 30%. Moreover, adding niobium not only improves the strength of steel, but can also improve other properties of the steel, increased toughness (the elasticity and hardness of a metal object); greater resistance to high temperature oxidations and corrosion; reduced steel

brittle transition temperature, and to lead to a good welding performance and formability. This allows for the use thinner plates to make lighter cars, which consume less fuel with reduced emissions (Picture 1.1.1.2). Furthermore, due to the low percentage of niobium added, the cost of steel increases only \$1 per ton. The low cost and high performance enhancement when niobium is added to steel, makes niobium very attractive to the steel industry, especially in developing new steel grades.¹⁵

Besides interesting applications in the steel industry, niobium also has great potential as a superconducting material.²³⁻²⁵ It is well known that, the ultra-low temperatures needed for superconducting materials are not easy to reach. The closer to the absolute zero and the higher the cost. Therefore, the aim is to find a superconducting material with a higher critical temperature. Under the standard atmospheric pressure, niobium has the highest critical temperature (-264 °C) of all the superconducting elements. Moreover, niobium alloy, such as niobium-titanium alloy, niobium-zirconium alloy, niobium-tantalum alloy all have higher critical temperatures.^{21, 26, 27} In particular, niobium-tin alloys and niobium-tin-germanium alloys have critical temperatures between -255 °C and - 252 °C. This means niobium and niobium-tin-germanium alloys have become the most important superconducting materials. With these, a great improvement in the transmission efficiency might be realized in the future.

In addition, niobium is used as a precious metal with gold and silver for making jewellery and commemorative coins (Picture 1.1.1.3). The multiple colours are generated by anodizing, where different thicknesses of a niobium oxide layer show different colours (green, blue, purple, pink and so on).²⁸



Picture 1.1.1.3 Collectable Euro coins produced by Austria minting. Pictures adapted from the Austrian mint website.²⁸

As a non-toxic element, niobium has been utilized as a constituent elements of Ti alloys, which can be used for biomedical applications because of their good biocompatibility and high corrosion resistance.²⁹ Recently Rubitschek *et al.*³⁰ have reported an ultrafine-grained niobium-zirconium (NbZr) alloy, which exhibits excellent corrosion resistance, fatigue strength, and crack propagation resistance in simulated body fluid, demonstrating that this NbZr alloy is an attractive new metallic material for biomedical implants.

The valence states of niobium include -1, +2, +3, +4 and +5, with +5 being the most stable valence state for niobium compounds.¹⁷ Niobium-containing compounds include NbCl₅, NbF₅, NbH, NbS₂, NbN, NbC, NbO_x, NbP and Nb organometallic compounds. Ziolek and Nowak have reviewed the structures, characterization and applications of niobium compounds.^{21, 31}

This Thesis mainly focuses on the applications of hydrated niobium pentoxide and niobium phosphate as solid catalysts in flow synthesis. The properties of these two Nb catalysts and their applications will be described in more detail in the following sections.

1.1.2. Niobium Pentoxide

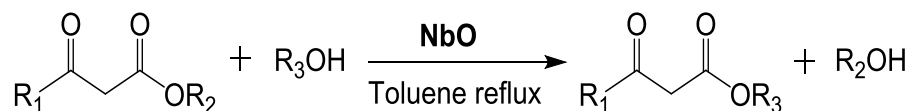
Niobium pentoxide is the most common niobium oxide. It is a white powder that is stable in air and insoluble in water. The structure of Nb_2O_5 probably consist of NbO_6 octahedra which are connected by edges and corners. Hydrated niobium pentoxide ($\text{Nb}_2\text{O}_5 \cdot n\text{H}_2\text{O}$) is usually called niobic acid (**NbO**), and has strong acidic properties on its surfaces.³² The acidic strength (H_0) of **NbO** is between -5.6 and -8.2, which is equal to that of a 70% H_2SO_4 solution.³¹

NbO has two types of acidic sites on its surface, Lewis acid sites and Brønsted acid sites.³³ Generally, the number of Lewis acid sites will increase with increasing pretreatment temperatures up to 500 °C, and then decrease at higher temperatures; the amount of Brønsted acid sites is largest at 100 °C and decreases at higher temperatures. Hydrated niobium oxide starts to crystallize at 580 °C, and its strong acidic properties disappear when it is heated to temperatures higher than 530 °C.³⁴

Many metal oxides are acidic after heat treatment at high temperature (100 °C – 300 °C), but when they are placed in an aqueous medium their surface acidity quickly decreases or disappears. By contrast, the **NbO** can retain high acidity in the presence of water above 300 °C.³⁵ Therefore, **NbO** is used as a solid acid in acid-catalysed reactions such as esterification,^{36, 37} hydrolysis, dehydration.³⁸⁻⁴¹

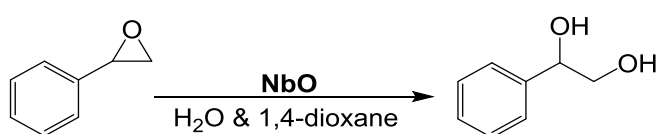
By using **NbO** as catalyst, the esterification of acrylic acid with methanol can reach 95% conversion, coupled with extremely high selectivity 100%.⁴² Moreover, after a 60 hour reaction, the activity of **NbO** did not change appreciably, which shows that **NbO** has a long life-time and highly stable catalytic activity. In addition, **NbO** has been investigated to catalyse the transesterification of β -keto esters with several kinds of

alcohols (Scheme 1.1.1), leading to good conversion and moderate to good isolated product yields.⁴³



Scheme 1.1.1 NbO catalytic transesterification of β -keto esters with alcohols.⁴³

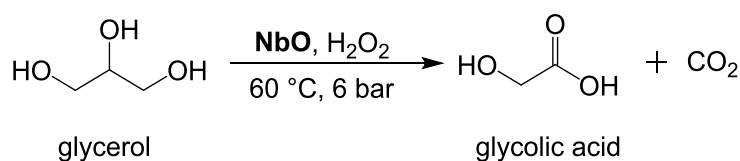
The high water tolerance of **NbO** allows it to be used as a catalyst in aqueous or other water containing reactions. Several studies have been reported in the literature which illustrate that **NbO** has high catalytic activity for the hydrolysis of phenyloxirane.^{44, 45} Sugi and co-workers compared the use of different catalysts for hydrolysis of phenyloxirane in aqueous solution (Scheme 1.1.2).⁴⁶ **NbO** exhibited the highest activity among the typical solid acids (H-ZSM, SiO₂-Al₂O₃ and H-Nafion). Moreover the selectivity to phenyl-1, 2-ethanediol can reach 100% in an aqueous reflux with **NbO**.



*Scheme 1.1.2. Phenyloxirane forms phenyl-1, 2-ethanediol by hydrolysis over **NbO** catalyst.⁴⁶*

Besides the good performance in acid-catalysed reactions, **NbO** has also been applied in oxidation⁴⁷ and photochemistry⁴⁸⁻⁵⁰. Ziolek *et al.* reported using **NbO** and Ta₂O₅ in the oxidation of glycerol to glycolic acid with hydrogen peroxide (Scheme 1.1.3).⁵¹ The study revealed that peroxo radical species, formed in the interaction of H₂O₂ with **NbO**, have higher activity in the oxidation of glycerol than Ta₂O₅. Moreover,

100% selectivity to glycolic acid can be obtained (at 7% glycerol conversion) with amorphous **NbO**, which is much higher than the selectivity obtained using gold modified carbon and TiO₂ (40–50%). This makes amorphous **NbO** a very promising support which could be modified, for example by the addition of gold, for use in the oxidation of glycerol to glycolic acid with H₂O₂.

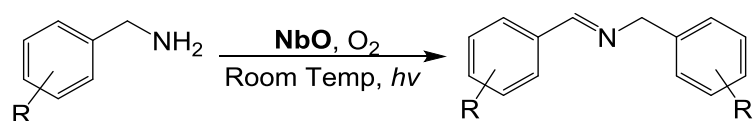


Scheme 1.1.3 NbO catalytic oxidation of glycerol to glycolic acid with 100% selectivity.

In terms of photochemistry, **NbO** presents a band gap (~ 3.4 eV) similar to that of TiO₂, which makes **NbO** is an ideal candidate for UV-light sensors. Costa *et al.* compared the activity of **NbO**, TiO₂ and ZnO in the photo degradation of indigo carmine dye.⁴⁹ After 9 reaction cycles, TiO₂ and ZnO suffered an abrupt loss of their catalytic activity, while **NbO** maintained 85% of its original catalytic activity even after 10 reaction cycles.

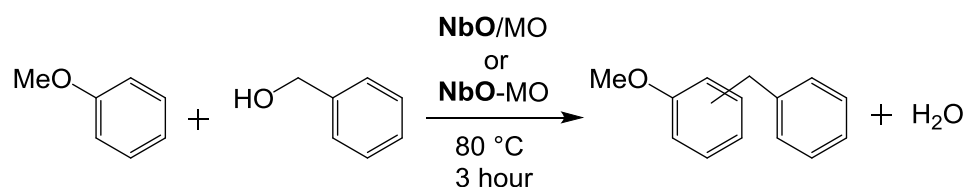
Moreover, the transparency to visible light, can also be expected from **NbO** sensor. Examples of using **NbO** for photo oxidation are supplied by Tanaka's group.^{48, 52} **NbO** was used as a photo catalyst for 1-pentanol oxidation. The reaction was performed at the atmospheric pressure and room temperature in a batch reactor with flowing O₂. **NbO** exhibits a higher activity and the highest selectivity to partial oxidation products compared to other metal oxides. Based on this research, they further studied the selective photo oxidation of amines over **NbO**.⁵³ Various benzylamines were investigated and successfully converted to their corresponding imines in excellent yields (95-99%), as shown in Scheme 1.1.4. It is noted that some of these photo

oxidations catalysed by **NbO** can be achieved under visible light ($\lambda > 390$ nm) irradiation, although **NbO** does not absorb visible light. The authors proposed a possible mechanism that a new absorption (at about 350 nm and overlapped with region of > 390 nm), which is ascribed to the surface complex consisting of adsorbed amines and **NbO**, can achieve a direct electron transfer from a donor level consisting of a N 2p orbital derived from adsorbed amine species.



*Scheme 1.1.4 Photo oxidation of benzylamine over **NbO** under visible light.⁵³*

Due to the outstanding optoelectronic performance, **NbO** has been developed into various nano structures to enhance its activity.^{50, 54-56} Novel **NbO** nanosheets were synthesized by Luo et al.⁵⁴ The synthesized products were then used as the electrode material for lithium ion intercalation. Cyclic measurements indicate that this electrode composed of **NbO** nanosheets exhibits a high reversible charge/discharge capacity and cycling stability, making it a potential candidate as a positive electrode material for lithium ion batteries.



*Scheme 1.1.5 Friedel-Crafts benzylation of anisole over **NbO** containing or supported mixed oxides (MO) catalysts.⁵⁴*

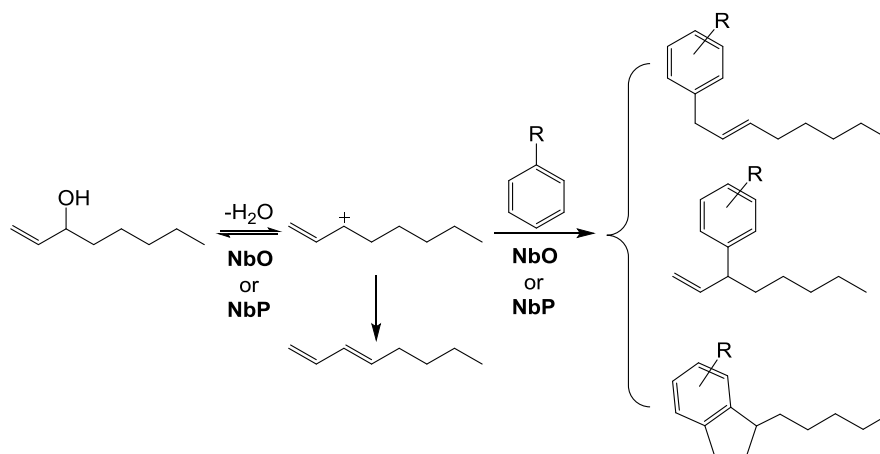
In addition, **NbO** exhibits a pronounced effect as a support for metal and metal oxide catalysts. Mixed oxides containing **NbO**, and **NbO** supported on the other oxides, also show the above effect.^{21, 57, 58} Yamashita *et al.* reported a detailed study of **NbO**, both loaded onto supports and mixed with other oxides (Scheme 1.1.5).⁵⁹ Different support catalysts have been tested, including SiO₂, TiO₂, Al₂O₃ and MgO. The **NbO** supported catalysts were tested for the Friedel-Crafts benzylation of anisole, and the following sequence of activities was found: **NbO**/SiO₂ > **NbO**/TiO₂ > **NbO**/Al₂O₃ > **NbO**/MgO. The activity of **NbO**/SiO₂ was much higher than the non-supported **NbO**. Mixed oxide catalysts were then prepared containing mixtures of MoO₃ and WO₃ with **NbO**, and both **NbO**-MoO₃ and **NbO**-WO₃ showed improved activities, which were much higher than either the supported catalysts or non-supported **NbO**.

1.1.3. Niobium Phosphate

To enhance the surface acidity at higher temperatures, **NbO** can be pretreated with phosphoric acid.⁶⁰ This leads to the formation of amorphous niobium phosphate (**NbP**) on the surface of **NbO**. **NbP** has the similar acidic and catalytic properties to **NbO** but at higher maximum operation temperature. Okazaki *et al.* reported that the amorphous **NbP** shows stronger surface acidity ($H_0 < -8.2$) than **NbO** (-5.6 to -8.2), and its crystallization temperature is up to at 530 °C.⁶¹ Furthermore, the strong acid property of **NbP** still exists when it is preheated to temperatures higher than 230 °C.

Carlini *et al.* reported a comprehensive study of the properties of both **NbO** and **NbP**.⁶² This revealed that **NbO** only has NbOH groups, whereas **NbP** contains both POH and NbOH groups. The POH groups are characterized by a stronger Brønsted acidity than NbOH groups, which leads to **NbP** displaying stronger acidity than **NbO**.

The Lewis acid strength is similar for both kinds of Nb catalysts and are assigned to coordinative unsaturated Nb⁵⁺ sites. In addition, **NbP** has a larger number of surface acid sites than **NbO**. All of these result in a superior acidic activity of **NbP** compared to **NbO**.

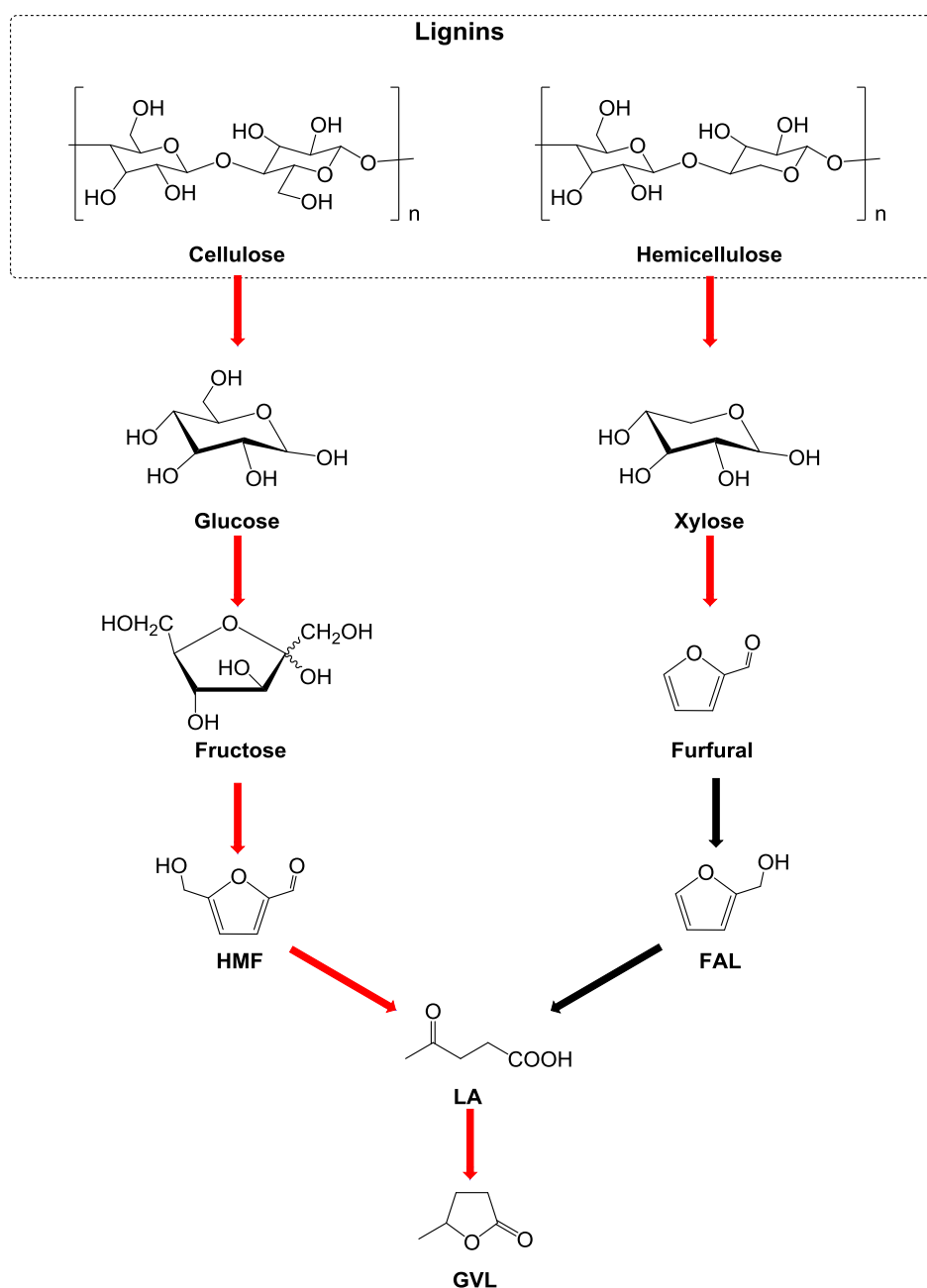


Scheme 1.1.6 Alkylation of aromatic compounds with 1-octen-3-ol over Nb catalysts.⁶³

A catalytic activity comparison of **NbO** and **NbP** was evaluated in the alkylation of anisole and toluene with 1-octen-3-ol (Scheme 1.1.6).⁶³ **NbP** exhibited a higher catalytic activity than niobic acid for the anisole alkylation and the selectivity for monoalkylation products was > 80%. However, in both cases, the catalytic activity for the alkylation of toluene was less than the corresponding alkylation of anisole, due to the lower degree of activation of toluene for aromatic electrophilic substitution compared to anisole. In this Thesis, **NbO** and **NbP** will be used to catalyse the alkylation of aniline with dimethyl carbonate and methanol. Comparison of the acidic activity of these two catalysts will be discussed in more details in Chapter 3.

As discussed above, Nb catalysts show high activity for various reactions, especially in aqueous reactions, which makes **NbO** and **NbP** attractive catalysts for biomass conversion. **NbO**, **NbP** or supported catalysts have been investigated for various biomass conversion processes which are summarised in Scheme 1.1.7 (with red

arrow), including the conversion of glucose into 5-(hydroxy-methyl)furfural (HMF),⁶⁴,
⁶⁵ direct conversion of cellulose to HMF,^{66, 67} dehydration of xylose to furfural,⁶⁸
 production of furfural from hemicelluloses⁶⁹ and production of γ -valerolactone (GVL)
 by hydrogenation levulinic acid (LA).⁷⁰



Scheme 1.1.7 The pathway (with red arrow) of biomass conversion over niobium containing catalysts.

Besides the conversions mentioned in Scheme 1.1.7, Nb catalysts have been used as supporting materials to synthesis multifunctional catalysts for the direct conversion of biomass to liquid alkanes and arenes.^{71, 72} Xia *et al.* reported a **NbP** supported Pd catalyst for the hydrodeoxygenation of furan-derived adducts to liquid alkanes. A greater than 90% yield of octane was obtained, and the Pd/**NbP** showed excellent activity and stability with almost no decrease in activity over a 256 hour reaction.⁷¹

In addition, several groups have studied the use of **NbO** or **NbP** as catalysts in conversions of the biodiesel by-product glycerol, such as esterification³⁷ and dehydration.^{40, 73-75} Rao *et al.* used **NbP** catalysts, calcined at different temperatures, to dehydrate glycerol to acrolein in the vapour phase.⁷⁵ With calcined **NbP** catalysts, the conversion of glycerol can be obtained in the range of 75–100% with 69–86% selectivity to acrolein. The **NbP** catalyst calcined at 550 °C showed higher selectivity to acrolein than was achieved at other calcination temperatures. This selectivity is attributed to the presence of only moderate acidic sites after calcination at 550 °C with the majority of them Brønsted acidic sites.

The outstanding performance of Nb catalyst in biomass conversion inspired us to explore their applications further in this Thesis in combination with continuous flow processes. Studies presented in Chapter 4 will describe using **NbP** to synthesise the more complex compound quinoline, from the biomass by-products glycerol and solketal via the Skraup synthesis.

1.2. Flow Chemistry

Over the past hundred years, chemists have contributed to the research on a wide range of topics including chemical mechanism, catalysis, synthesis, and combinatorial chemistry which has led to numerous remarkable developments in the field of chemistry.^{76, 77} However, the research into modern chemical technology began just a few decades ago.

Batch reactors which are inexpensive and versatile have become the major experimental approach and indeed have been used in chemistry laboratories for many years. However, on larger scale, the deficiencies of batch reactors/reactions become evident. These include inefficient dissipation of heat, poor mixing and problems in product purification. The question of how to convert from bench-scale to commercial plant scale in a safe, low-waste, and energy efficient way is a major challenge which we are facing now.^{78, 79} Continuous flow processes are recognised as an effective approach in overcoming these constraints in many cases.⁸⁰ The following sections will discuss the superiorities of continuous flow reactors in detail.

1.2.1. Better Performance in Reactions Involving Gases

Chapter 5 describes photo-oxidation using gaseous oxygen as a reactant in a continuous flow process. Flow reactors have particular advantages for reaction involving gaseous reactants, which will be described briefly in this section.

Gaseous reagents can often be considered to have a high atom efficiency as starting materials in chemical production. However, due to the poor solubility of such

gases in typical reaction solvents, the usage of gases in a batch reaction always requires a large stoichiometric excess, while the poor interfacial mixing leads to extended reaction times. Moreover, reactions involving toxic and dangerous gases such as CO, H₂ or O₂ increase the difficulty of operation.

Flow reactions proceed in relatively small reactors, which means that the interfacial area is comparatively larger than in a batch reactor, and thus gives rise to a decrease in reaction time.⁸¹ Baxendale and his co-worker have summarised the interfacial surface area of various batch and flow reactors (Table 1.2.1).⁸²

Table 1.2.1 Interfacial Area of different batch reactors vs flow reactors ^a

Reactor Type	Interfacial Area (m ² m ⁻³)
5 mL round-bottom flask	141
50 mL round-bottom flask	66
250 mL round-bottom flask	38
Tube reactor (horizontal and coiled)	50-700
Tube reactor (vertical)	100-2000
Micro flow channel (gas-liquid)	3400-18000

^a Reproduced from Baxendale *et al.*⁸² and Seeberger *et al.*⁸³

Although a reaction carried out in a small round bottom flask has relative good interfacial area (around 100 m² m⁻³ in a 5 mL flask), the area decreases rapidly with increasing flask size (to around 30 m² m⁻³ in a 250 mL flask). By comparison, a tube flow reactor could achieve a much larger interfacial value between gas and liquid. This is especially the case in the micro-flow reactors, where the interfacial area is 30 times or even more than in traditional batch reactors.

Moreover, by adjusting the flowrate, the reagents in microchannel can create a Taylor flow. Taylor flow is a type of gas–liquid flow pattern that consists of elongated

bubbles, with an equivalent diameter usually many times that of the channel diameter, separated by liquid slugs (Figure 1.2.1).⁸⁴ The recirculation of the liquid inside the slug can significantly enhance mixing, increase mass transfer across phase boundaries, and reduce dispersion.⁸⁵⁻⁸⁷

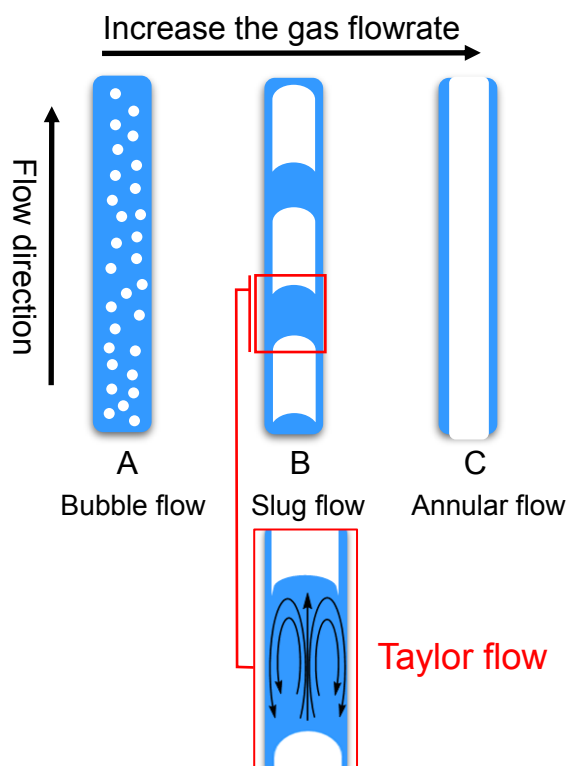
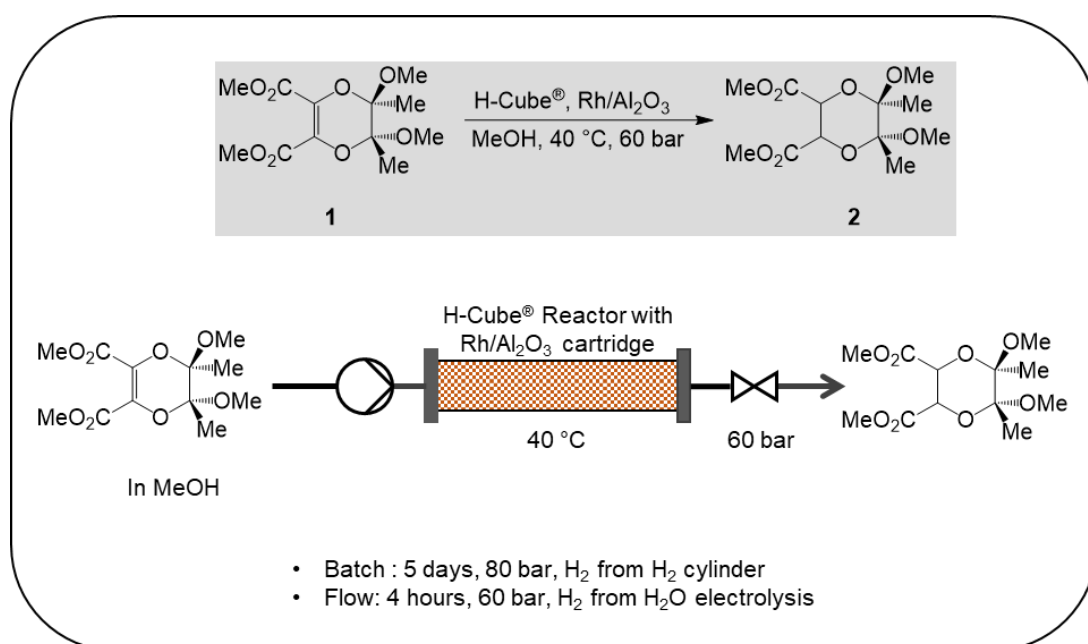


Figure 1.2.1 Illustration of gas-liquid flow pattern (White: gas phase. Blue: liquid phase). A). Bubble flow. B) Taylor flow or slug flow. C) Annular flow.

In addition, a flow system can be sealed to avoid the hazards of gas escape and to protect the air-sensitive chemicals. If using a micro-flow reactor, the amount of hazardous gas required is small, reducing the risk of operation further. Moreover, by using a stainless steel flow reactor, the closed system could be operated under a high pressure (100 bar or more), which increases the gas solubility and also benefits liquid phase reactions involving low boiling point liquids.

Ley's group have performed a detailed study on the hydrogenation of alkene **1** to **2** (Scheme 1.2.1), and compared the performance of this reaction in batch reactor

with that of a flow process.⁸⁸ The results showed that in the batch reactor this reaction required multiple days with very high H₂ pressure (80 bar). However, when the reaction was carried out in a commercially available H-Cube[®] flow reactor, the reaction time was greatly shortened to 4 hours. What is more, the H-Cube[®] can generate hydrogen gas from electrolysis of the water, which can supply feedstock for the reaction, avoiding the need to store hazardous H₂ gas cylinders. As a result, the whole system pressure could be reduced to 60 bar, which is lower and safer than the batch reaction. In addition, the subsequent separation and reuse of the catalyst from the reaction was possible, which gave rise to a substantial increase in efficiency.



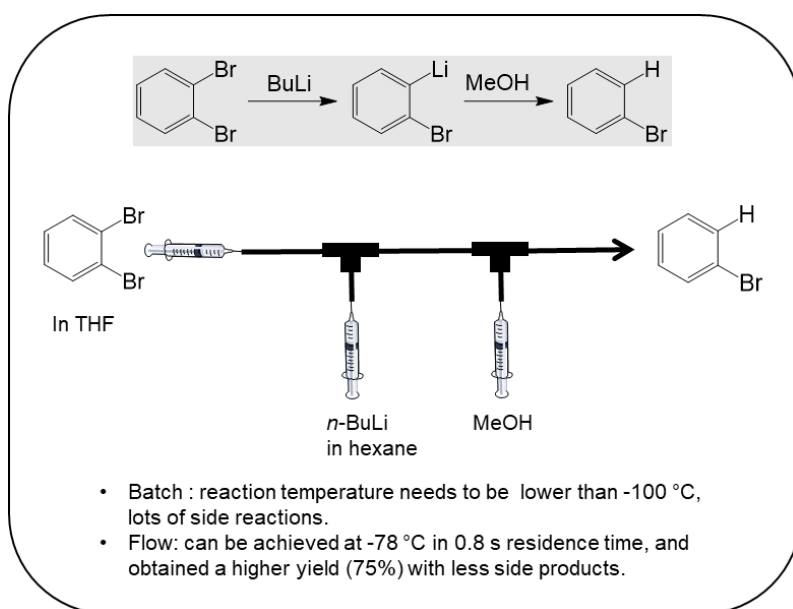
*Scheme 1.2.1 Continuous hydrogenation of an alkene with heterogeneous catalysts in a commercial flow reactor.*⁸⁸

Similar advantages apply to the photo reactions using gaseous oxygen carried out in this work, which are described in more details in Chapter 5.

1.2.2. Efficiency in Heat Transfer

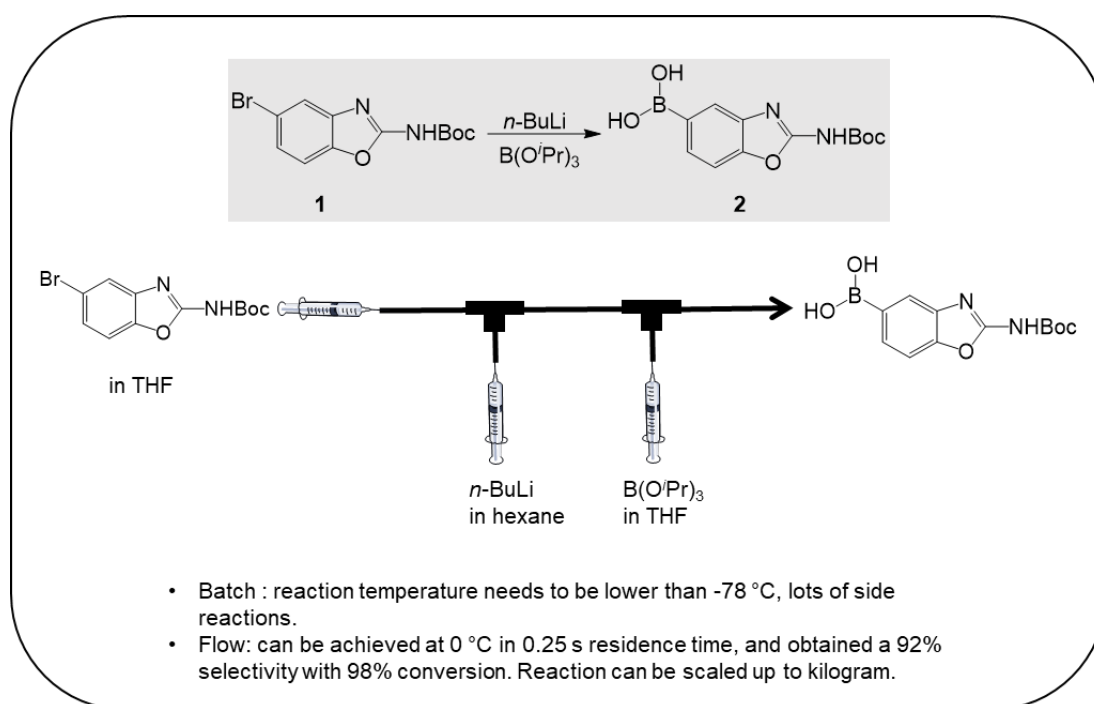
This Thesis involves the use of niobium compounds as high temperature solid acid catalysts. Therefore, this section explores the thermal efficiency of flow reactors, which can be cooled or heated more easily than batch reactors or with similar productivities.

For temperature dependent reactions, productivity is highly influenced by heating or cooling the system. In exothermic reactions, efficient cooling could reduce the side reactions and avoid potentially dangerous safety issues.⁸⁹ Compared to a batch reactor, the dimensions of a micro flow reactor are smaller, which is of benefit, not only in term of mixing, but also for controlling the heat generation and removal. Moreover, a continuous flow system avoids the tedious/complex operations associated with certain batch reactions, such as slowly adding the reagent in a drop-wise fashion to prevent a temperature spike, which saves a lot of time and energy.



Scheme 1.2.2 Continuous lithiation of o-dibromobenzene in microtube reactor.⁹⁰

Usutani *et al.* have carried out the lithiation of *o*-dibromobenzene, a very fast and highly exothermic reaction that is commonly involved in pharmaceutical syntheses, in a stainless steel micro flow reactor (Scheme 1.2.1).⁹⁰ Conventionally, the lithiation of *o*-dibromobenzene is carried out in a batch reactor at $-100\text{ }^{\circ}\text{C}$ or, below to mitigate the exotherm which would promote a side reaction and generate benzyne. By performing the reaction in a micro flow system instead, the same reaction can be successfully carried out at a higher temperature of $-78\text{ }^{\circ}\text{C}$, using 0.8 s reaction time, and with an increased yield of bromobenzene 75%.



Scheme 1.2.3 Continuous lithiation–borylation of aryl bromide **1** to a kilogram-scale.⁹¹

Based on this research, more recently Usutani and his group have developed a flow process for lithiation–borylation to a kilogram-scale (Scheme 1.2.3).⁹¹ The continuous lithiation–borylation of aryl bromide **1** was carried out in a 2.17 mm diameter and 550 mm long stainless steel tube with two Swagelok T piece (id 1.3 mm)

as mixers. Compound **1**, *n*-BuLi and B(O^{*i*}Pr)₃ were pumped at 110.0 mL/min, 20.8 mL/min, and 20.0 mL/min, respectively. The residence time for lithiation is as short as 0.25 s. The reaction was run at 0 °C for 10 h 14 min, and afforded compound **2** in 92.0% purity with 4.4% debromination and 98.2% conversion. It is notable that, when lithiation–borylation of Compound **1** was attempted in batch, complex mixtures of products were collected even at temperature as low as at –78 °C. Using a continuous flow system has resulted in a great improvement in the productivity and safety of the operation.

1.2.3. Efficiency of Irradiation

The study in Chapter 5 describes the photochemical synthesis of artemisinin, which was carried out in a continuous photo reactor that was designed in-house to maximise the light exposure of the reagents. This section gives a brief discussion of the advantages of continuous processing in photochemistry.

Photochemistry, which use photons as ‘traceless and green reagents’ to activate molecules, is considered to be a potential pathway in green and sustainable chemistry.⁹²⁻⁹⁵ One essential parameter for photochemistry is the efficiency of the irradiation of the reaction mixture. According to the well-known Beer–Lambert–Bouguer law (Eq 1), the attenuation of light is correlated with the molar extinction coefficient of the light absorbing molecules (ϵ), their concentrations (c) and the path length of the light propagation (l).

$$A = \epsilon cl \quad (1)$$

Assuming the concentration of the absorbing molecules is held consistent, increasing the reactor size will decrease the light intensity reaching the centre of the

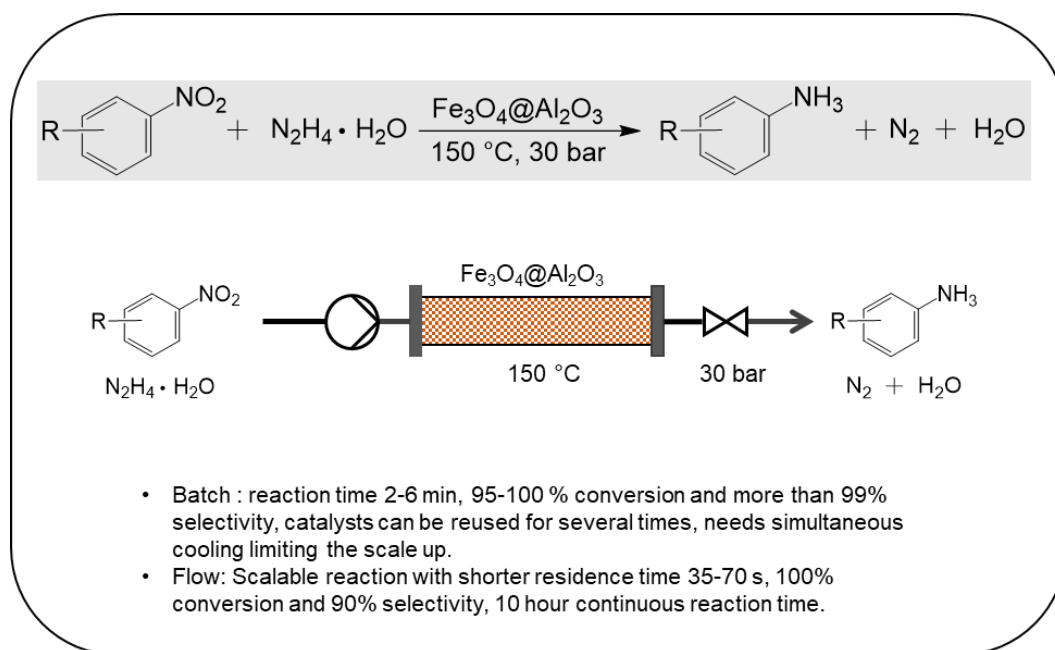
reactor, resulting in a lower efficiency of the photochemical process. For conventional batch flasks, a 1 cm dimension would be a very small size. However, flow reactors can be made in a much smaller size, while maintaining a similar productivity, especially for microflow reactors (dimension below 500 μm).⁹⁶ The relatively small size of flow reactor could supply a sufficient exposure of light to photochemical process.

Besides this, the advantages of continuous flow processes such as described previously efficient mixing, fast heat exchange etc. can also be beneficial to photochemistry. These have been reviewed by several authors.^{83, 92, 97, 98} More details of photochemistry will be discussed in Chapter 5.

1.2.4. Catalyst Recycling

In this work, niobium compounds are used as solid catalysts for Friedel-Crafts reactions (Chapter 3) and Skraup reactions (Chapter 4) in continuous flow processes. Therefore, this section explores catalyst recycling in flow reactors.

Beyond the advantages of mixing, heat exchange and irradiation, catalyst recycling is another potential advantage of flow processes. Especially for heterogeneous reactions, where reactants continuously flowing through a highly concentrated fixed-bed catalyst provides efficient contact between reactants and catalyst, which can improve the reaction efficiency and increase the turnover frequency. Moreover, using a fixed-bed catalyst also avoids a catalyst-separation step after the reaction, saving time and solvent usage. As the catalyst is continuously flushed with the reactants and solvent, coking can be reduced, improving the lifetime of the catalyst.



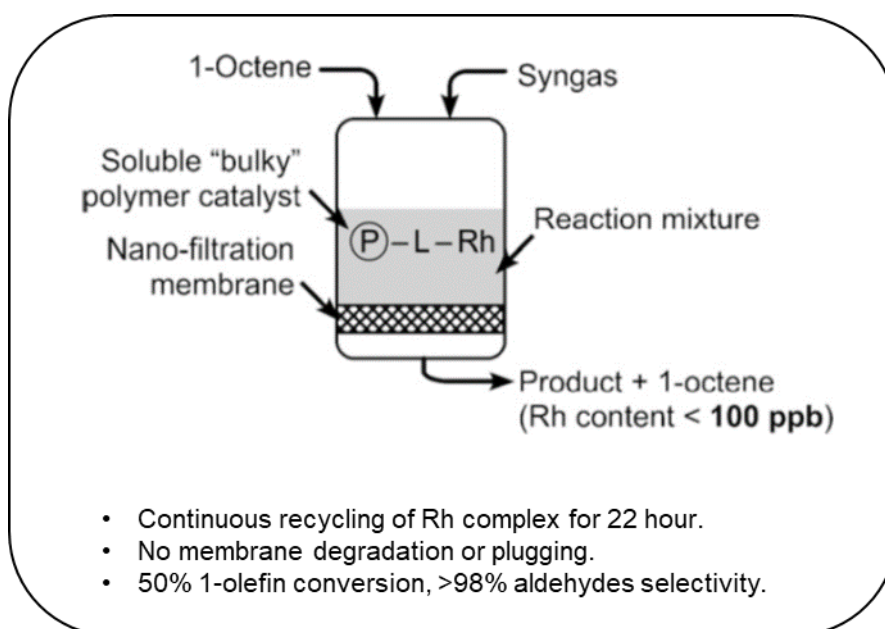
Scheme 1.2.4 Continuous reduction of nitroarenes to anilines.⁹⁹

Kappe's group reported the use of alumina-supported iron oxide nanoparticles ($\text{Fe}_3\text{O}_4@\text{Al}_2\text{O}_3$) to catalyse the reduction of nitroarenes to anilines in both batch and continuous flow system (Scheme 1.2.4).⁹⁹ Initially, the reaction was carried out in batch reactors using microwave heating. Various nitrobenzene derivatives were investigated at 150 °C with 2–6 min reaction times. The $\text{Fe}_3\text{O}_4@\text{Al}_2\text{O}_3$ showed excellent activity, and could be reused several times without a significant decrease in activity. The reaction was then moved to a commercial high-temperature and high-pressure flow device. The $\text{Fe}_3\text{O}_4@\text{Al}_2\text{O}_3$ nanoparticles were packed into an exchangeable catalyst cartridge. The optimised conditions in flow reactor are at 0.5 mL/min flowrate, 150 °C under 30 bar pressure with a residence time of 35-70 s, which gave a full conversion of the nitrobenzene derivatives and over 90 % selectivity. The nano- $\text{Fe}_3\text{O}_4@\text{Al}_2\text{O}_3$ catalyst demonstrated stable reduction of nitrobenzene (0.5 M in MeOH) for more than 10 hours on stream at a productivity of 30 mmol/h (0.72 mol per day). However, long-term

stability studies have revealed that higher flowrates caused mechanical stress in the catalyst bed and changing the solvent to acetonitrile led to slow deactivation over time.

Catalyst recycling is obviously applicable to heterogeneous catalysts in continuous flow systems, and moreover it can also be appropriate for homogeneous reactions.¹⁰⁰⁻¹⁰²

Homogeneous catalysis usually gives outstanding performance in the catalyst activity, chemoselectivity, and enantioselectivity.¹⁰³ However, tedious separation steps and the lack of recycling methodologies currently restrict its applications to valuable fine-chemicals. So far, several strategies have been developed for the recycling of homogeneous catalysts, which can be broadly grouped into two types. The first type uses some kind of support, soluble¹⁰⁴ or insoluble (such as silica^{105, 106} or polymer beads¹⁰⁷), to link the active catalyst. And the separation process is accomplished by filtration techniques.¹⁰⁸



Scheme 1.2.5 Continuous 1-olefin hydroformylation using homogeneous catalyst. Picture is reproduced from the reference.¹⁰⁹

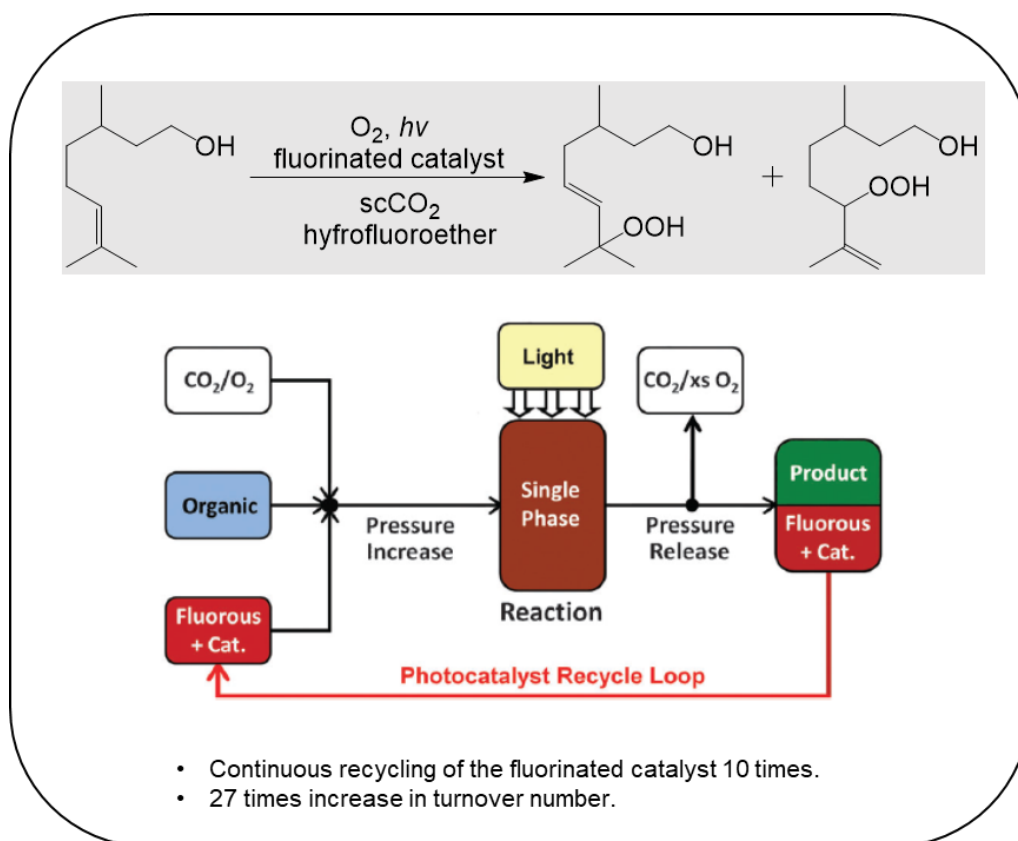
An example of homogeneous catalysts bound to a polymer support for continuous hydroformylation was reported by Subramaniam's group (Scheme 1.2.5).¹⁰⁹ The homogeneous rhodium catalyst was supported by polymer-bound bulky phosphite ligands, which increased the molecular weight of the rhodium catalyst to prevent it from passing through the filtration unit. The reaction was performed in a loop reactor, with a nanofiltration membrane installed, where the solution was continuously pumped in; only products could cross the membrane and go out. The reaction was successfully carried out for 22 continuous loops and achieved a 50% 1-olefin conversion and 98% aldehyde selectivity without any membrane degradation or plugging.

However, for continuous flow reactions, the heterogeneous or immobilised homogeneous catalyst can be consumed (via deactivation or leaching) over time.¹⁰² So careful consideration must be given to ways of avoiding catalyst deactivation or leaching and methods for reactivating used catalyst.

Another type of homogeneous catalyst recycling methodology employs a biphasic system, where the catalyst selectively dissolves in one phase and the products dissolve in the other phase.^{100, 110} After separation of the two phases, the phase preferentially containing catalyst can be recycled in the system. The reported biphasic systems include aqueous & organic solutions, supercritical fluids,¹¹¹ ionic liquids,¹¹² and fluorinated solvents.¹¹³

A detailed study on continuous fluorinated biphasic separation has been carried out at the University of Nottingham (Scheme 1.2.6).¹¹³ The liquid organic reagent, and a highly fluorinated photocatalyst were combined with CO₂/O₂ to give a monophasic mixture under high pressure. After the reaction, releasing the pressure formed a biphasic liquid mixture. The denser fluorinated phase, containing the photocatalyst was then continuously pumped back into the reactor. After 10 cycles, the catalyst still retained

high catalytic activity (75% compared with fresh catalyst). In contrast with the same reaction carried out in a batch reactor, with fresh catalyst for each reaction the utilisation of the catalyst has dramatically increase.



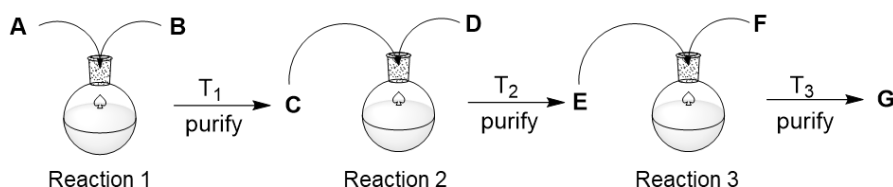
Scheme 1.2.6 Continuous recycling of homogeneous catalyst by adopting a biphasic system. Picture is reproduced from the reference.¹¹³

1.2.5. Multi-Step Reaction Unit

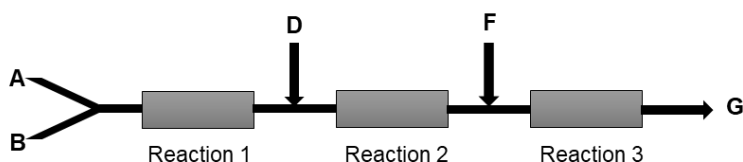
The synthesis of fine chemicals usually requires several steps (Scheme 1.2.7 A), and each synthetic step may require different reaction conditions (varied temperatures, solvents, new reagents etc.). Furthermore, after each step, the product may need to be isolated and purified to avoid the influence of undesired components in the next synthetic step.¹¹⁴ These operations all require energy, materials and labour, and generate

waste. Continuous flow process, which could combine several reaction, separation, purification steps within one processing sequence (Scheme 1.2.7 B), has great potential to minimise such resource and labour intensive operations.¹¹⁴⁻¹¹⁸

A : Conventional multi-step batch synthesis



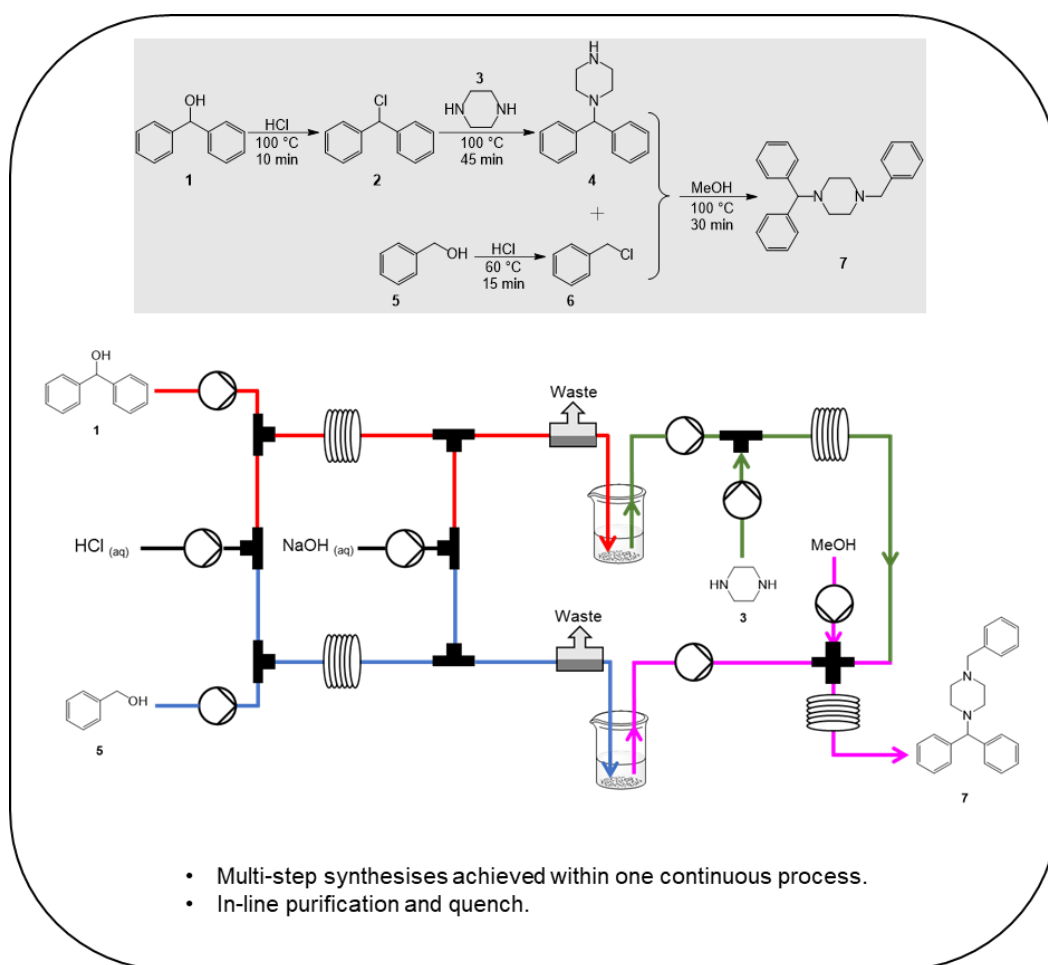
B : Continuous multi-step synthesis



Scheme 1.2.7 Multistep synthesis in batch vs in flow.

Hessel's group has developed a four-step continuous flow process, equipped with inline separation and quench, for the synthesis of cinnarizine by an amine alkylation using the newly synthesised intermediate alkyl chlorides (Scheme 1.2.8).¹¹⁷ The reaction starts with diphenylmethanol chlorodehydroxylated **1** (in acetone) heated at 100 °C and 6.9 bar for 10 min. This is followed by an inline separation, with a liquid-liquid membrane separator, and quench with aqueous sodium hydroxide, to give a 97% yield of chlorodiphenylmethane **2**. (Step 1, red line) Then this solution is used to react with piperazine **3** at 150 °C and 17.2 bar for 45 min generating benzhydrylpiperazine **4** (95% yield). (Step 2, green line). Meanwhile, the chlorodehydroxylation of cinnamyl alcohol **5** was carried out to synthesize cinnamyl chloride **6** at 60 °C and 6.9 bar for 15 min, with inline separation and quench giving a yield of 95%. (Step 3, blue line). Finally

compound **6** (generated from step 3) and compound **4** (generated from step 2), are combined with methanol (which is used to prevent precipitation of the HCl salts) are heated at 100 °C at 6.9 bar for 30 min yielding cinnarizine **7**. (Step 4, pink line). The overall process was completed in 90 min and an 82% isolated yield of cinnarizine **7** was achieved.



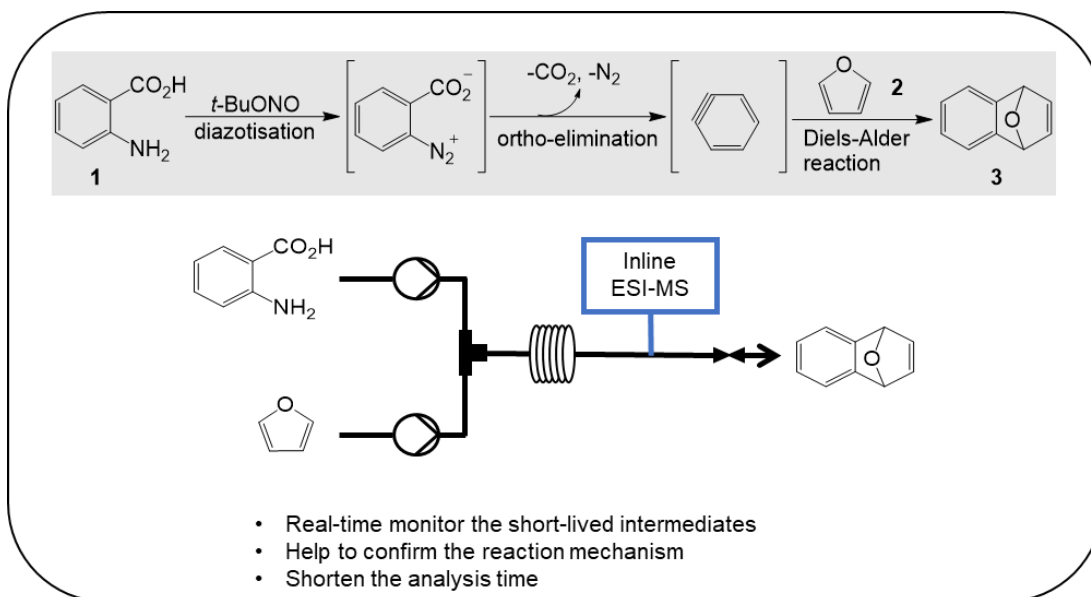
Scheme 1.2.8 Multistep synthesis of cinnarizine with inline purifications.¹¹⁷

1.2.6. Real-Time Monitoring and Automation

A self-optimisation system, for studying the activity of niobium catalysts in the continuous methylation of aniline, is described in Chapter 3. Therefore, a brief discussion of the benefits of the integration of on-line or in-line analysis instruments with continuous flow processes is given in this section.

Continuous flow chemistry is drawing more and more attention from both research groups and industry, owing to its superiority in heat exchange, mixing, and productivity compared with batch synthesis. Employing inline (such as UV-Vis,¹¹⁹ IR,¹²⁰ Raman spectroscopy,¹²¹ NMR¹²²) or online (GC,¹²³ HPLC¹²⁴) analysis instruments, can allow real-time monitoring of continuous flow processes, including the catalyst information on activity, hazardous species generation, and product output.^{125, 126, 127.}

The lifetime of intermediate products is usually very short, which makes them hard to track in batch reactions. The real-time monitoring of flow processes could help to detect short-lived intermediates during the reaction progress and provide data to help confirm the reaction mechanism. Ley's group have developed a compact lab scale electrospray ionisation mass spectrometer ESI-MS device facilitated with a continuous flow reactor (Scheme 1.2.9).¹²⁸ This system was used to monitor the reaction species from the diazotization of anthranilic acid **1** to benzene **2** followed by a Diels–Alder condensation with furan **3**. A number of intermediates, including an explosive diazotised intermediate, and several competitive reaction pathways were identified, and the reaction conditions were optimised based on the MS data collected.

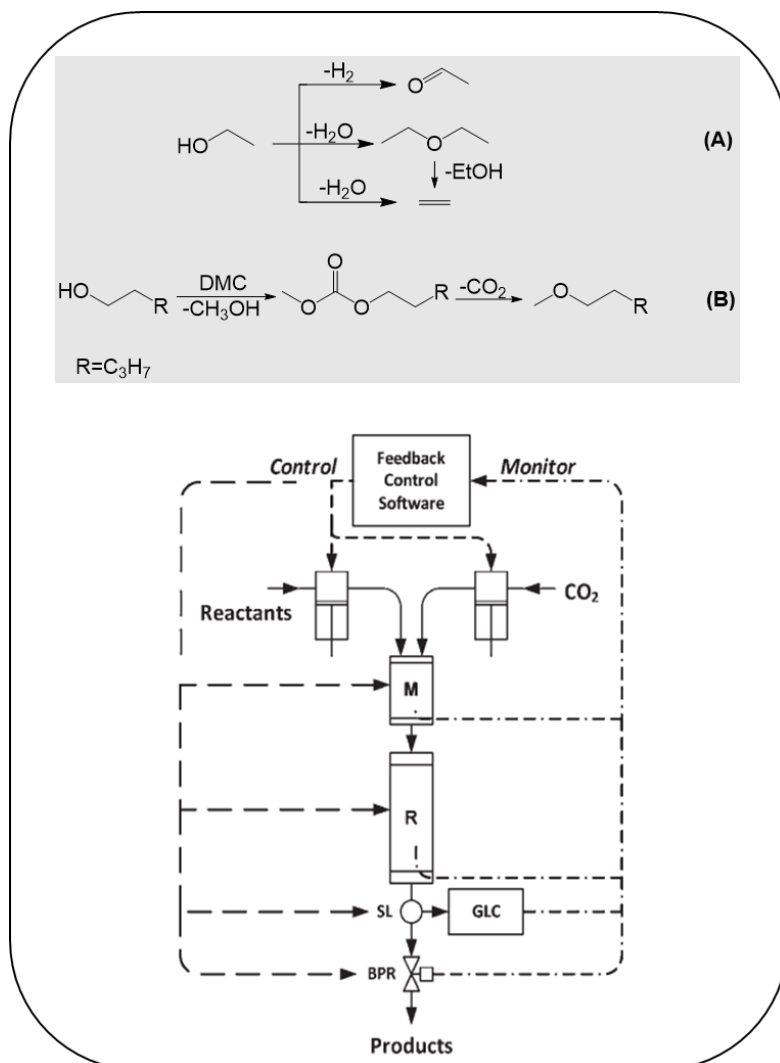


Scheme 1.2.9 In-line monitoring the diazotization of anthranilic acid **1** to benzene **2** with furan **3** by ESI-MS.¹²⁸

The integration of real-time analysis into continuous flow systems greatly shortens the data processing time, and provides a chance to tune the reaction parameters during the synthetic process.¹²⁹ What is more, based on the inline or online data collected, feedback algorithms and real-time reaction optimisations can be employed to search for the optimal conditions to maximise properties such as: conversion of starting reagents, selectivity for a desired product, yield and productivity. This could provide a better design of the reaction with less time, labour and materials required.^{130, 131}

In one example, Parrott *et al.* developed a self-optimisation system (Scheme 1.2.10), which consisted of a GLC and an automated flow reactor.¹³² By involving the super modified simplex algorithm (SMSIM),¹²³ the reaction parameters such as pressure, temperature, the flowrates of CO_2 and organic substrates can be self-adjusted to improve the yield of the desired product. Two reactions were investigated in this system, including the dehydration of ethanol (Scheme 1.2.10. A) and the carboxymethylation of dimethylcarbonate DMC (Scheme 1.2.10. B). Three parameters of the reactions

(pressure, temperature and CO₂ flowrate) were varied simultaneously. The time needed for the optimisation process was therefore greatly reduced.



Scheme 1.2.10 The concept of self-optimising process. Picture is reproduced from the reference.¹³²

This work represented a significant step forward in the use of optimisation algorithms for scCO₂ reactors. However, it is not merely the maximum yield of a certain product, which can be optimised. The conditions could also be optimised for different criteria, such as maximising or minimising the ratio of two products, minimising the production of an unwanted by-product, or even minimising the E factor (kg waste/kg

product) of the reaction, which is particularly interesting in the context of Green Chemistry.^{133, 134}

The same self-optimisation system was employed for the study of aniline methylation in this work. The set-up and operation procedure of this system are described in Chapter 2. The operation principle of SMSIM algorithm is discussed in Chapter 3.

1.2.7. Scale-up

In this work, a scaled-up flow reactor was built and tested for the synthesis of quinoline, as is described in Chapter 4. Thus, this section illustrates the possible ways to scale-up flow processes.

The volume of reactor used in continuous flow processes can range in scale from litres to micro litre. In particular, micro flow reactors it can be μL in size, which allows precise control of the reaction conditions such as temperature, pressure, flowrate and residence times, and for the safe use hazard reagents.⁹⁸ The use of the micro flow reactors provides an efficient way to gather large sets of data with small amount of materials, which is appropriate for biological and chemical research.

However, the purpose of research is often to lead eventually to commercial production. Therefore, how to scale up reactions is a key issue in the chemical industry. Scale up of a batch reaction can be performed by using a bigger reactor and larger amounts of reagents, which could cause problems in heat transfer and mixing, resulting in a lower yield of product and higher risks in operation. Alternatively, one could use a larger number of small batch reactors, followed by parallel collection, isolation and separation, but this needs more labour, time and resources and generates more waste. By comparison, scale up of a flow reaction can be achieved with a parallel array of

similarly sized reactor, or by operating a single reactor for a longer time under the same conditions to meet the required output. Of course, bigger size (volume) flow reactors can also be employed, similarly to problems experienced when scaling up the batch reaction the reaction conditions may need to optimise again. But for ‘flash reactions’ (very quick reactions) or violently exothermic reactions, using a bigger size of flow reactor might sacrifice the advantages of flow systems in terms of heat transfer and mixing.

The use of commercially available flow reactors in laboratory scale research is a potential solution for the transition of academic technology to industry. These kinds of flow reactors have been designed for scale up and flexibility, which is suitable for both laboratory research and industry scale production. The chemistry is the same as the size of reactor does not change. Therefore industry can use the same reactor under the same condition as developed in lab research. Besides, the commercial availability of flow reactors makes it easier for more chemistry researchers to use continuous flow technology. Companies designing and manufacturing flow reactors include Alfa Laval, Corning, Microinova, Chemtrix, Syrris, FutureChemistry and many more.⁹⁶

1.2.8. Limitations and Exploration

The discussions above are on the advantages of continuous flow chemistry, which fit the concept advocated by green chemistry, high efficiency, energy saving and low risks. However, continuous flow processes also have limitations, such as being unsuitable for very slow reactions, handling solid products and high capital costs.

Table 1.2.2 Reaction Time Dependence on Temperature.^a

Temperature (°C)	Times (red: hour region, blue: minute region, black: second region)									
20	1	2	4	6	8	12	24	48	96	172
30	30	1	2	3	4	6	12	24	48	86
40	15	30	1	5	1.5	2	3	6	12	24
50	8	15	30	45	1	1.5	3	6	12	22
60	4	8	15	23	30	45	1.5	3	6	11
70	2	4	8	11	15	23	45	1.5	3	5
80	56	2	4	6	8	11	23	45	1.5	3
90	28	56	2	3	4	6	11	23	45	1
100	14	28	56	1	2	3	6	11	23	40
110	7	14	28	42	56	1	3	6	11	20
120	4	7	14	21	28	42	1	3	6	10
130	2	4	7	11	14	21	42	1	3	5

^a. Table is reproduced from reference.¹³⁵

As discussed in section 1.2.1 to 1.2.3, flow processes can supply high efficiency in mixing, heating transfer and irradiation, and all these advantages benefit the flash reaction.^{136, 137} In flow reactors, good-mixing can be achieved before the flash reaction occurs, which gives a high selectivity of the desired product. On the other hand, for time-consuming reactions, which need a long reaction time, the short resident times typical in flow processes may not be enough to for the reaction to reach completion. In some cases higher temperature may help to decrease the reaction time. Table 1.2.2 illustrates the theoretical decrease in the reaction time by increasing temperature.¹³⁵ But for the low temperature time-consuming homogeneous reactions, such as some

enantioselective reactions which need to be carried out at low temperature for long time to ensure high asymmetric induction, flow processes may not be ideal.⁹⁸

Dealing with the formation and processing of solid products, which can cause blockages in flow reactors, is another challenge for continuous flow processes. Solid build up usually comes about at narrow tubing connectors or backpressure regulators. One solution to prevent the accumulation of solid is to introduce an auxiliary solubilizing solvent prior to the problematic site to solubilise the solid. However, solvent chosen is limited by the need to avoid causing side reactions. Another solution is reported by Ley and co-workers, using a commercially available agitating cell reactor to maintain solids in suspension.¹³⁸ This method has been successfully applied to a salt-forming reaction. But for micro flow reactors, processing solids (with the exception of the micro- or nanoparticles), is still not possible.⁹⁶

Another consideration is the cost of a flow process. Building a flow process is more complex and costly than conventional batch reactors. However, with the development of 3D-printing technology, the robust and inexpensive 3D-printed flow process devices, which are easily connected to build up complex, custom-made flow systems, could be a possible way to reduce the cost.¹³⁹

However, we should not only consider the economic cost of processes, but also the time and energy demand, so as to minimise the effect on the environment. Continuous processes have obvious superiorities in safety, time and energy saving. Therefore, the relative merits of continuous or batch process should be evaluated on a case-by-case basis.¹⁴⁰

Thesis Aims

To conclude the introductory chapter, the main aim of this work is to explore the applications of Nb catalyst (**NbO** and **NbP**) in continuous flow synthesis. This can be future divided into the following flow areas.

1. To investigate the acidic activity of **NbO** and **NbP** in the continuous alkylation of aniline by employing a self-optimisation system.
2. To compare the activity of Nb catalysts to $\gamma\text{-Al}_2\text{O}_3$ in the methylation of aniline with DMC and methanol.
3. To convert biomass products to more valuable chemicals over a **NbP** catalyst in a continuous flow process.
4. To investigate the immobilisation of photosensitisers on Nb catalysts and what effect this has on their activity in the continuous photo-oxidation reactions.

Figure 1.2.2, has been created to help to decide whether a flow reactor is suitable for a given reaction or research.^{83, 89} Although this diagram was published after the experimental work for this thesis had finished, it applied to the various reactions studies to demonstrate their suitability of the flow chemistry.

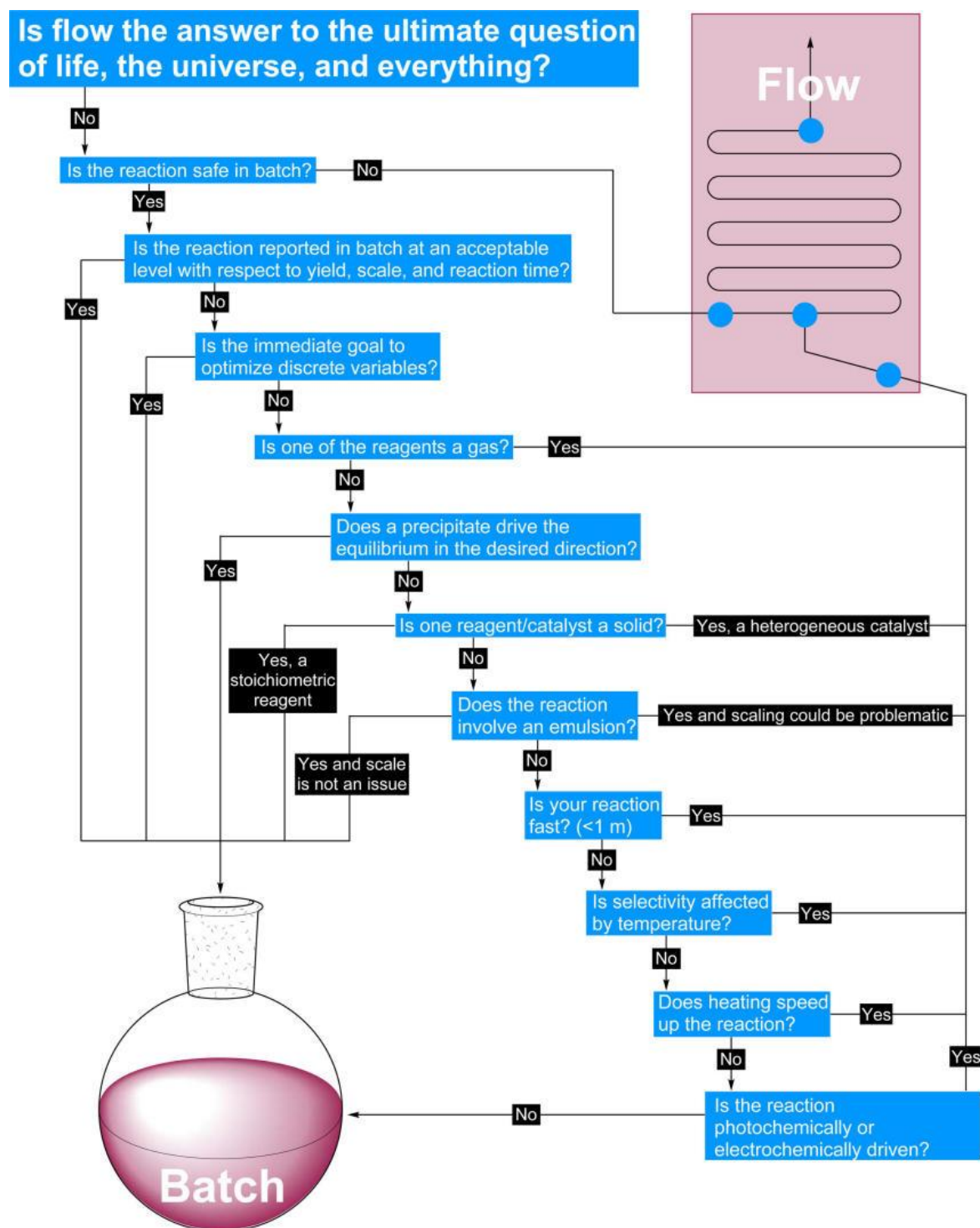


Figure 1.2.2 Roadmap for the decision of flow process. Picture is adapted from reference.⁸³

Chapter 2. Experimental

This Chapter describes the main equipment, experimental methods, and analytical techniques used in this Thesis.

Firstly, a description of main devices used for the construction of the continuous flow systems, including high pressure and high temperature rigs and high pressure photo-oxidation rig, is given in Section 2.1.

The continuous high pressure and high temperature systems, used to conduct Friedel-Crafts reactions (Chapter 3) and Skraup reactions (Chapter 4), as well as its standard operating procedures are described in Section 2.2. The continuous high pressure photoreactor used to conduct photo-oxidations (Chapter 5), and its standard operating procedures are described in Section 2.3.

The on-line GC analytical method, used to monitor the flow reaction performance is described in Section 2.4. The general analytical techniques used for the identification and quantification of the products are given in Section 2.5. A list of the chemicals including the relevant solid acids and gases used in this Work is given in Section 2.7.

2.1. Devices for The Continuous Flow Systems

Continuous flow reactions have been conducted at the University of Nottingham for two decades, through numerous evolutions by various generations of students and postdoctoral researchers.^{113, 132, 141-144} The work presented in this Thesis is in attempt to expand these existing technologies and flow systems by the combination with Nb solid acids.

Two kinds of flow rigs are used in this Thesis, a high pressure and high temperature flow system and a continuous high pressure photo-oxidation system, both of which are built up from a series of stainless steel components. Here a number of common devices are listed for convenience.

2.1.1. Organic Delivery Unit

Jasco HPLC Pump: All the organic reagents used in the continuous flow reactions in this work are delivered by Jasco™ PU-980 high performance liquid chromatography (HPLC) pumps.

The efficiency of the HPLC pumps should be tested regularly, by recording the time take to fill a certain volume container at a fixed flowrate. Before each experiment, the HPLC pumps should be primed with the desired solutions and pressurised against a closed tap to a higher pressure than the desired system pressure, to ensure that the organic reagents can be pumped into the system properly.

2.1.2. Gas Delivery Units

Jasco CO₂ Pump: The work described in Chapter 3 and Chapter 5 used supercritical CO₂ as a solvent. The CO₂ is delivered into continuous flow systems by

Jasco™ PU-1580-CO₂ pumps, in which the gaseous CO₂ is first cooled to liquid CO₂ (-10 °C) before being pumped into the system.

The efficiency of the CO₂ pumps should be tested regularly using a bubble flow meter. Before each experiment, the CO₂ pump should be pressurised against a closed tap to a higher pressure than the system pressure, to ensure that CO₂ can be pumped properly into the system and to avoid back flow of the organic reagents into the CO₂ pump.

O₂ dosing unit: Photo-oxidation reactions, described in Chapter 5, use O₂ as a reagent. The gaseous O₂ is delivered into the continuous flow system by a dosage unit (Rheodyne® 7000L or Vici® equivalent), which transfers O₂ at cylinder pressure, which must be higher (by at least 20 bar) than the system pressure, via a pressure gradient into the system (illustrated in Figure 2.1.1.)¹⁴⁵ The dosage unit contains a six port HPLC switching valve to which with two small closed ended sample loops are attached. The six ports are joined together in pairs by a 3-slot rotor seal. At any one time, one of the sample loop is filling with O₂ from the cylinder and the other is supplying O₂ to the system due to the pressure difference. The rotor position is then switched, and the other sample loop is filled with O₂ whilst the full loop supplies O₂ to the system.

The loop volume and switching rate can be varied to alter the amount of O₂ dosing into the system. To avoid the O₂ forming large slugs and to improve the mixing, the switching rate should be between *ca.* 4 and 14 seconds and the loop volume should be below 300 µL.¹⁴⁵

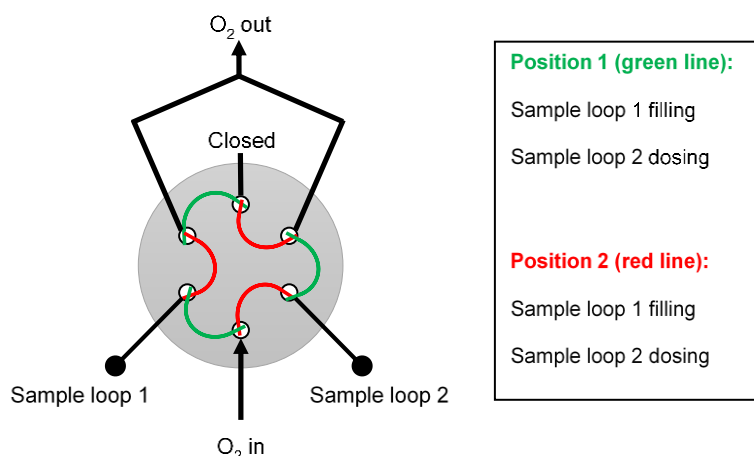


Figure 2.1.1 The Rheodyne switching valve alternates between positions 1 and 2, such that there is always one sample loop filling and another dosing simultaneously.¹⁴⁵

CAUTION:

- The O_2 concentration for oxidation reactions must be kept below 8 mol.% to stay below the system flammability limit.¹⁴⁶
- The O_2 cylinder pressure must be at least 20 bar higher than the required system pressure to avoid the organic mixture flowing back into the oxygen line which could cause a major potential hazard. A check valve needs to be installed between the oxygen dosage unit and premixer to further reduce the risks of low oxygen pressure.
- For the system pressure trips, the high pressure system trip must always be set to a lower pressure than the low pressure trip on the O_2 cylinder, to ensure that all the HPLC pumps and O_2 dosage unit stop before a potential back-flow occurs.

2.1.3. Pressure Control

Back Pressure Regulator: For all the high pressure experiments, system pressure is controlled by a Jasco™ BP-1580-81 back pressure regulator (BPR).

The BPR should be cleaned frequently by flushing with an appropriate solvent (such as *iso*-propanol), to remove any residual reagents from around the needle and keep the BPR operating properly.

A pressure transducer (RDP electronics), which is linked to the trip system, is placed between pre-mixer and HPLC pumps and used to monitor the system pressure.

2.1.4. Temperature Control Units

Heating: The work described in Chapter 3 and Chapter 4 was carried out at high temperatures (150 °C to 350 °C). To achieve these temperatures, the tube mixer and reactor are surrounded by aluminium heating blocks, fitted with cartridge heater whose temperature is controlled by programmable proportional integral derivative (PID) controllers (Eurotherm 2216) with K-type thermocouples to monitor the temperature.

Cooling: Grant LTD6/20 cooling baths are used to control the photoreactor temperature and to prevent overheating LED blocks, via the circulation of a cooling mixture of ethylene glycol and water.

2.1.5. Irradiation

LED light: The photo-oxidation reactions described in Chapter 5 were irradiated by 15 LED arrays (3 blocks, each containing 5 Citizen Electronics Co. Ltd 1000 lumen white light LED).

2.1.6. Safety Control

Trip system: As all the continuous flow experiments presented in this Thesis are under high pressures (50 bar to 200 bar) and some of them are operated at high temperatures (150 °C to 350 °C), pressure trips and temperature trips are fitted to each

rig. In the event of an over-pressure or over-temperature developing, the flow system will automatically shut down to prevent failure.

For the high pressure and high temperature rigs used in Chapter 3 and Chapter 4, a system over-pressure is set to be 10 bar over the desired operating pressure and an over-temperature of the heating blocks (controlling the temperature of the mixer and reactor) is set to be 10 °C above the desired temperature. In the case of either over-pressure or over-heating, the trip system will shut down the heat controller and all the HPLC pumps, but the CO₂ pump remains on in an attempt to clear the reactor blockage safely and to cool down the system temperature. In case of the system pressure continue to rise, a built in pressure trip on the CO₂ pump, which is set to below the maximum operation pressure of the rig, will be activated and stop the CO₂ pump.

In terms of the continuous photochemical reactions presented in Chapter 5, beside of the system over-pressure and over-temperature trips, an under-pressure trip for the oxygen cylinder, located prior to the O₂ dosing unit, must be set higher (by at least 20 bar higher) than the high pressure system trip to prevent possible back flow of organic material into the oxygen line. In the case of either over- or under-pressure or over-temperature, the trip system will shut down the heater controllers, HPLC pumps, oxygen dosage unit and light source, but leave CO₂ pump on in order to clear the reactor blockage safely and to further dilute the O₂ in the system.

For all the flow rigs, the BPR is not connected to trip system as, in case of a trip, it would fully open and vent the entire contents of the rig.

Prior to each experiment, the trip system must be tested to ensure that each element is functioning correctly.

Emergency shut-down: An emergency shut-down button is built into each rig, to allow instant switching off of all equipment connected to the trip system in the case the system is not automatically tripped.

2.1.7. Data Recording

PicoLogger: Data logging, such as flowrate, reactor temperature (internal and external) and system pressure, is performed using a TC-08 PicoLogger™ unit and PicoLog logging software.

2.1.8. Tubing, Fittings and Valves

1/16" (outer diameter) stainless steel tubing supplied by Swagelok® is used for the usual transfer of material throughout the flow rigs, and is connected to equipment via genuine Swagelok® fittings. Manual needle valves were supplied by the High Pressure Equipment Company (HiP 15-11AF1) or Scientific Systems, Inc (SSI, flat valves).

2.2. High Pressure and High Temperature Continuous Flow Reactor

The high pressure and high temperature continuous flow rigs, including a single reactor rig and a scaled-up triple reactor rig, used to perform the experiments presented in Chapter 3 and Chapter 4, are described in this section.

2.1.9. Design

The high pressure and high temperature continuous flow rig, used to perform the reactions described in Chapter 3 and Chapter 4, is built from 316 stainless steel components, including 1/16" tubing for usual materials transfer, and two 1/4" tubes (0.049" wall thickness, 15.6 cm in length and 1.83 ml volume) used as a pre-mixer and a reactor. The pre-mixer is packed with sand, and the reactor is filled with fresh niobium catalysts (**NbO** or **NbP**) prior to each experiment. The pre-mixer and reactor have frits installed on both ends of the tube to avoid the sand or catalyst powder escaping into the rest of the pipework.

The construction of high pressure and high temperature continuous flow rig is shown in details in Figure 2.2.1. CO₂ is delivered by a Jasco PU-1580-CO₂ pump, and the organic reagents are introduced into the system by Jasco PU-980 HPLC pumps. All the organics and the CO₂ are first pumped into the pre-mixer, where they are preheated and mixed. The mixture then flows into the reactor where the reactions take place. Both pre-mixer and reactor are heated by cartridge heaters located within aluminium heating blocks that are controlled by Eurotherm 2616 heater controllers. The system temperatures (internal and external temperature of both the pre-mixer and reactor) are recorded by Picologger. The system pressure is monitored by a pressure sensor placed up stream of the pre-mixer. Between the reactor and BPR, a Shimadzu Gas Chromatography 2010 is installed to allow real-time analysis of the mixture. The system trip and emergency trip are set to avoid the risks of either overheating or overpressure.

2.2.1. Scaled-up Reactor

A multi-pass reactor was used for large-scale Skraup synthesis as described in Section 4.8. This scaled-up flow rig is designed by connecting 4 tubes in series,¹⁴⁷ where the first one is filled with sand and used as pre-mixer **M** and the following three reactors **R** filled with **NbP** catalyst that 3 times as much as in a single reactor (as shown in Figure 2.2.2).

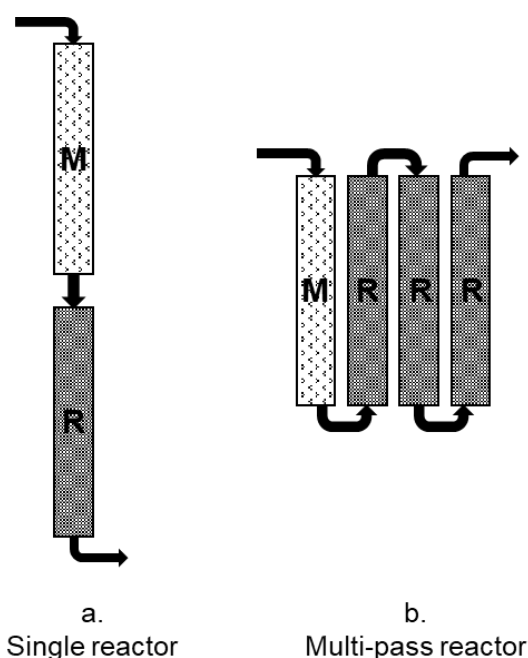


*Figure 2.2.2 Schematic of the continuous single reactor vs multi-pass reactor. The tubular multi-reactor comprised 4 tubes are arranged in series (stainless steel tubing 1/4" o.d., 75 mm in length). The organic reagent firstly pass through the pre-mixer (**M**) which is packed with sand, and then flow into the reactor (**R**) that filled with Nb catalysts. The multi-pass reactor can be filled with 3 times as much Nb catalyst as the single reactor.*

Compared to using a larger size single reactor, this multi-pass reactor can could reduce the heat conduction and safety issues at high pressure and high temperature reaction conditions, and is more suitable on a lab scale.

2.2.2. Standard Operating Procedure

For safe operation, proper high pressure training should be undertaken before operating any high pressure experiment. The maximum pressure and temperature trips should be set depending on the desired reaction condition but must be below the temperature and pressure limits of the high pressure reactor and heating blocks (350 °C and 250 bar).

The following procedures apply to both single pass and multi-pass high pressure and high temperature rigs.

Start-up Procedure

- Fill the reactor with niobium catalyst, and then reseal it into the flow system.
- Check the flow system for leaks, by pumping CO₂ into the system to the desired pressure and using Snoop™ leak detection liquid to test every fitting.
- If all the fittings are pressure-tight, heating blocks are installed around both the pre-mixer and the reactor. Ensure all thermocouples are attached and heating elements are not corroded.
- Check system pressure and temperature trips, for example by attempting to increase the pre-mixer temperature to higher than the set trip temperature.
- The CO₂ pump has an inbuilt pressure trip, which is typically set to 10 bar higher than the system over-pressure trip, to ensure CO₂ continuous to be pumped through the system if the other trips are activated.
- Set the starting conditions (CO₂ flowrate, organics flowrates and temperature) for the experiment as desired, starting the equipment in the order described below.
- Start the CO₂ pump first, and then turn on the heating controllers.

- Start the organic pumps against their corresponding closed taps to ensure that the pump head is not vacated by CO₂ when the tap is opened.
- Open the appropriate taps to allow the organic feeds to flow into the system.
- The flow reaction needs approximately 10-20 mins to reach a stable state before samples are taken.

For real-time monitoring and automated operation, the following procedures need to be carried out next:

- Turn on GC-2010 and the connected desktop computer. Open LabSolution™ software and choose the appropriate method file. Then create a batch file to collect multiple chromatographs. Start the Picologger to record the conditions simultaneously.
- Open the MATLAB GUI program, which was developed in-house,¹³² to control the HPLC pumps, CO₂ pump, the heating controllers and the BPR, allowing different reaction conditions to be programmed at various times throughout the experiment. Choose the SMSIM algorithm for self-optimisation operation.
- Once the program is started, the system is under automated control and the reaction progress is automatically logged to a text file.

Shutdown Procedure

- Close valves V3 and V4 isolating the organic feeds, and turn off the HPLC pumps.
- Stop heating controllers.
- Leave CO₂ to flush the system for 20 to 30 mins until the system temperature has cooled to room temperature.

- Close valve V2, isolating the CO₂ pump, and turn off CO₂ pump.
- Release the system pressure by gradually decreasing the set pressure at the BPR in roughly 20 bar step, allowing approximately 10 seconds in between.
- To prevent the leaking of CO₂, once the system is fully depressurised, the BPR is set at a safety pressure of 100 bar.

Emergency Shutdown Procedure

In the event of an emergency where the system is not automatically tripped, the following procedure should be followed:

- Hit the red emergency stop button located on the trip box. This will turn off the heaters and the HPLC pumps.
- The system must be allowed to cool for as long as is necessary. Do not remove the blast shield or attempt to release the pressure before the temperature readings are both below 40 °C.
- Release the pressure slowly by reducing the set pressure at the BPR in 20 bar increments, allowing approximately 10 seconds in between.
- CAUTION: If a blockage has occurred, sections of the rig may still be under pressure. Check the various pressure transducer readings (system, pumps and BPR). Undo any connections very carefully, with the fume hood sash as low as is practical. A full face shield is available.
- When the pressure and temperature hazards have been dealt with, press the square reset button on the side of the trip box to allow full power back to the rig.

2.3. High Pressure Continuous Photoreactor

The continuous photo-oxidation reactions described in Chapter 5 are performed in a modified high pressure photoreactor, which was designed in-house by Dr Jessica Bellamy and Dr Richard Bourne.¹⁴⁵ This new photoreactor allows for the incorporation of different lengths of sapphire tubing, which increases the versatility of the reactor by changing the reactor volume. The efficiency of this second generation high pressure continuous photoreactor has also been found to be higher than the first generation.¹⁴⁵

2.3.1. Design

The main component of the photoreactor is a sapphire tube (Saint-Gobain Crystals, 10 mm O.D., 1 mm wall thickness, 120 mm long), which is held in place by two EPDM O-rings which are compressed against the sapphire to create a seal. A LexanTM tube is placed around the sapphire tube to improve the safety of the reactor and also to create a space between these two tubes for the circulation of coolant to control the internal reactor temperature (as shown in Figure 2.3.1).

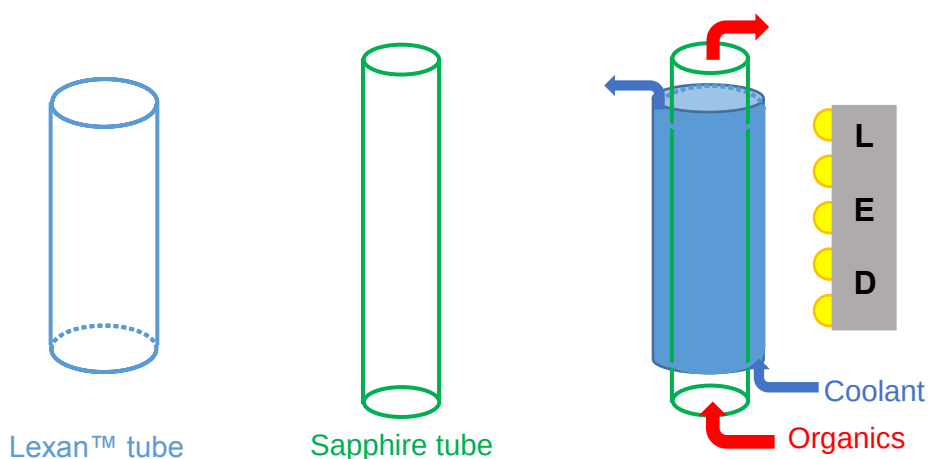


*Figure 2.3.1 Schematic of the sapphire tube reactor. A LexanTM tube is held around the sapphire tube to improve the safety of reactor, in the event of reaction failure, and also allow the coolant circulate to control internal reactor temperature. In the case of the arrows, *red* represents the direction of organic flow and *blue* shows the direction of the coolant flow.*

The body of the reactor is constructed from three 316 stainless steel supporting struts, which allow the sapphire tube to be completely exposed in the centre to maximise the irradiated area as shown in Figure 2.3.2. In addition, these three struts can be exchanged for longer ones, allowing a correspondingly larger size sapphire tube reactor to be used for scaled-up reactions. Three modified LED blocks with a total of 15 LED arrays (3 x 5 x Citizen Electronics Co. Ltd 1000 lumen white light) are used as light source, which are positioned around the reactor. Six blocks (30LEDs) can be fitted around the larger volume reactor.



Figure 2.3.2 Photographs of sapphire tube photoreactors. Picture a shows the sapphire tube reactor is held in the centre of photoreactor and is exposed by LED blocks (actually 3 LED blocks can be fitted, but for the easy exhibition, there were only 2 LED installed when the photo was taken). Picture b show a small and a larger volume reactors.

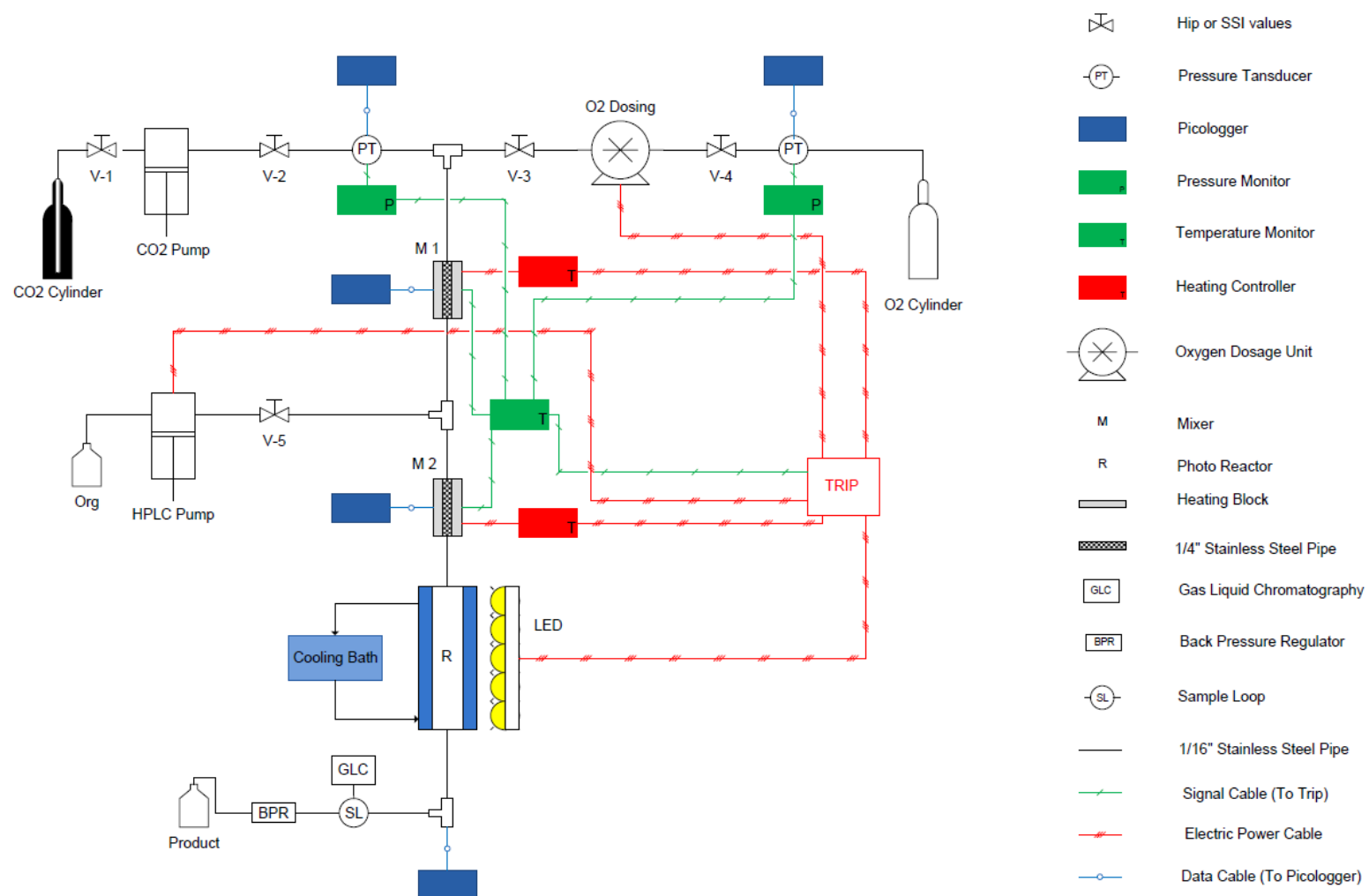


Figure 2.3.3 Schematic diagram for the equipment used for continuous photo-oxidation reactions in Chapter 5.

Figure 2.3.3 shows the schematic of the continuous flow photo-oxidation reactor system. CO₂ is pumped by a Jasco PU-1580-CO₂ pump, and O₂ is dosed into the system via a modified Rheodyne switching valve. CO₂ and O₂ are first mixed in a static mixer 1, which is heated to 50 °C, prior to mixing with the organic reagents. The organic reagents are introduced into the system by a Jasco PU-980 HPLC pumps and are mixed with gases in mixer 2. The fluid then flows through the sapphire tube reactor where it is subjected to visible light irradiation using an array of LEDs. The pressure of the system is controlled at its outlet using a BPR and the product is collected at this point.

2.3.2. Standard Operating Procedure

Before performing any high pressure experiment, a high pressure training should be taken. For high pressure photo-oxidation reactions, careful calculation of the oxygen concentration in reaction mixture is required, which must be kept below ca. 8 mol % to stay below the system flammability limit.

Start-up Procedure:

- Calculate the required pump flow rates, Rheodyne switching time and sample loop sizes for the reaction to be performed. Attach the correct sample loops to the Rheodyne dosing unit.
- Set system high pressure and low pressure trip.
- Fill the reactor with immobilised photocatalysts, and then reseal it into the flow system.
- Check the flow system for leaks, by pumping CO₂ into the system to a desired pressure and using Snoop™ leak detection liquid to test every fitting.

- If all the fittings are pressure-tight, ensure that all thermocouples are correctly attached, that all pressure transducers are calibrated and working, and that the pressure and temperature trips are working and set correctly.
- The CO₂ pump has an inbuilt pressure trip, which is typically set to 10 bar higher than the system over-pressure trip to ensure CO₂ could be pumped through the system if the other trips are initiated.
- Set the starting conditions (CO₂ flowrate, organics flowrates, BPR pressure) for the experiment as desired.
- Turn on the cooling bath. Set the mixer heaters 1 and 2, and cooling bath to the desired temperatures. Set the correct switching time on the Rheodyne dosing unit, starting the equipment in the order described below.
- Start the Picologger recording on the PC.
- Start the CO₂ pump first and allow the system time to reach pressure.
- Allow the system time to reach temperature.
- Start the Rheodyne dosing unit, and open valve V3 to allow oxygen to enter the system.
- Allow the system time to equilibrate (20 min).
- Turn on light source.
- Pump the organic feed against a closed tap to ensure that the pump head is not backfilled by CO₂ when open the tap.
- Allow the system time to equilibrate (min).
- The rig is now under starting conditions.

Shutdown Procedure:

- Switch off the light source.

- Close valve V4 then stop HPLC pump.
- Close valve V3 then turn off the Rheodyne dosing unit.
- After 10 minutes, turn off mixer heaters and cooling bath.
- Allow the system to purge with CO₂ and the temperature to equilibrate (30 mins).
- Close valve V1, isolating the CO₂ pump, and stop the CO₂ pump.
- Release the pressure slowly by reducing the set pressure at the BPR to atmospheric pressure in 20 bar increments, allowing approximately 10 seconds in between.

Emergency Shutdown Procedure

In the event of an emergency where the system is not automatically tripped, hit the red emergency stop button located on the trip box. And follow the procedures described below:

- Hit the red emergency stop button located on the trip box. This will turn off the heaters and the HPLC pumps.
- The system must be flushed with CO₂ as long as is necessary. Do not remove the blast shield or attempt to before releasing the pressure.
- Release the pressure slowly by reducing the set pressure at the BPR in 20 bar increments, allowing approximately 10 seconds in between.
- CAUTION: If a blockage has occurred, sections of the rig may still be under pressure. Check the various pressure transducer readings (system, pumps and BPR). Undo any connections very carefully, with the fume hood sash as low as is practical. A full face shield is available.
- When the pressure and temperature hazards have been dealt with, press the square reset button on the side of the trip box to allow full power back to the rig.

2.4. On-line Gas Chromatography.

The integration of gas chromatography (GC) into the high pressure and high temperature continuous flow system permits the real-time monitoring of reaction processes, which was firstly reported by reported by Dr. Benjamin Walsh and further developed in the research group by Dr. Richard Bourne and Dr. Andrew Parrott.^{123, 132, 143} This real-time analysis greatly shortens the data processing time. Furthermore, for high pressure reactions or reactions containing gaseous reagents, online GC can take samples directly from the reaction steam without the need for depressurisation and hence, avoiding the loss of volatile species.

2.4.1. Auto Sample Loop

The online GC sampling is performed via a high pressure sample loop (HPSL), which is installed into the carrier gas line, just prior to the injector. This makes it possible to introduce material from the flow reactor into the injector, as it joins the carrier gas flow. Once the sample enters the injector, the operation of the GC continues as normal.

Here a commercially-available electronically-actuated 4 ports rotor injector (VICI®R EPC14W.06) is used as auto HPLS. The rotor has 4 slots each with a volume of 0.06 μL , and two of these slots are aligned so that they allow passage of fluids between two pairs of ports, as shown by Figure 2.4.1. The first pair of ports (A and B) are connected to let the carrier gas pass through the HPSL and supply the GC. Another pair of connected ports (C and D) permits the reaction stream emerging from the reactor

to pass through the HPSL before continuing onto the BPR. Following an external signal, the rotor injector rotates anticlockwise so that the slot containing the reaction mixture (red) from the flow reactor is now aligned between the ports connecting the carrier gas source and the injection chamber of the GC. The flowing carrier gas stream transfers the material in the slot into the injection chamber of the GC, thus providing a means of analysing of all the components in the reaction stream without manually collecting samples. During this injection, a spare slot is aligned between the ports connecting the outlet of the reactor and the BPR, so that disruption to the product flow is minimised. After 0.1 s the rotor injector rotates clockwise back to the original position.

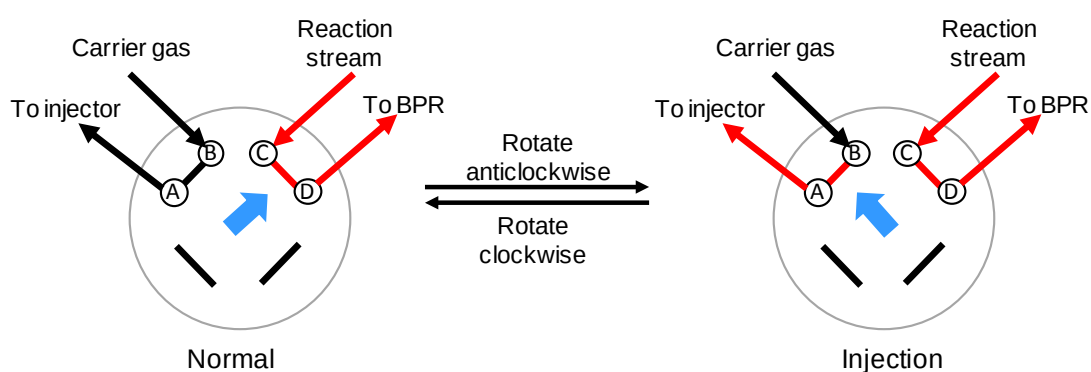


Figure 2.4.1. Schematic showing the two positions of the rotor injector in the HPSL. Ports A and B connect the carrier gas supply (shown in black) to the injector chamber of the GC, ports C and D connect the product stream (shown in red) emerging from the reactor to the BPR. Generally, the rotor is in the normal position. During sampling the rotor injector rotates anticlockwise to the inject position, transferring the reaction mixture in the sample slot into the carrier gas stream of the GC, and then rotates clockwise back to the normal position.¹⁴⁵

2.4.2. GC Methods

GC/FID analysis was run on a Shimadzu GC-2010 spectrometer using a Econo-Cap™ EC™-1 Capillary column (L=30 m, Ø=0.32 mm, film=1.0 µm). Two different

GC-methods were developed to analyse the reaction mixtures in Chapter 3 and Chapter 4 respectively.

Method 1 used in Chapter 3: hold at 50 °C for 2 min, ramp to 75 °C at 30 °C/min, ramp to 100 °C at 30 °C/min, ramp to 125 °C at 10 °C/min, ramp to 135 °C at 10 °C/min, ramp to 170 °C at 25 °C/min, ramp to 200 °C at 10 °C/min, pressure 1.60 bar, purge 3.0 ml/min, split ratio 100.

Method 2 used in Chapter 4: hold at 75 °C for 2 min, ramp to 280 °C at 30 °C/min, hold for 10 min, pressure 1.60 bar, purge 3.0 ml/min, split ratio 95.

2.5. Analysis

Proton ^1H NMR and carbon ^{13}C spectra were recorded on a Bruker DPX300 spectrometer at 300MHz and 75MHz respectively. The analysis was performed using CDCl_3 as reference with 7.27 ppm for ^1H -NMR and 77.00 ppm for ^{13}C -NMR, and data analysis was carried out using MestreNova. Mass spectrometry analysis was realized on a Bruker MicroTOF equipped with an Electron Spray Ionization method. Samples were diluted in acetonitrile or methanol prior to automated injection into the spectrometer.

Ultraviolet-visible absorption (UV-vis) spectra were recorded on an Agilent diode array 8453 spectrometer and were analysed using HP UV-Visible ChemStation (revision A.06.04) software. The diffuse reflectance UV-vis spectrum was recorded using an Ocean Optics USB2000+ UV-vis spectrometer, equipped with an Ocean Optics UV-Vis-NIR lightsource (DT-MINI-2-GS) fitted with a fibre optic to guide the light into the instrument (part number P200-2-VIS-NIR), and was collected using Ocean Optics

SpectraSuite (version 6.1). A silicon background plate and the reference spectrum was recorded for this background.

2.6. Data Processing and Error Analysis

2.6.1. Solubility calculation via UV-vis spectrophotometer.

The solubility of TPP in different solvents shown in Section 5.2.1 were calculated by UV-vis spectrophotometer. Firstly, five different known concentrations of TPP solutions were prepared and measured by UV-vis spectrophotometer. A standard linear equation was then calculated at λ_{max} to obtain the relationship between concentration and absorbance as shown in Figure 2.6.1.

Then a saturated solution of TPP was prepared as following: dissolve a large portion of TPP into solvent, mix and stir until it will not dissolve further amount. Then filtration or centrifugation is necessary to remove non-dissolved material. The clear saturated solution of TPP was then measured by UV-vis spectrophotometer to obtain the absorbance at same λ_{max} . The solubility of TPP can then be calculated by applying the standard linear equation obtained in the first step.

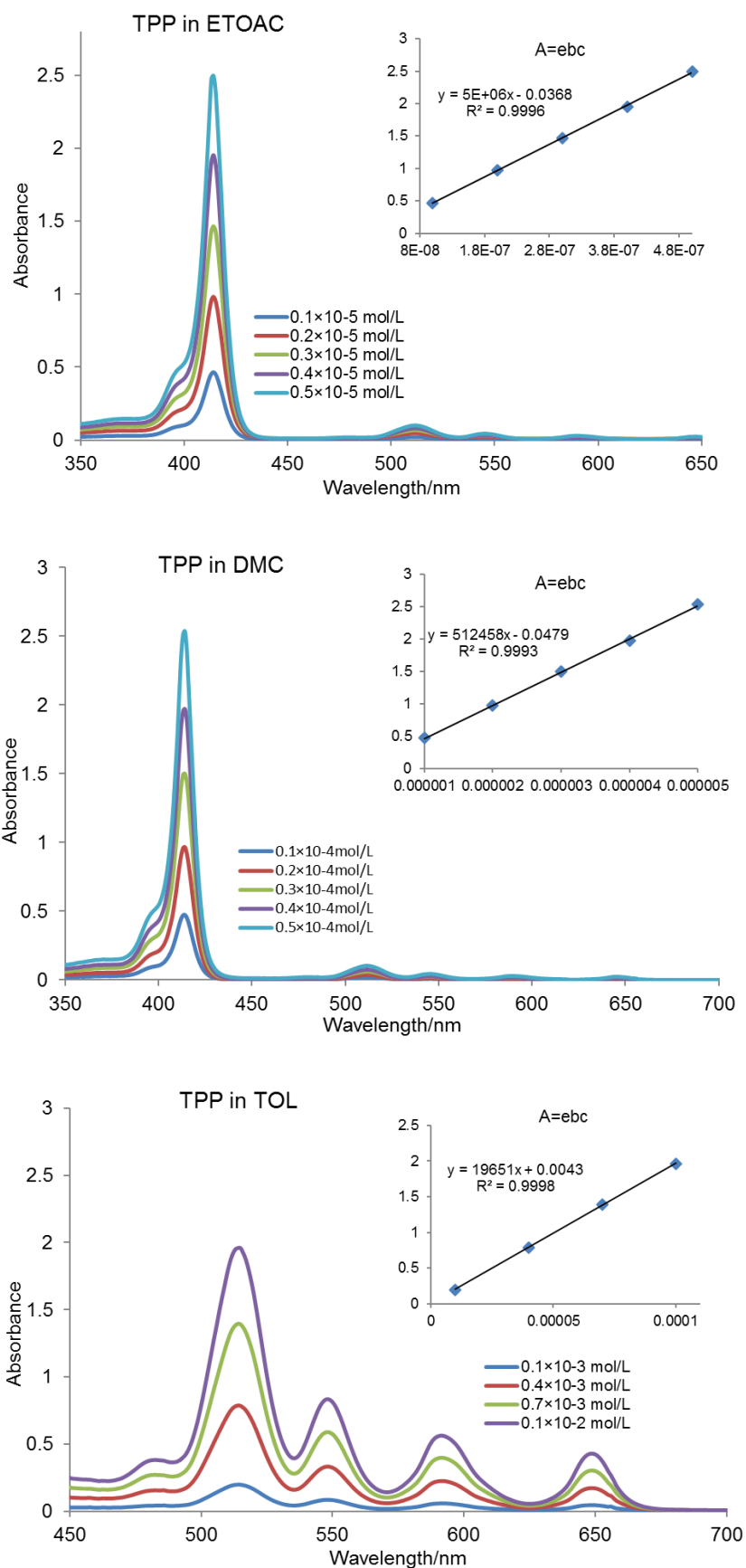


Figure 2.6.1 UV-vis spectrum for TPP solubility calculation in different solvents

2.6.2. Error Analysis

The standard deviation σ in Section 3.4 was calculated following the equation:

$$\sigma = \sqrt{\frac{\sum(\bar{x} - x_i)^2}{n - 1}}$$

Where x_i are the observed values of the sample items and $\bar{x}$ is the mean value of these observations, while the n stands for the number of the samples.

2.7. Materials

The common materials used in this work are summarised in the following tables along with the supplier and purity.

2.7.1. Solid Acids

Niobium pentoxide hydride (**NbO**) and niobium phosphate hydride (**NbP**) (w = 0.98) were supplied by Companhia Brasileira de Metalurgia e Mineração in Brazil.

2.7.2. Gases

Table 2.7.1 A list of the common gases used throughout the course of this Thesis.^a

Gas	Purity (%)
Carbon dioxide	99.800
Oxygen	≥ 99.500
Hydrogen	> 99.980
Air	N.A.
Helium	> 99.990

^a All gases used were supplied by BOC. Air, H₂ and He were used for GC analysis.

2.7.3. Organic Substrates

Table 2.7.2 *A list of the common materials used throughout the course of this Thesis.^a*

Compound	Purity (%)	Supplier
Methanol	> 99.0	Fisher Chem. Co.
Ethanol	> 99.0	Fisher Chem. Co.
Toluene	> 99.0	Fisher Chem. Co.
Ethyl acetate	> 99.0	Fisher Chem. Co.
Acetic anhydride	> 97.0	Fisher Chem. Co.
Anisole	> 99.0	Fisher Chem. Co.
Phosphate acid	> 98.0	Fisher Chem. Co.
Dimethyl carbonate	> 99.0	Alfa Aesar Chem. Co
<i>iso</i> -propanol	> 99.8	VWR®
Aniline	> 99.0	Sigma Aldrich®
Solketal	> 99.0	Sigma Aldrich®
Glycerol	> 97.0	Sigma Aldrich®
<i>meso</i> -tetraphenylporphyrin	> 99.0	Sigma Aldrich®
Dihydroartemisinin acid	> 99.0	Sanofi Aventis
Biphenyl	> 99.0	Sigma Aldrich®

^a The chemicals mentioned above were used as received without further purification.

Chapter 3. Niobium Compounds Catalysed Friedel-Crafts Alkylation

In this Chapter, an automated continuous flow system was used to investigate the activity of Nb acid catalysts on the alkylation of aniline (AN) with different alkylation reagents.

A brief introduction of the automated flow system was presented in Section 3.1, as well as the self-optimisation algorithm. Then, an exploratory experiment of AN alkylation with dimethyl carbonate (DMC) was carried out with **NbO** catalyst, which was real-time monitored by on-line GC. The results showed that the **NbO** can catalyse the Friedel-Crafts alkylation of AN with DMC, as described in Section 3.2. A possible mechanism was then discussed in Section 3.3.

A temperature ramp reaction was then designed to explore the influence of temperature on the catalytic capability of the Nb acid catalysts and to collect the useful information for the further self-optimisations (Section 3.4). Then the self-optimisations for different AN alkylation products were carried with both **NbO** and **NbP** catalysts, as described in Section 3.5. The results presented in this Chapter are summarised in Section 3.6.

3.1. Background

As described in Section 1.2.6, Chapter 1, integrating on-line or in-line analytics with continuous flow systems could provide a simple way to collect a large number of data in real-time, including distribution (or selectivity) of products, activity and stability of catalysts. Moreover, by applying feedback algorithms, automated continuous flow processes make it is possible to influence the reaction outcome by varying the reaction parameters, such as temperature, reaction time and stoichiometry of reagents, to maximise the production of desired products or to collect useful kinetic data. The process automation associated with flow chemistry can greatly shorten the data analysis time and provide a better design of the reaction with less time, labour and material required. This is often referred to as self-optimisation.

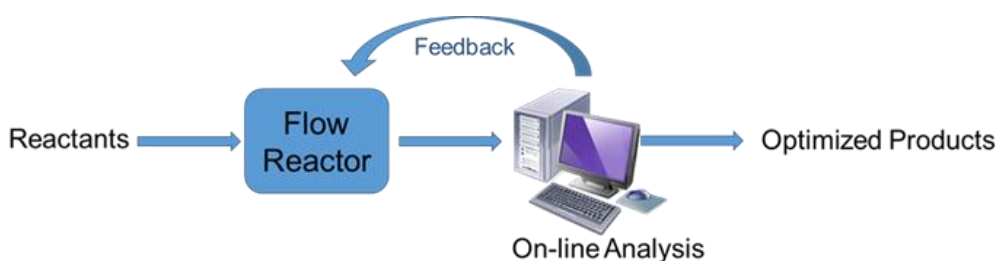


Figure 3.1.1 The concept of a self-optimizing continuous flow system.

In a general approach, an automated flow process is comprised of reagent delivery devices (pumps), temperature controllers (heating or cooling), an on-line or in-line analytical instrument and a computer with a algorithm (LabVIEW or MATLAB) installed (Figure 3.1.1). The real-time data of a flow process, which is collected by an

in-line or on-line analytic, is fed to the computer which is in turn connected to the pumps and temperature controllers. The algorithm calculates the data, suggests a new reaction condition and controls the delivery system (pumps), or temperature controllers to reach that desired condition. Then data from the new condition is obtained and the process repeats itself until a maximum of the desired parameter is identified.

The integration of GC into the high pressure and high temperature continuous flow system permits the real-time monitoring of reaction processes. This was first reported in our research group by Dr. Benjamin Walsh in 2005,¹⁴³ where the online GC can take samples directly from the reaction stream without the need for depressurisation and hence, avoiding the loss of volatile species. This system was then further developed to be automated with a super modified simplex algorithm (SMSIM) by Dr. Richard Bourne and Dr. Andrew Parrott.^{123, 124} The SMSIM algorithm is an improved version of the NMSIM (modified simplex) algorithm, which is based on the simplex optimisation method introduced by Spendley *et al.*¹⁴⁸⁻¹⁵⁰

A simplex is a k -dimensional geometrical figure with $k + 1$ vertices, where k is the number of variable factors being investigated, and the coordinate of each vertex represents a separate set of reaction condition. For example, a single factor Simplex ($k = 1$) is a line of two vertices, a two factor Simplex ($k = 2$) is a triangle of three vertices and, and a three factor Simplex ($k = 3$) is a tetrahedron of four vertices. Figure 3.1.2 demonstrates the outlines of the first three Simplexes, as the higher dimensions cannot be visualised easily.

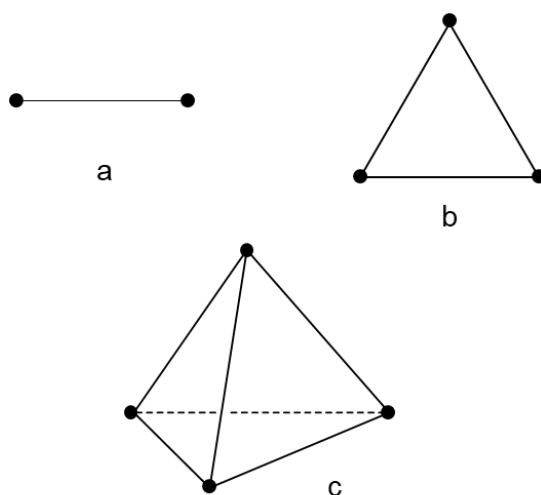


Figure 3.1.2 The concept of Simplexes with one, two, or three factors. (a) Single factor Simplex which is a line, (b) 2-factor Simplex which is a triangle and (c) 3-factor Simplex which is a tetrahedron.

In order to discuss the calculation by Simplex algorithm in a visual way, here a two variable factor (such as temperature and reaction time) Simplex is chosen as a model. To start the 2-factor Simplex optimisation, a set of initial conditions (3 different reaction conditions) is required to be pre-set. Once all these three initial reactions have been conducted, 3 vertices of the first Simplex are then ranked in order and labelled the Best, **B**, Next-Worst, **N**, and Worst, **W**, according to the magnitude of the response (such as yield) at each vertex. The coordinates of a mid-vertex, **P**, are calculated from the average of coordinates **B** and **N**. Then a new vertex is identified, which is the reflected vertex **R** generated by reflecting an equal distance from **W** through **P**, which means moving away from the worst response region and towards a better response region. The second Simplex is then conducted at the coordinates of **R**. The optimisation process will be repeated until the response (such as yield) reaches a maximum. Figure 3.1.3 shows the first three calculations for a two factor Simplex system.

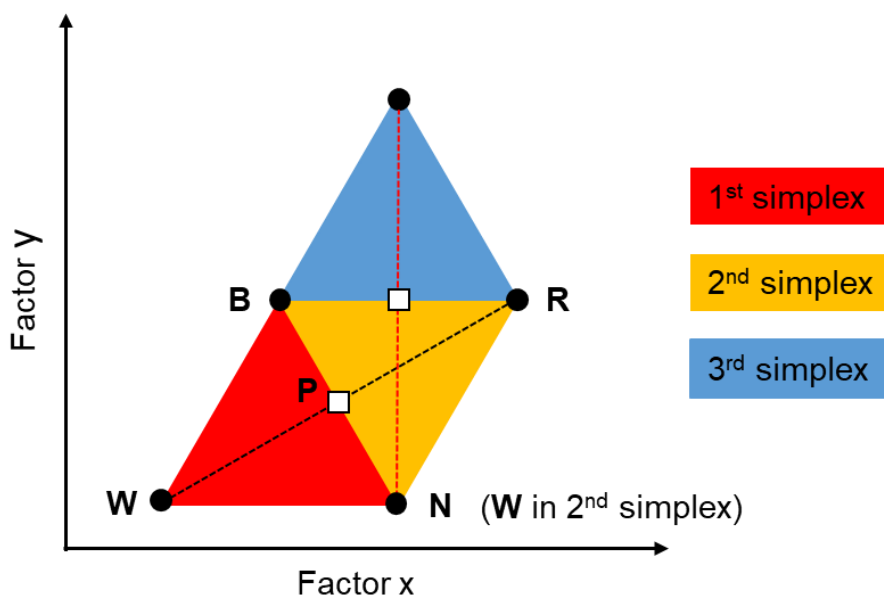


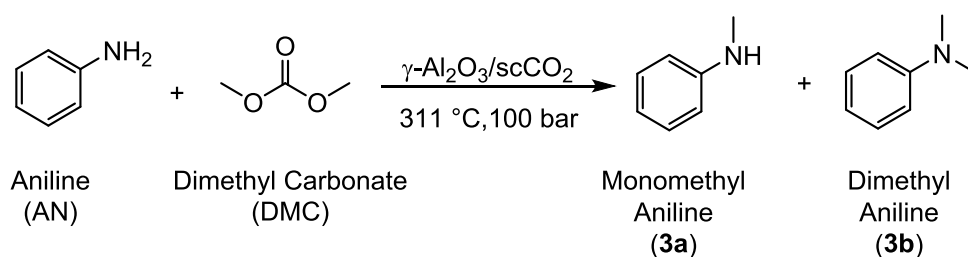
Figure 3.1.3 Diagram illustrating the first three calculations of a 2-factor Simplex optimisation progress. ● represents each reaction conditions; □ is calculated from the average of coordinates *B* and *N*; *R* is the reflecting from *W* through *P*; the coloured areas represent different Simplexes.¹⁴⁸

The automated continuous flow system discussed above was used at the beginning of this Thesis with the aim to obtain a broad knowledge of the activity of Nb acid catalysts and to also familiarise with the operation and maintenance of the high-pressure continuous flow system.

3.2. The Exploratory Experiment

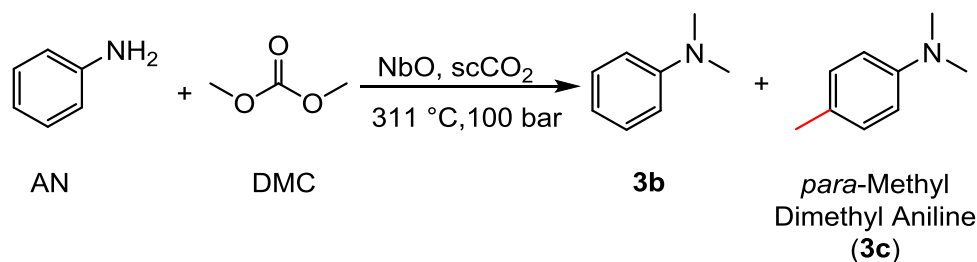
To investigate the catalytic ability of Nb catalysts and the operational conditions in continuous flow system, exploratory experiments are started with a model reaction, alkylation of aniline (AN) with dimethyl carbonate (DMC), which had been studied previously in the group using γ -Al₂O₃ (Scheme 3.2.1).¹⁵¹

With $\gamma\text{-Al}_2\text{O}_3$ as a catalyst, two products, monomethyl aniline (**3a**) and dimethyl aniline (**3b**), were obtained via alkylation of AN with DMC. Further optimisation for **3b** illustrated that a 97% yield can be obtained at 311 °C, 100 bar, with the flowrates of CO_2 1 mL/min, DMC (0.275 M in Tol) at 0.45 mL/min and AN (0.275 M in Tol) at 0.16 mL/min individually.



*Scheme 3.2.1. The alkylation of AN with DMC over $\gamma\text{-Al}_2\text{O}_3$ catalyst to form monomethyl aniline (**3a**) and dimethyl aniline (**3b**). Under optimised conditions (311 °C, 100 bar; AN 0.16 mL/min, DMC 0.45 mL/min), a 97% yield of **3b** can be obtained.¹⁵¹*

To compare with $\gamma\text{-Al}_2\text{O}_3$, the alkylation of AN with DMC was conducted with **NbO** catalyst (1 g) under the same optimised conditions for **3b** as using the $\gamma\text{-Al}_2\text{O}_3$ catalyst. The reaction was carried out continuously for 26 hours, and 100% conversion of AN was achieved. Besides product **3b** (71% yield), a new product was obtained with **NbO** catalyst and identified as *para*-methyl dimethyl aniline (**3c**) as shown in Scheme 3.2.2. This is likely to be underwent a Friedel-Crafts alkylation.



*Scheme 3.2.2. The alkylation of AN with DMC over **NbO** catalyst forming **3b** and **3c** via a F-C alkylation processing at 311 °C, 100 bar, with the flowrates 0.16 mL/min of AN (0.275 M in Tol) and 0.45 mL/min of DMC (0.275 M in Tol). The reaction was carried out for 26 hours, and gave and 29% yield of compound 5.*

The Friedel-Crafts alkylation (F-C alkylation) was developed in 1877, by Charles Friedel and James Mason Crafts, in which a hydrogen atom of an aromatic or a heteroaromatic compound is replaced by an alkyl group as shown in Figure 3.2.1. It is an important organic synthesis process in both petroleum and chemical industries.

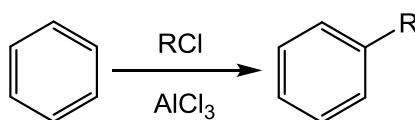


Figure 3.2.1. Friedel-Crafts alkylation of benzene with alkyl chloride with AlCl_3 as a catalyst.

The traditional catalysts for F-C alkylation are Lewis acids such AlCl_3 , FeCl_3 , BF_3 , ZnCl_2 , and TiCl_4 . Additionally, strong Brønsted acids including sulfuric acid, hydrofluoric acid or super acids can also accelerate this transformation. The initial alkylating reagents usually are alkyl chlorides. However, the stoichiometric or super stoichiometric amounts of a Lewis acid or Brønsted acid and toxic alkyl halides used to perform the reaction become major drawbacks of F-C alkylation. With a view to being environmental friendly, new catalytic approaches have been developed, some of which use solid acids such as clays and zeolites.¹⁵² Also the alkyl halides have been replaced

by less toxic alkylating reagents such as alcohols, activated double bonds and styrenes.¹⁵³

Here **NbO** solid acid showed the catalytic activity for F-C alkylation of AN with DMC is impressive. According to the literatures,^{154, 155} modified **NbO** catalyst, such as sulfated mesoporous **NbO** and Nb–W mixed oxides, have been shown to catalyse Friedel–Crafts alkylation. Here without any pre-treatment **NbO** showed remarkable acidic activity, which is higher than $\gamma\text{-Al}_2\text{O}_3$, for the F-C alkylation of AN with DMC leading to a 29% yield of **3c**, which could be improved under optimised the conditions that will be discuss in Section 3.5

The alkylation of AN with DMC over **NbO** catalysts has been carried out for 26 hours at 311 °C, the activity of **NbO** did not show any decrease and 100 % conversion of AN was observed. However, the selectivity of **3b** and **3c** did change considerably as shown in Figure 3.2.2.

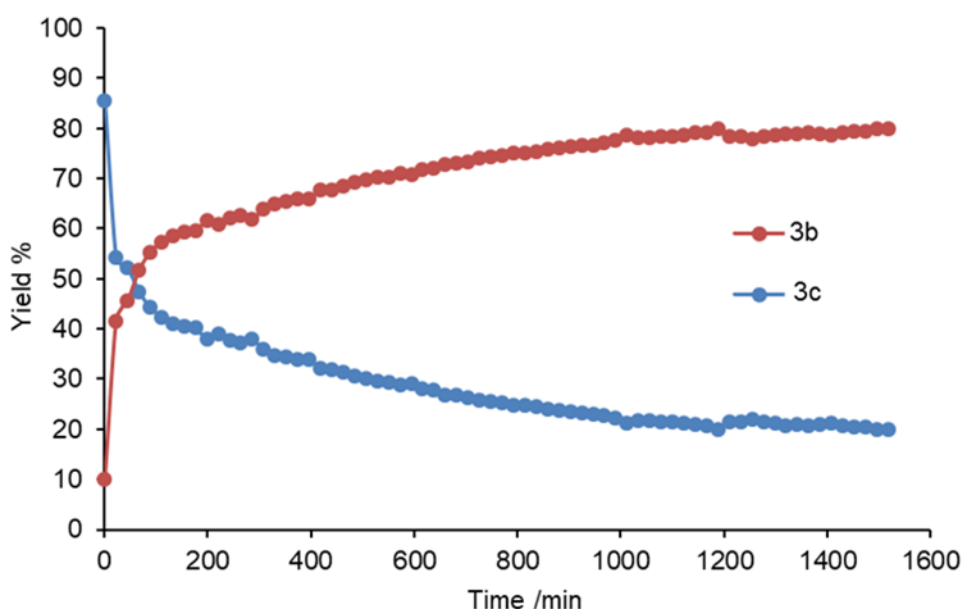
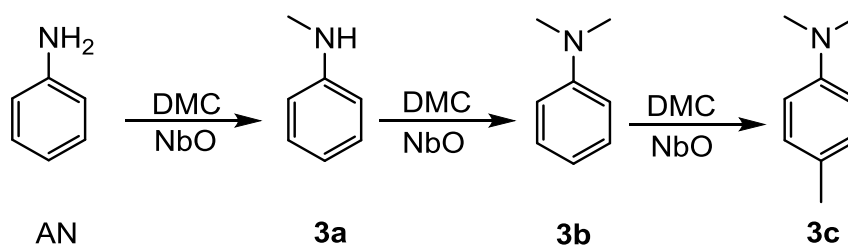


Figure 3.2.2. The distribution of AN alkylation products (**3b** and **3c**) catalysed by **NbO** for 26 hours at 311 °C with the flowrates 0.16 mL/min of AN (0.275 M in Tol) and 0.45 mL/min of DMC (0.275 M in Tol).

At the beginning of reaction, **NbO** catalyst favoured the formation of the F-C alkylation product **3c** (86% yield). However, the yield of **3c** decreased rapidly to 42% in the next 2 hours and declined to around 20% after 20 hours. In contrast, the yield of **3b** was low (10%) at the start, then increased dramatically in the following 2 hours from 14% to 58% and kept rising for the next 20 hours becoming stable around 78%. The varied selectivity of different products is due to the gradual alkylation of AN, which **3c** was formed by the alkylation **3b**, **3b** was generated from **3a** and **3a** was the 1st step AN alkylation product (shown in Scheme 3.2.3). At beginning of the reaction, the alkylation occurred preferentially at the NH₂ group to form **3a**, which reacted further to **3b**, as the alkylation at the NH₂ group is easier than at benzene ring. Therefore, there was sufficient **3b** generated rapidly once the reactants flowing into catalyst bed. These formed **3b** then continuously passed through reactor and contacted with fresh **NbO** catalyst. Then further F-C alkylation of **3b** to **3c** occurred leading a high yield of **3c** in the earlier flow reaction. With time, as the reactor reached a steady state, more and more acid sites were occupied by the NH₂ group alkylation resulting the formation of **3b** increasing dramatically. When the system reached an equilibrium, the selectivity for both **3b** and **3c** became stable.



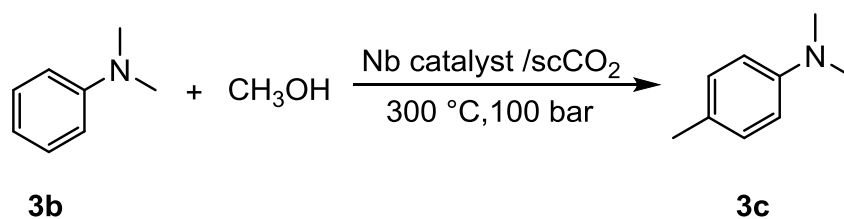
*Scheme 3.2.3 The progressively alkylation of AN over **NbO** solid acid.*

3.3. Short Study of Possible Mechanism

According to the literature,¹⁵⁶ DMC is not stable at the surface of acid catalysts and could decompose into methanol (MeOH), dimethyl ether, CO₂ and some small amount of other organic products such as methane. And this decomposition could be responsible for the alkylation of AN. Therefore, a control experiment was carried out to investigate the stability of DMC in the continuous flow reactor with **NbO** acid catalyst from 100 °C to 300 °C. The results revealed that DMC started to decompose from 150 °C, and increasing temperature expedited the rate, by 300 °C it is completely decomposed at a flowrate of 0.3 mL/min. Therefore, it is assumed that MeOH could be the actual the alkylation reagent that reacts with AN. This assumption was then tested by the alkylation of **3b** with MeOH under the same condition mentioned above. As the alkylation of benzene ring is much harder than NH₂ group, and if it could accomplish the F-C alkylation, it should easily alkylate the NH₂ group.

The alkylations of **3b** with MeOH were conducted over with **NbO** and **NbP** separately, in order to compare the acidic activity of these two Nb solid acids for the F-C alkylation (Scheme 3.3.1). The results were shown in Figure 3.3.1. Reactions were carried out for 26 hours, with a 0.275 M solution feed of AN at a flowrate of 0.16 mL/min in Tol and a 0.275 M solution feed of MeOH in Tol at a flowrate of 0.44 mL/min.

The activity of **NbO** and **NbP** catalysts decreased slightly shortly after the beginning of the experiment and then became stable. The **NbP** showed higher activity than **NbO** for the F-C alkylation, for which a 50% yield of **3c** was obtained using **NbP** and 39% using **NbO**.



*Scheme 3.3.1 The F-C alkylation of **3b** with MeOH over Nb solid acids (**NbO** or **NbP**) at 300 °C, 100 bar in the continuous flow reactor.*

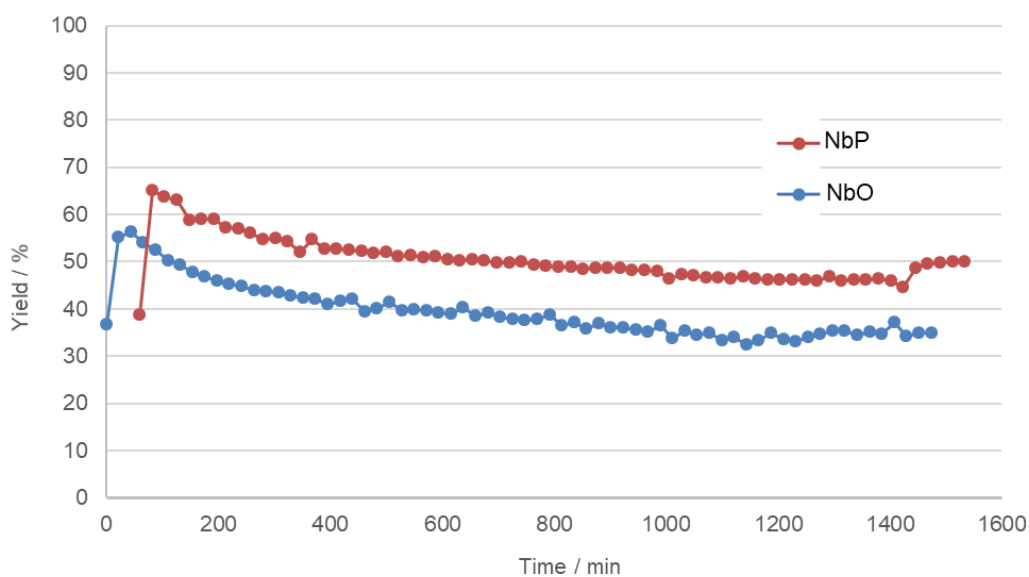


*Figure 3.3.1 The acidic activity comparison of **NbO** and **NbP** for the F-C alkylation of AN with MeOH. **NbP** catalyst showed stronger activity than **NbO** as leading a higher yield of **3c** (50%) than **NbO** (39%).*

3.4. Temperature Ramp Reaction

A benefit of the integration of a continuous flow process with on-line GC analysis and automated programming is that an automated temperature ramp reaction could be easily set up and run, with the aim to investigate the temperature effect on the activity of Nb solid acids (**NbO** and **NbP**) for AN alkylation and the selectivity of different alkylation products. The real-time sampling and automated program provides

a chance to design a continuous flow reaction that can be processed at varied conditions as desired without complex manual operations, which saves the labour, time, and resources.

The automated temperature ramp reaction was programmed to be heated up and cooled down twice, to investigate the catalyst deactivation after experiencing at varied temperatures. This is an essential issue for the further self-optimisation operation, which the reaction conditions change at each Simplex. Different from homogenous catalysts, the solid catalyst for a continuous heterogeneous reaction can deactivate over time or through varied reaction conditions such as coking generation at high temperatures, which will influence the accuracy of self-optimisation results.

The programming of the automated temperature ramp reaction is shown in Figure 3.4.1. The reaction was designed to start from 100 °C and increase to 300 °C with 50 °C step, and each temperature (100 °C, 150 °C, 200 °C, 250 °C and 300 °C) was held for 1 hour to allow three on-line samplings. After the first temperature heating routine the system reached 300 °C, it was then cooled down to 100 °C in 1 hour and then was give the heating process for a second time. When the temperature rose to 300 °C again, the system was held at this temperature for 2 hours with 6 on-line samples taken. The flow reactor was then cooled down with 50 °C step to 100 °C after every 90 mins, and 4 on-line sample were taken at each temperature step.

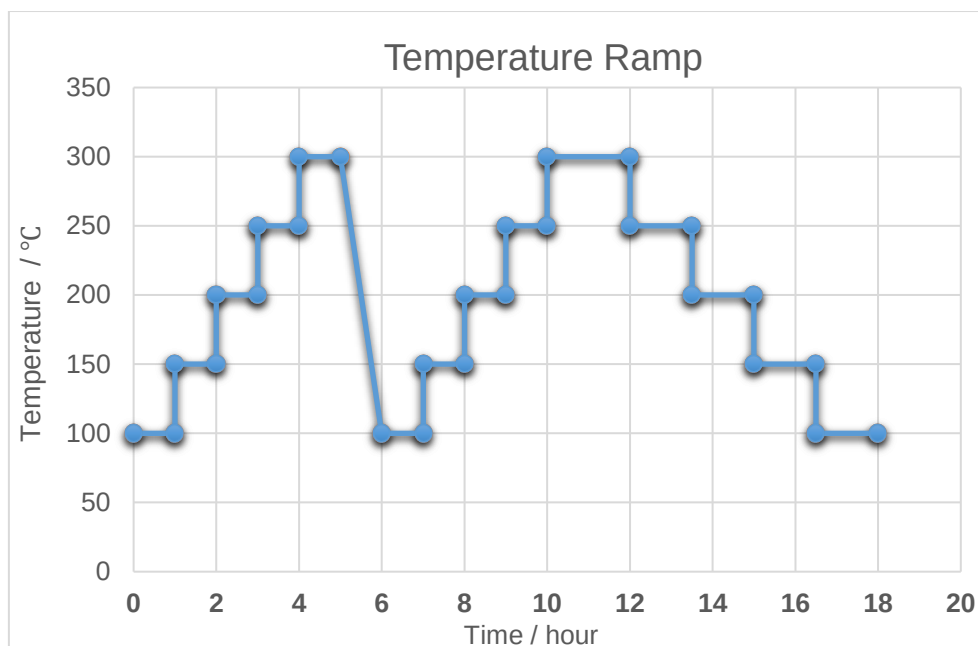


Figure 3.4.1 Figure 4: The design of automated temperature ramp reaction by returning to the same reaction temperature for three times after cooling or heating, to investigate the stability of Nb solid acid catalysts for the alkylation of AN with DMC over time and varied conditions. The temperature was set between 100 °C and 300 °C with a 50 °C step. During the temperature rising process, each reaction condition was held for 1 hour and 3 on-line GC samples were taken. During temperature declining period, each step was held for 1.5 hours to allow sufficient cooling, and during this time 4 online-GC samples were taken to monitor the reaction.

Both **NbO** and **NbP** were used as solid acids for the alkylation of AN with DMC through the temperature ramp programming, and the results are shown in Figure 3.4.2 and Figure 3.4.3. The on-line samplings were summarised according to the reaction temperatures, which is convenient to compare the activity of Nb catalysts at the same reaction condition after experienced varied processing. As there was no reaction occurred at 100 °C with either **NbO** or **NbP** catalysts, the figures presented the results at 150 °C, 200 °C, 250 °C and 300 °C. The abscissa showed on-line sample number, which were divided into 3 groups based on the temperature programming including first heating process, second heating process and the cooling process. For example, in Figure 3.4.3 sample No 5, 6, 7 were taken at 150 °C during the first heating process, sample 23, 24, 25 were recorded at same temperature (150 °C) but during the second

temperature rising period, and sample 46 to 49 were taken after the system were cooled to 150 °C through the temperature declined period. (NOTE: the first sample of each group marked with 'a' were taken before the system became steady, and sample 8 is missing due to unexpected software shutdown.)

Using fresh **NbO** as a catalyst, the alkylation of AN with DMC occurred from 150 °C (Figure 3.4.2 **A**), and only mono-methylation product **3a** was formed with a yield around 18 % at 150 °C (average value of sample 5 and 6). After experiencing the first heating processing and the system temperature being cooled down 150 °C for the first time, no reaction happened (sample 22-24), which indicated that the activity of **NbO** decreased. Same situation was observed during the cooling processing at 150 °C, where sample 45 was taken during the temperature changing from 200 °C to 150 °C containing the product **3b** formed at 200 °C.

As shown in (Figure 3.4.2 **B**), the dimethyl production **3b** was started to be formed at 200 °C. When the system first was heated to 250 °C (sample 9), the yield of dimethyl product **3b** (46 %) was higher than monomethyl product **3a** (27 %), which showed that the generated **3a** was easy to experience a further methylation at NH group to yield **3b**. This was also obtained during the second heating processing (sample 26 and 27). But for sample 42 to 44, which were taken during the last declining period, there were more **3a** than **3b** obtained, indicating the decreasing of **NbO** activity after experiencing two times heating processing. Sample 9, 25 and 41 were taken before the system becoming steady, so there were residue formed during the temperature changing, such as sample 9 and 25 contained **3a** generated when the system temperature increased from 150 °C to 200 °C, and sample 41 contained product **3b** formed during temperature cooling from 250 °C to 200 °C. Similar situation happened at every first sample in the same sample group, including sample 10, 28, 37, 13, and 31 in Figure 3.4.2.

As for the results at 250 °C (Figure 3.4.2 C), high yield of **3b** (above 90 %) were obtained, for sample 11-12, 29-30,38-40, during the whole temperature ramp reaction. Small amount of the **3a** (yield below 10 %) was observed at the last cooling processing (sample 38-40) due to the **NbO** deactivation. The F-C alkylation happened at 300 °C, and was obtained the highest yield 77% at sample 14 (Figure 3.4.2 D). After experiencing varied temperature processing, the yield of **3c** decreased to around 60 % and became stable (sample 34 to 36).

In conclusion, the alkylation of AN with DMC using **NbO** as a catalyst, via a temperature ramp processing, demonstrated the influence of temperature on the activity of **NbO** catalyst. The NH₂ group alkylation started from 150 °C yielding **3a**, and became more active as temperature increasing to form **3b**. The F-C alkylation of AN can only be achieved at high temperature 300 °C. This brief product distribution will help to identify the search area for the further self-optimisation. Besides, slight deactivation of **NbO** was observed after three times drastic temperature varying process (100°C - 300 °C) for 18 hours, which is acceptable for the next step self-optimisation process.

The results for using **NbP** as a catalyst for the alkylation of AN via the temperature ramp processing were shown in Figure 3.4.3. The product distribution was similar to using **NbO** as catalyst, while the **NbP** showed a higher activity than **NbO**. For example, at 200 °C using fresh **NbP** catalyst, a 75% yield of **3b** was obtained with 100% AN conversion (sample 9 and 10 in Figure 3.4.3 B) which was higher than using fresh **NbO** catalyst that gave a 46% yield of **3b** with 74% AN conversion (sample 9 in Figure 3.4.2 B). This is correspond to the higher acidity and surface area of **NbP** than **NbO** as shown in Table 3.4.1.

Table 3.4.1 Main properties of the Nb catalysts.³⁹

Sample	Surface area (m ² /g)	$r_{p,av}$ (nm)	Effective acidity (μequiv/g)	
			Cyclohexane	Methanol
NbO	108	2.5	207	71
NbP	142	3.1	400	151

Besides, the activity of **NbP** catalyst was more stable than **NbO** catalyst, for example at 150 °C there was (about 10%) **3a** formed when using **NbP** catalyst even after 18 hours varied temperature processing (Figure 3.4.3 sample 47-49), which cannot be achieved with **NbO** catalyst. The only obvious deactivation of **NbP** catalyst was observed at the reactions conducted at 200 °C, which the formation of **3b** decreased with time. However, for the reactions carried out at high temperatures (250 °C and 300 °C), **NbP** catalyst maintained stable activity, which would be suitable for the further self-optimisation reaction. The yields of **3a**, **3b** and **3c** for the alkylation of AN with DMC catalysed by **NbO** and **NbP** through temperature ramp reaction are shown in table Table 3.4.2 and Table 3.4.3.

Table 3.4.2 Yields of **3a**, **3b** and **3c** for the reaction of AN and DMC catalysed by **NbO** through temperature ramp reaction

	150 °C			200 °C			250 °C			300 °C		
	3a (%)	3b	3c	3a (%)	3b (%)	3c	3a (%)	3b (%)	3c	3a	3b (%)	3c (%)
1st Heating	13.8±0.1	-	-	30.5±3.8	35.3±14.0	-	-	99.6±0.4	-	-	17.3±3.4	77.5±2.9
2nd Heating	-	-	-	37.8±0.0	43.0±0.5	-	-	97.9±0.4	-	-	35.0±3.4	61.3±3.2
Cooling	-	-	-	40.9±0.8	26.1±1.4	-	4.7±0.7	93.7±0.0	-	-		

Table 3.4.3 Yields of **3a**, **3b** and **3c** for the reaction of AN and DMC catalysed by **NbP** through temperature ramp reaction.

	150 °C			200 °C			250 °C			300 °C		
	3a (%)	3b (%)	3c	3a (%)	3b (%)	3c (%)	3a	3b (%)	3c (%)	3a (%)	3b (%)	3c (%)
1st Heating	17.1±2.4	2.6±0.7	-	21.1±2.7	75.2±3.9	-	-	99.8±0.3	0.3±0.2	2.4±0.1	7.3±0.6	68.8±2.5
2nd Heating	8.5±1.2	2.9±0.2	-	24.5±0.9	64.1±3.2	3.5±1.6	-	97.2±0.3	2.9±0.3			
Cooling	5.7±0.3	1.7±0.2	-	30.9±1.6	52.0±3.2	0.7±0.3	-	95.1±1.1	4.8±1.1	2.5±0.0	13.0±1.7	69.9±0.5

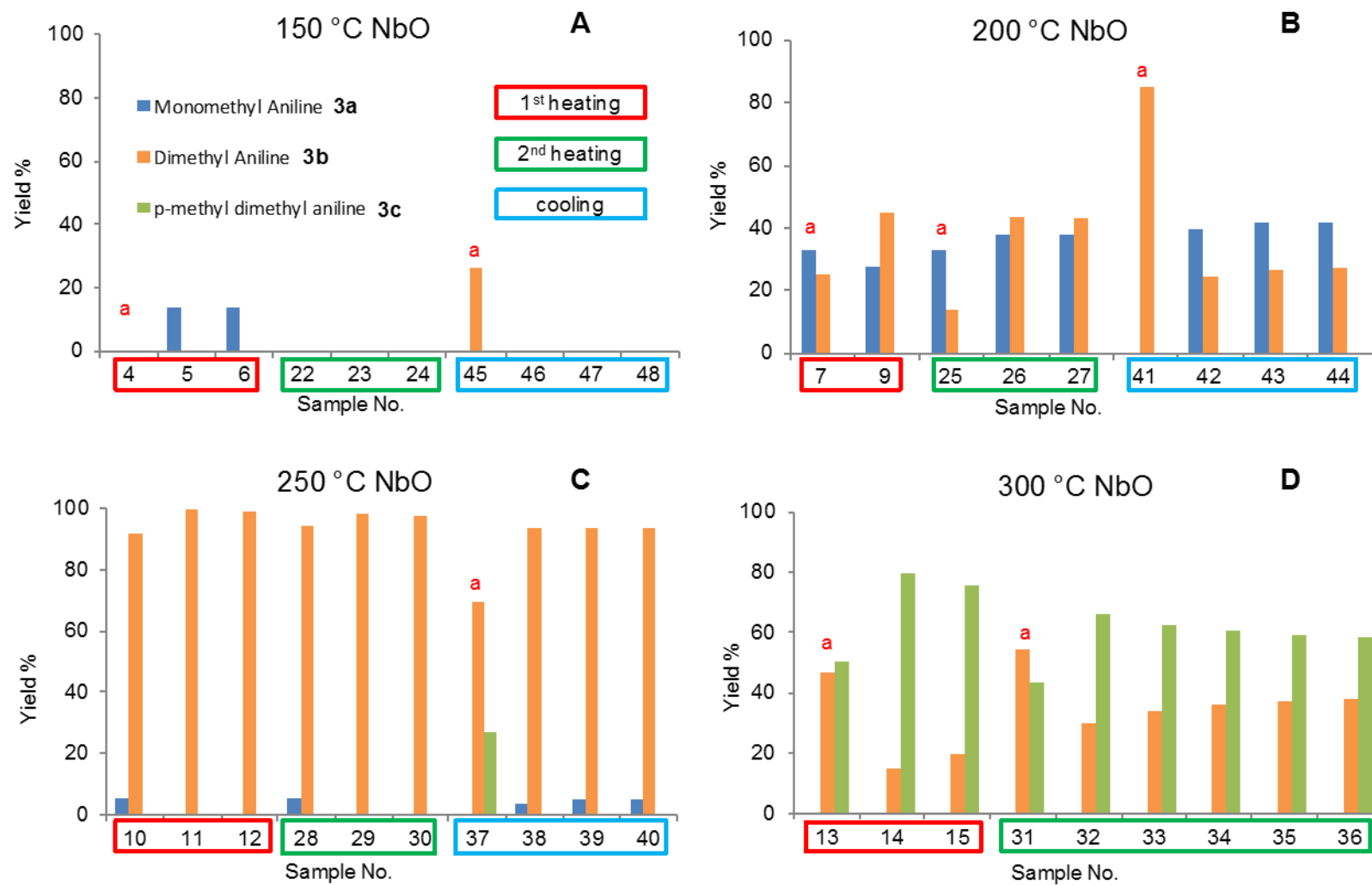


Figure 3.4.2. Results of temperature ramp reaction with NbO

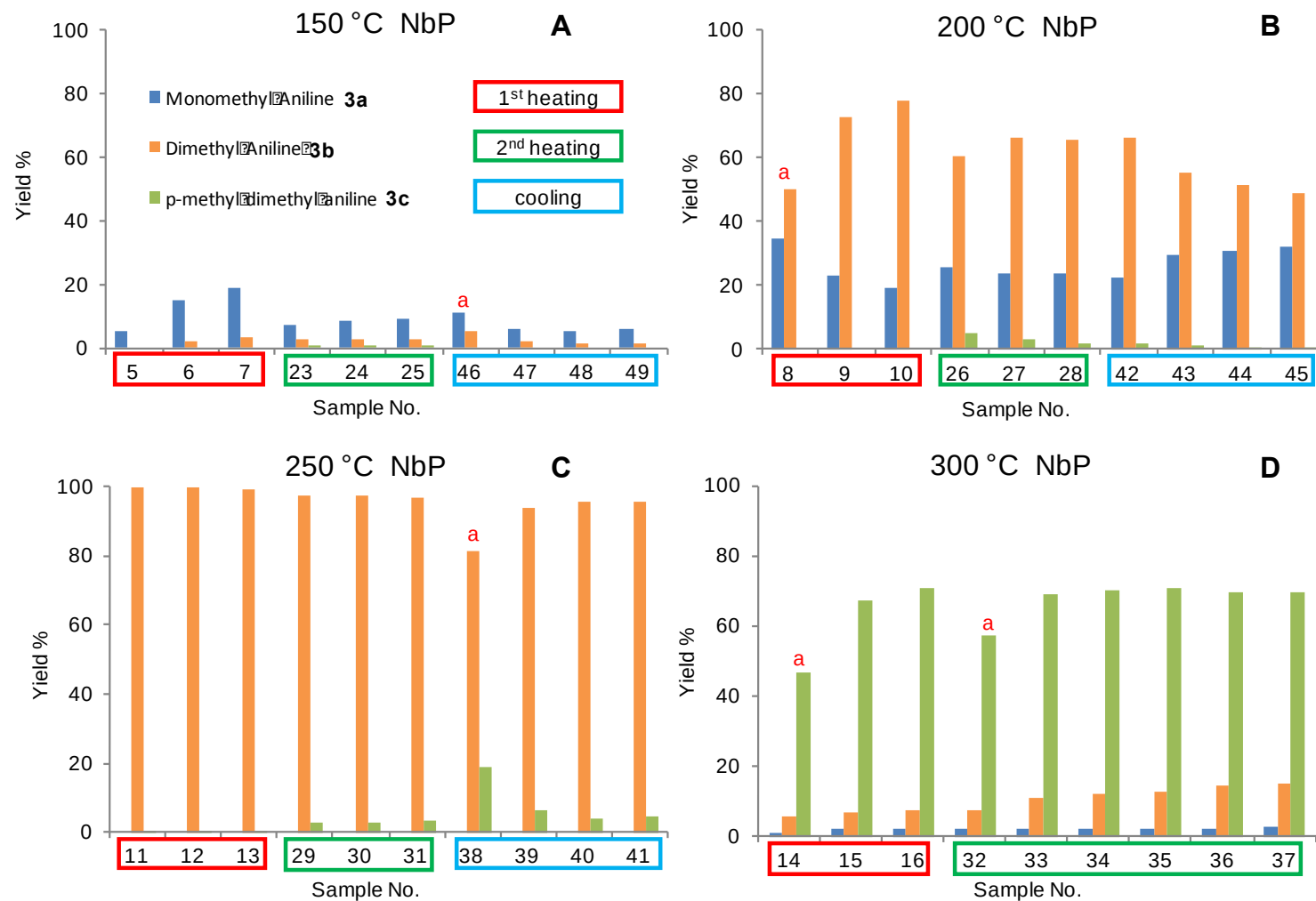


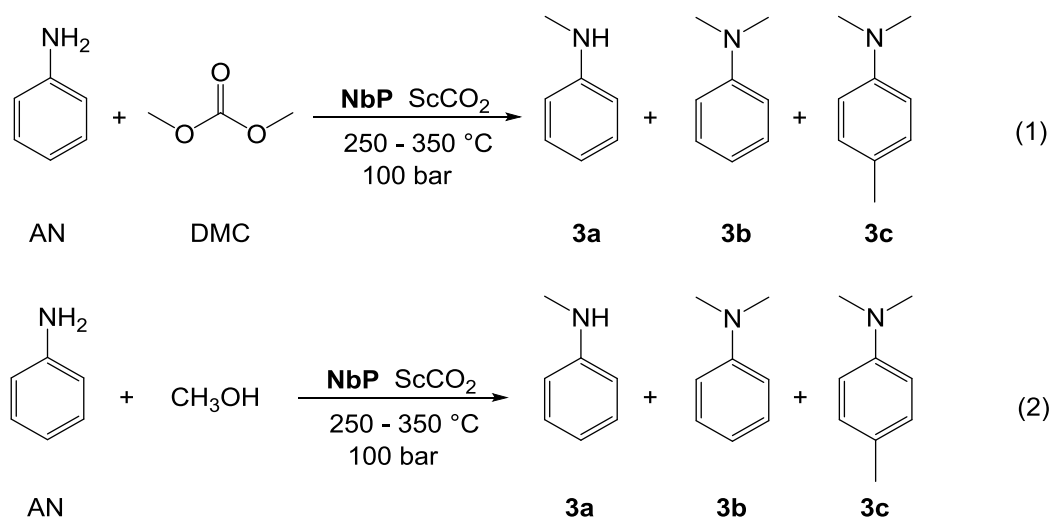
Figure 3.4.3 .Results of temperature ramp reaction with **NbP**.

3.5. Self - Optimisation for Different Alkylation Products

The self-optimisation continuous flow system described in Section 3.1 will be used to investigate reaction conditions for the maximum yield of different AN alkylation products.

3.6.1. Using Different Alkylation Reagents

The first alkylation product chose to be optimised was **3c**. As **NbP** showed higher catalytic activity than **NbO**, **NbP** was chose as a catalyst for the self-optimising compound **3c** first. Two different reagents, DMC and MeOH, were used to alkylate AN, separately. The reactions were shown in Scheme 3.5.1



*Scheme 3.5.1. The alkylation AN with two different reagents, DMC or MeOH, using **NbP** as a catalyst.*

Three reaction parameters have been investigated at the same time by the self-optimisation process, including reaction temperature, flowrate of AN and flowrate of the alkylation reagent (DMC or MeOH). According to the results of temperature ramp reactions, there was few **3c** formed at 250 °C with **NbP** as a catalyst, and the maximum temperature the flow system can be operated is 350 °C. Therefore, the temperature range to be investigated for optimising **3c** was set from 250 °C to 350 °C. The flowrate range of each reactant was set to be varied from 0.1 mL/min to 1 mL/min. The system pressure was kept at 100 bar with a 1 mL/min flowrate of CO₂. The starting condition was set at 300 °C, 0.16 mL/min AN (0.275 M in Tol), 0.48 mL/min DMC (0.275 M in Tol) or MeOH (0.275 M in Tol), which has been found to give a better yield of **3c**.

For AN alkylation with DMC, the self-optimising program constructed 26 Simplexes with a total of 93 vertices (different reaction conditions). The optimisation pathway is shown in Figure 3.5.1. The conditions did not change significantly after the 78th vertices at which point the yield of **3c** reached 73%. The highest yields of **3c** was obtained, via the self-optimisation process, was 82.2% which appeared at the very beginning of the tests, the 3rd vertices (313 °C, 100 bar, 0.16 mL/min AN and 0.71 mL/min DMC).

Using MeOH as an alkylation reagent, the optimisation program built 17 Simplexes about 59 vertices in all. The experiment process is shown in Figure 3.5.2. The optimal point was the second vertices with 71.3% yield of **3c**. The reaction condition was at 313 °C, 100 bar, with 0.16 mL/min flowrate of AN and 0.48 mL/min of MeOH. After the 42th vertices the conditions did not modify much, and at this point the yield of **3c** was 71%.

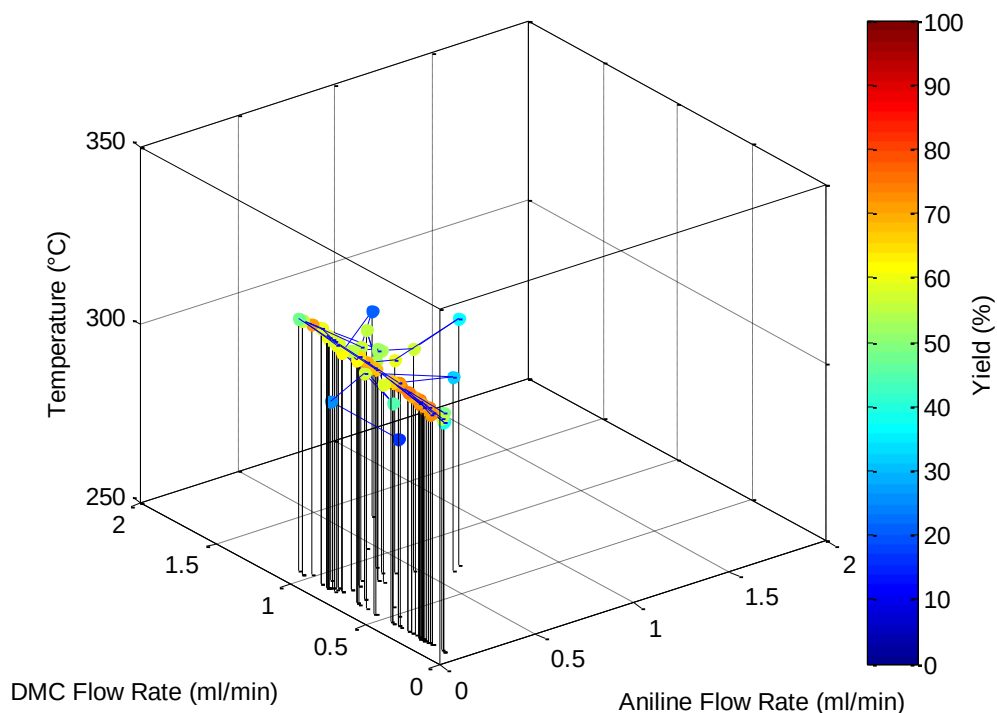


Figure 3.5.1. The optimisation pathway for **3c** using DMC as an alkylation reagent. The temperature ranged from 300°C to 322°C; and the flowrates of DMC and AN varied from 0.1 to 1.32 mL/min, 0.1 to 0.67 mL/min separately. The optimal point was at 313 °C, 0.16 mL/min AN and 0.71 mL/min DMC giving 83% yield of **3c**.

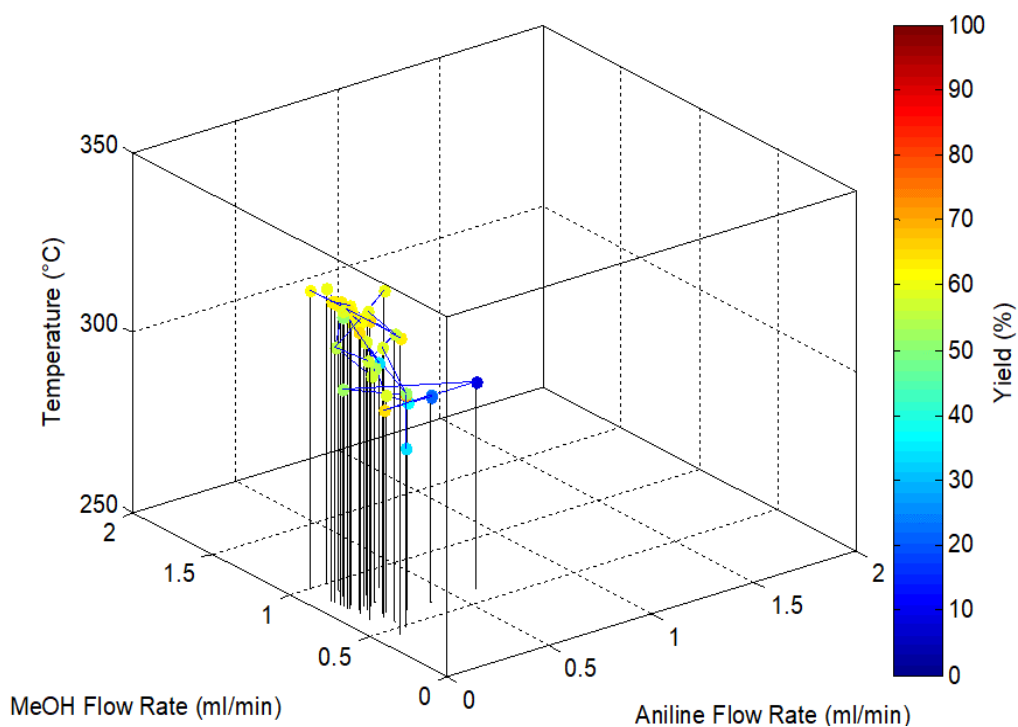


Figure 3.5.2. The optimisation pathway for **3c** from the reaction of AN with MeOH. The temperature ranged from 300°C to 333°C, and the flowrates of MeOH and AN varied from 0.48 to 1.0 mL/min, 0.1 to 0.61 mL/min, separately. The optimal point was at 313 °C, 0.16 mL/min AN and 0.48 mL/min MeOH giving 71% yield of **3c**.

The results of the optimisations for **3c** using different alkylation reagents for the AN alkylation were summarised in Table 3.5.1. The optimal reaction temperature and AN flowrate for these two optimisation are the same. The optimal flowrate of DMC 0.71 mL/min was higher than MeOH 0.48 mL/min, which gave a higher yield of **3c** (83%). Even though the optimisation pathway has tested the vertices with high ratio of MeOH to AN, the obtained yield of **3c** was lower than 71%, such as at 320 °C, with 0.1 mL/min flowrate of AN and 0.84 mL/min of MeOH giving a 68% yield of **3c**. Therefore, DMC was considered to be a more active alkylation reagent than MeOH, and it will be used in the next step optimisation processing for different alkylation products.

*Table 3.5.1. The optimal conditions for **3c** via self-optimisation processing of AN alkylation with different reagents catalysed by **NbP** catalyst.*

Alkylation reagent mL/min		AN mL/min	Temperature °C	Yield of 3c %
DMC	0.71	0.16	313	83
MeOH	0.48	0.16	313	71

3.6.2. Using Different Nb Catalysts

Then the self-optimisations for the three different AN alkylation products, **3a**, **3b** and **3c**, were carried out using DMA as an alkylation reagent. Both **NbO** and **NbP** were investigated in the self-optimisation processing.

The temperature range to be investigated for optimising each alkylation product was set based on the temperature ramp reaction. For optimising **3c**, the temperature was set to be varied from 250 °C to 350 °C. For **3b** optimisation, the temperature range was from 200 °C to 350 °C. For optimising **3a**, the temperature range was set to be from 150 °C to 250 °C. The flowrate range of each reactant was set to be varied from 0.1 mL/min to 1 mL/min. The system pressure was kept at 100 bar with a 1 mL/min flowrate

of CO₂. The starting condition was set at 300 °C for **3c**, 200 °C for **3b** and **3a**, with a flowrate 0.16 mL/min AN (0.275 M in Tol) and a flowrate 0.48 mL/min DMC (0.275 M in Tol). The optimal conditions for each product with different catalysts were summarised in Table 3.5.2. The results of using γ -Al₂O₃, which were the previous work done in the group, were presented here to compare the activity of the different catalyst in the alkylation AN.¹⁵¹

Table 3.5.2. The optimal conditions for the AN alkylation products via self-optimisation processing with DMC using different catalysts.¹⁵¹

	γ -Al ₂ O ₃				NbO				NbP			
	Yield	T	AN	DMC	Yield	T	AN	DMC	Yield	T	AN	DMC
	%	°C	mL/min		%	°C	mL/min		%	°C	mL/min	
3a	66	348	0.24	0.45	45	224	0.15	0.49	45	191	0.35	0.87
3b	98	344	0.17	0.50	97	258	0.10	0.55	88	241	0.10	0.38
3c	-	-	-	-	52	315	0.16	0.48	83	313	0.16	0.71

For the di-methylation product **3b**, similar optimal yield were obtained with **NbO** and γ -Al₂O₃ as catalysts. Using **NbO** as a catalyst the optimal temperature was much lower (224 °C) than using γ -Al₂O₃ (348 °C). However, for the mono-methylation product **3a**, the optimal yield with **NbO** was about 20% lower than with γ -Al₂O₃. This was probably due to that **3a** was easier underwent a further alkylation to form **3b** by **NbO** catalyst than by γ -Al₂O₃, which also indicated that the activity of **NbO** was higher than γ -Al₂O₃. As for the F-C alkylation, γ -Al₂O₃ cannot achieve.

Then the activity comparison between **NbP** and **NbO**: For the mono-methylation product **3a**, the optimal yields were similar with either **NbO** or **NbP** catalyst. However, when using **NbP** as a catalyst, the optimal temperature was lower and the total flowrate of the reagent mixture was much higher than using **NbO** catalyst. This meant that a higher out-put at lower temperature was achieved by **NbP** than by

NbO. As for the F-C alkylation product **3c**, the optimal yield with **NbP** (79%) was higher than with **NbO** (52%). Therefore, in total, Nb catalyst showed a strong activity in the alkylation of AN with DMC, and can achieve the F-C alkylation which $\gamma\text{-Al}_2\text{O}_3$ cannot, especially for the **NbP** catalysts performed better than **NbO** catalyst.

3.6. Conclusions

In this Chapter, an automated continuous flow reactor with on-line GC analysis was used to explore the activity of Nb catalysts in the alkylation of AN with DMC or MeOH.

The initial experiments indicated that both of **NbO** and **NbP** catalysts had high acidic activity, which can achieve Friedel–Crafts alkylation of AN with DMC or MeOH that cannot be performed by $\gamma\text{-Al}_2\text{O}_3$.

To explore the influence of temperature on the catalytic capability of these two Nb catalysts, temperature ramp reactions were designed and carried out. The results showed that the Friedel–Crafts alkylation of AN with DMC only occurred at high temperatures (around 300 °C).

Based on the products distribution investigated in the temperature ramp reactions, the optimisations for different AN alkylation products were then investigated via the automated continuous flow system. Two alkylation reagents were tested in the self-optimisation for **3c** using **NbP** as a catalyst, and DMC showed more active than MeOH, which gave a higher optimal yield of **3c** (83%) with DMC than 71% with MeOH. Both **NbO** and **NbP** were investigated in the self-optimisation reactions and **NbP** showed a stronger activity in the alkylation of AN with DMC than **NbO**.

Chapter 4. Niobium Phosphate Catalysed Skraup

Reaction for Quinoline Synthesis

This Chapter describes the first application of niobium Phosphate (**NbP**) in the synthesis of quinolines via the Skraup reaction in continuous flow process. The concept started with the aim of converting the biomass by-product, glycerol, to value-added chemicals, and the Skraup reaction was chosen as it uses glycerol directly, to react with aniline to synthesise the heterocyclic compound quinoline. A brief review of the applications of quinolines and the Skraup reaction is presented in Section 4.1.

Then, an exploratory experiment was carried out, reacting glycerol and aniline with **NbP** catalyst in aqueous solution. The optimised quinoline yield was 10%, which was limited by the high polarity and density of glycerol. Therefore, an alternative starting reagent solketal, the isopropylidene acetal protected form of glycerol, was investigated, which can achieve a higher yield of quinoline (30%) (Section 4.2). Following this, a control experiment and the analysis of by-product summarised in Section 4.3.

Optimisation of the synthesis of quinoline is then considered, investigating the effects of varying four reaction parameters: feedstock ratio (Section 4.4), temperature (Section 4.5), pressure (Section 4.6), and flowrate (Section 4.7).

In section 4.8, the scale-up of this reaction in a series of connected reactors was demonstrated, with a view to increasing the productivity. The possible mechanism of the **NbP** catalysed Skraup reaction is discussed in Section 4.9.

Two anilines derivatives, 4-methoxyaniline and 4,4'-methylenedianiline, were used to react with solketal in order to demonstrate that **NbP** could be extended to catalyse the Skraup reaction more widely, as described in Section 4.10.

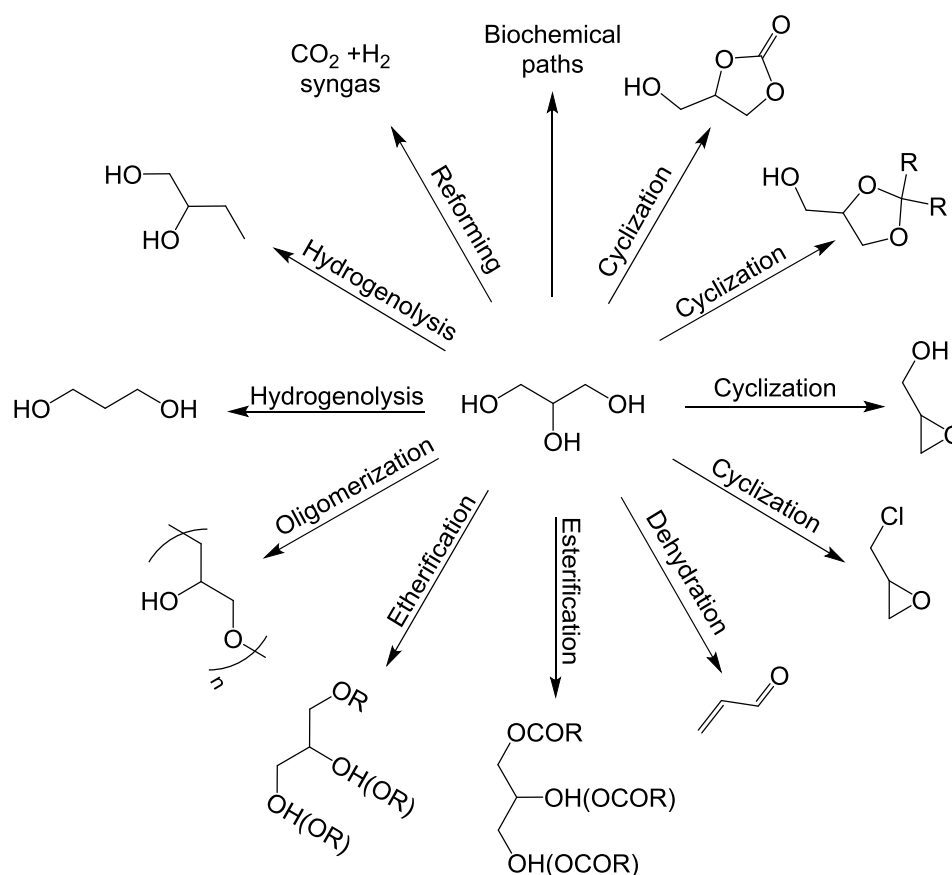
The results presented in this Chapter are summarised in Section 4.11, and the characterisation of the relevant compounds is presented in Section 4.12 for convenience.

4.1. Background

The use of renewable resources as replacements for fossil fuels conforms to sustainable development strategy. In this regard, biodiesel can be seen as a promising source of organic carbon to replace fossil fuels and to produce organic chemicals. Normally biodiesel is produced from the transesterification of vegetable oil or animal fats with methanol, under basic catalysis conditions.¹⁵⁷ In the United States, the production of biodiesel has increased significantly from 2.27 million litres in 1999 to 7.1 billion litres in 2016.^{41, 158} Biodiesel production in the EU which has also risen dramatically was estimated to be about 10.7 billion litres in 2010 and is forecast to increase to about 14.1 billion litres in 2017.¹⁵⁹ In addition to the desired product biodiesel, glycerol is also generated as a by-product at approximately 10 wt% mass

balance.¹⁶⁰ This means that with the production levels of biodiesel rising, abundant amounts of glycerol are also generated.

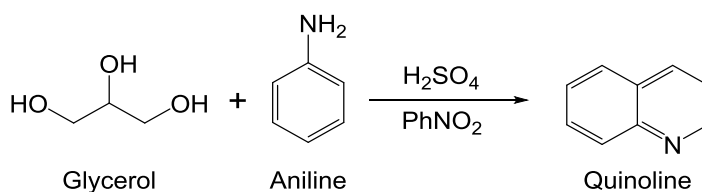
This leads to the obvious question of how best to use this additional glycerol. The traditional applications of glycerol include pharmaceuticals, cosmetics (hair and skin care), soaps and the personal-care sector. Besides this, glycerol can be used in food as sweetener, and as a wetting agent in tobacco. Some chemical functionalisation of glycerol is also carried out industrially, especially the synthesis of esters, polyethers and polyester resins.¹⁶¹ However, these applications still cannot compete with the huge amounts of glycerol produced by the biodiesel industry. Therefore, it is a key issue to find new or improved methods to convert this readily available, relatively low-priced glycerol into valuable products.



Scheme 4.1.1 Roadmap of glycerol conversion reactions.¹⁶²

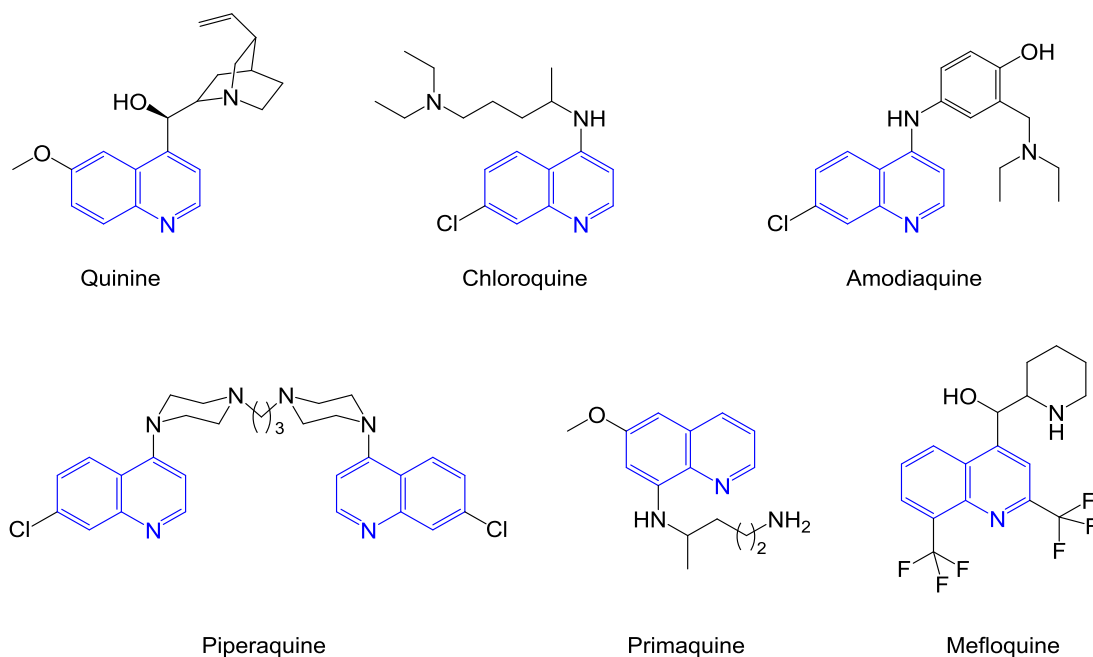
Glycerol is a good starting platform for the synthesis of other chemicals, especially oxygenated compounds, and several reviews on glycerol transformation have appeared in the literature in the past few years.¹⁶¹⁻¹⁶⁴ The conversion of glycerol to value-added chemicals by catalytic processes includes dehydration, reforming, oxidation, etherification, esterification, and hydrogenolysis (Scheme 4.1.1).

In addition to the conversions mentioned above, glycerol can also be used as starting reagent in the synthesis of complex compounds, such as quinoline, via the Skraup reaction (Scheme 4.1.2). Quinoline, which has a nitrogen-based heterocyclic ring, is not widely used itself, but can be easily modified to a multitude of functional compounds which have widespread applications in medicinal and industrial chemistry.¹⁶⁵⁻¹⁶⁷



Scheme 4.1.2 Skraup reaction

A quinoline type scaffold can be found in a wide range of biologically active molecules, including both pharmacologically active compounds and other natural products. The best-known drugs from the quinoline group are antimalarials. Malaria is a global disease but is especially prevalent in the tropical and subtropical regions. In 2015 alone, there were 212 million cases of malaria worldwide, resulting in an estimated 429,000 deaths, with 90% of the cases occurring in Africa.¹⁶⁸



Scheme 4.1.3 Quinoline antimalarials

The first effective treatment for malaria was introduced into Europe around 1640 and came from the bark of cinchona tree, which contains the compound quinine from the quinoline group. Due to the poor effectiveness of quinoline, new chemicals have since been developed based on its structure including: chloroquine, amodiaquine, piperaquine, primaquine, and mefloquine (Scheme 4.1.3).^{166, 169, 170}

In addition to their antimalarial properties, quinolines have drawn attention in the fields of organic light-emitting diodes (OLEDs) and organic photovoltaics owing to their electron-deficient heterocycle ring.¹⁷¹ If these electron-deficient heterocycles were connected to electron-rich molecules, they could form acceptor–donor systems with efficient intramolecular charge transfer. These systems could be further modified to enhance the spectroscopic and electrochemical properties of such compounds.¹⁷²⁻¹⁷⁴

A carbazole and quinoline combined donor-acceptor conjugated oligomer has been synthesised, which shows good solubility in common organic solvents and has a sharp absorption band at 275- 325 nm with a shoulder peak at 374 nm. Electrochemical

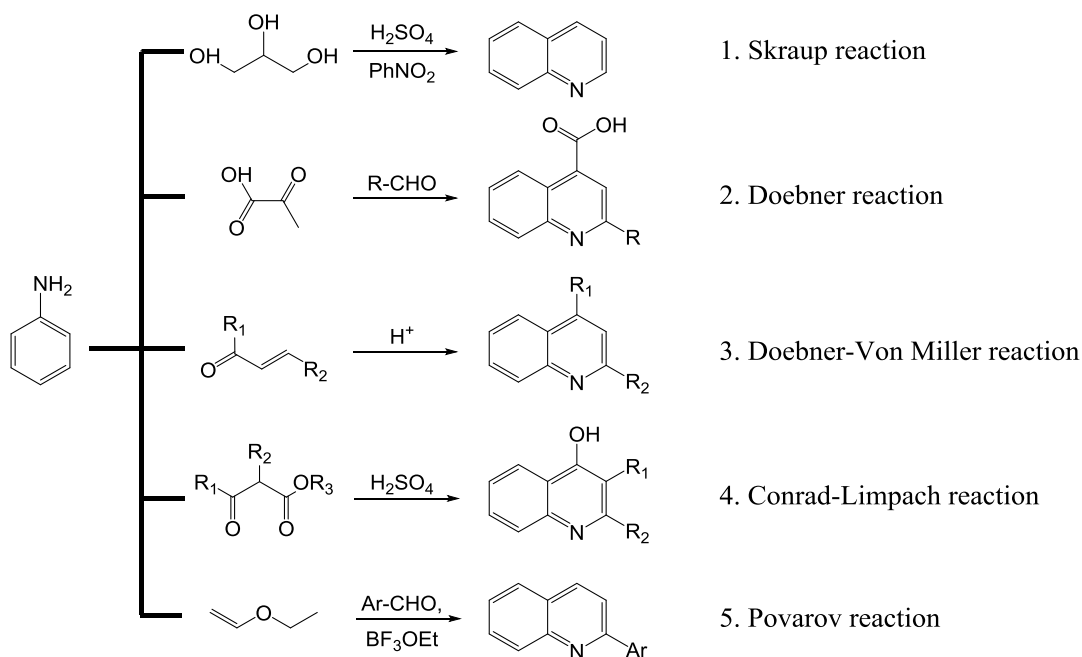
studies of this novel oligomer revealed that the HOMO and LUMO energy levels were -5.74 and -3.17 eV respectively, which suggested that this oligomer has great potential for OLED applications.¹⁷⁵

The synthesis of novel quinoline based heterocyclic compounds for blue lighting applications has been reported by H.C. Swart and co-workers.¹⁷³ Derivatives of 2,4-diphenylquinoline, 6-chloro-2,4-diphenylquinoline and 4,6-dichloro-2,4-diphenylquinoline were synthesized using a three-component domino reaction. These compounds were characterized by NMR, SEM, TGA, XPS and UV-vis. These organic phosphors showed bright emission in the blue region under an UV excitation wavelength of 325 nm with a power of 18 mW, and were found to be efficient candidates for use in organic blue light emitting devices.

Quinolines have also been used as fluorescent sensors to image metal ions in cells, tissues, and organisms benefitting from both their electronic and molecular structures.^{176, 177} The first use of quinolines as fluorescent indicators for metal ions dates back to 1968, when Mahanand and Houck used 8-hydroxyquinoline as a fluorescent stain for Zn^{2+} in human plasma.¹⁷⁸ Later Frederickson and co-workers screened several quinoline-based compounds and found that 6-methoxy-8-p-toluenesulfonamido-quinoline had the most intense fluorescence when complexed with Zn^{2+} as compared to related molecules.¹⁷⁹ Since then, a wide range of compounds based on quinoline structure have been investigated for use as fluorescent sensors.

Recently, Hyong-Jun Kim developed a new quinoline based fluorescent material, which overcomes the quenching and toxicity problems of traditional organic and inorganic fluorescent materials. These novel quinoline derivatives have been showed to have an enhanced photoluminescence, and could be highly interesting in the field of immunofluorescence labeling.¹⁸⁰

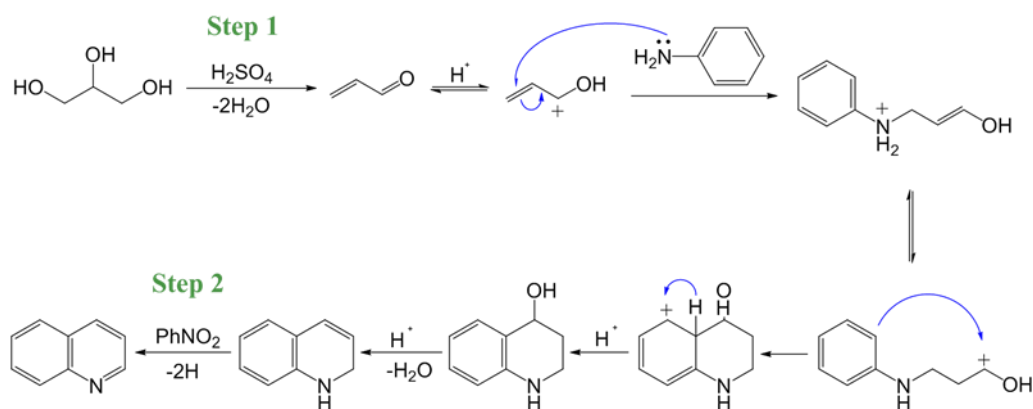
Since quinolines have a wide range of applications in both medicinal and industrial chemistry, varied methods have been developed for their synthesis (*Scheme 4.1.4*), including the Skraup reaction, Doebner reaction, Doebner-Von Miller reaction, Conrad-Limpach reaction and Povarov reaction.



*Scheme 4.1.4 Quinoline synthesis methods: 1, Skraup reaction; 2, Doebner reaction; 3, Doebner-Von Miller reaction; 4, Conrad-Limpach reaction; 5, Povarov reaction.*¹⁶⁵

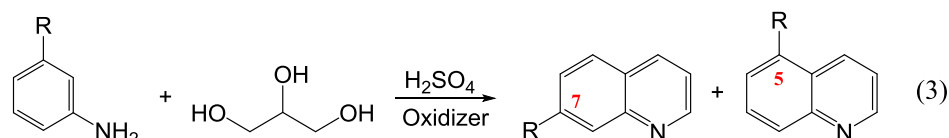
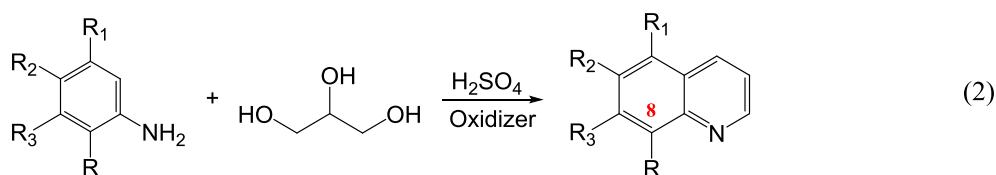
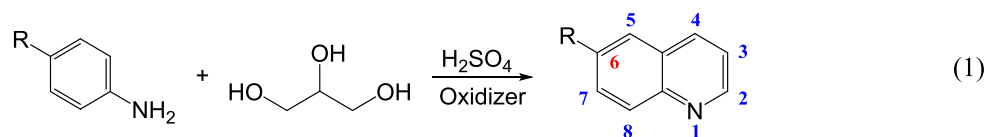
The Skraup reaction, which we are interested in, uses the biomass product glycerol, which is cheap and abundant, as a starting material to form the higher value heterocyclic compound quinoline (*Scheme 4.1.5*).¹⁸¹ The Skraup reaction was developed by Czech chemist Zdenko Hans Skraup in 1880, and was the first reported method to synthesize quinoline. It is carried out by heating a mixture of aniline, glycerol, high concentration sulfuric acid, and an oxidizing agent such as nitrobenzene. In general, a Skraup reaction proceeds via two steps: in the first step, sulfuric acid dehydrates the glycerol twice into acrolein, which reacts with aniline to form the 1,2-dihydroquinoline.

Then in the next step, an oxidizing agent (nitrobenzene) is required to form the fully aromatized heterocycle.



Scheme 4.1.5 The Skraup reaction mechanism.¹⁸²

Various substituted anilines have been used in the Skraup reaction to form different quinolines. *para*-Substituted anilines can close at either of the symmetrical *ortho*-positions resulting in 6-substituted quinolines (Scheme 4.1.6 (1)). If the substituent is at *ortho* position, only 8-substituted quinolines are formed, even if di-, tri-, and tetrasubstituted anilines are used (Scheme 4.1.6 (2)).¹⁸³⁻¹⁸⁵ Anilines substituted at the *meta* position can close at either *ortho* position and are converted into a mixture of 5-substituted and 7-substituted quinolines (Scheme 4.1.6 (3)).



Scheme 4.1.6 Substituted anilines for quinoline synthesis

More specifically, if the *meta*-substituent is a strong electron-withdrawing group (such as NO₂, CN), ring closure occurs preferentially at the position 2, favouring the formation of 5-substituted quinolines. The presence of strong electron-donating substituents (OMe, OEt, NMe₂) at position 3 of the initial aniline, promote cyclization at position 6, and the formation of 7-substituted quinolines as the main product. Weaker electron-donating substituents (Hal, Alk) at the *meta* position lead to a slight preference toward to the formation of 7-substituted quinolines.¹⁸⁵⁻¹⁸⁷

As mentioned previously, traditionally the Skraup reaction requires two steps under harsh conditions (at high temperature with excess amounts of concentrated sulfuric acid and a toxic oxidizer, nitrobenzene). Therefore, a range of modifications have been investigated to allow the desired reactivity to take place under milder conditions.

Instead of the large excess of concentrated sulfuric acid, lower concentration of hydrochloric acid, and the use of weaker acids, such as orthophosphoric acid and polyphosphoric acid have been employed, which allowed the required the temperature to be reduced from 130-150 to 60-100 °C.^{183, 188, 189} Additionally, Amarasekara's group

used a Brønsted acidic ionic liquid (1-(1-Alkylsulfonic)-3-methylimidazolium chloride) to catalyse the Skraup reaction obtaining a 78% yield of quinoline.¹⁹⁰

The oxidizing agent in the classical Skraup synthesis, nitrobenzene, has also been replaced by other more effective oxidizing agents such as arsenic pentoxide,¹⁹¹ iodine,¹⁹² and *m*-nitrobenzenesulfonic acid or its salts.¹⁹³ The use of microwave irradiation in place of the conventional heat sources was found to be an efficient heat source for the quinoline synthesis, which could reduce the reaction time and increase the quinoline yield.¹⁹⁴⁻¹⁹⁶

The modifications discussed above are all homogeneous reactions, however there are also examples of heterogeneous Skraup reactions which use mixed oxide catalysts.^{197, 198} In this method, one of the mixed metal oxides catalyses the glycerol dehydration, and the other is for the oxidative dehydrogenation of 1,2-dihydroquinoline.

Nb catalysts have proven to be efficient catalysts for the dehydration of glycerol to acrolein,⁷³⁻⁷⁵ however, they have also shown good performance in oxidation reactions.^{47, 57} Therefore, Nb catalysts are likely to be suitable catalysts for Skraup reactions, where the same catalyst could play two roles, catalysing both dehydration and oxidation.

The next sections describe the work carried for this thesis. Initially the Skraup reaction using **NbP** catalyst was investigated using glycerol and aniline as starting materials. However, problems were experienced in the introduction of glycerol, due to its polar and viscous nature, which prevented the direct pumping neat glycerol into the reactor on the lab scale. Therefore, the use of an alternative starting reagent, solketal, was also investigated. Solketal is a ketal produced from a condensation reaction between glycerol and acetone, both of which can be obtained from biomass production.¹⁹⁹

In this Chapter, the effects of different parameters, such as changing the starting reagents, reaction temperature, pressure and flowrate on the Skraup reaction using Nb catalysts were investigated. It should be noted that the some of the experiments described in this chapter were carried out in collaboration with Sandro Guidi from Università Ca' Foscari Venezia.

4.2. The Exploratory Experiment

The synthesis of quinolone **4a** using **NbP** as catalyst was first investigated using glycerol **4b** and aniline AN in a high-pressure continuous flow reactor (Figure 4.2.1). It should be noted that for the continuous flow reactions from Section 4.2 to 4.7 and 4.10, the high-pressure design of flow reactor, as described in Section 2.1.4, was used.

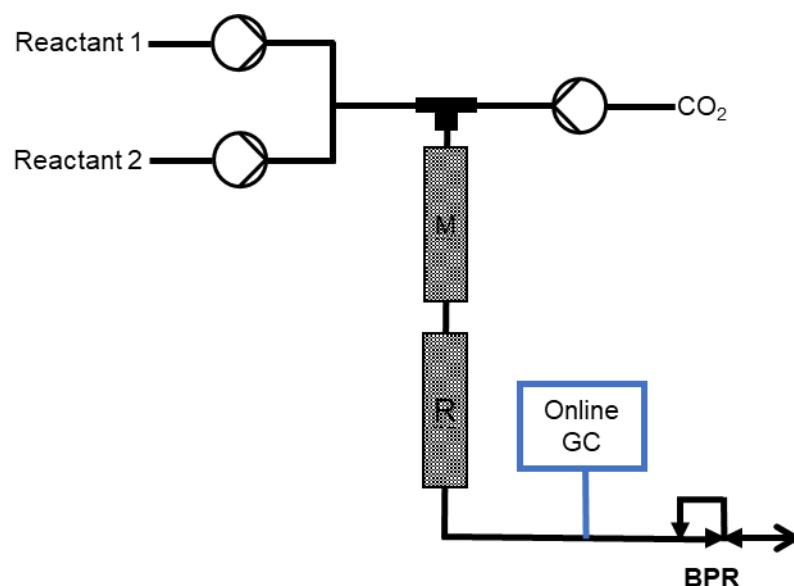


Figure 4.2.1 Simplified schematic apparatus for the continuous flow **NbP** catalysed quinoline synthesis, see Section 2.2 for full details.

Due to the polarity and viscosity properties of **4b**, it cannot be pumped directly into the reactor. If **4b** is to be pumped into the reactor in solution, an appropriate polar organic solvent must be chosen, which cannot react with aniline in the presence of an acid catalyst.¹⁵¹ Water was initially chosen as the solvent, as it is nontoxic and compatible with **NbP** catalyst. The highest yield of **4a** that could be achieved using water as a solvent was only 10%, despite a range of parameters being tested. Even though this yield was low, it was an encouraging proof of concept, showing that it is possible to carry out the Skraup reaction using a Nb catalyst.

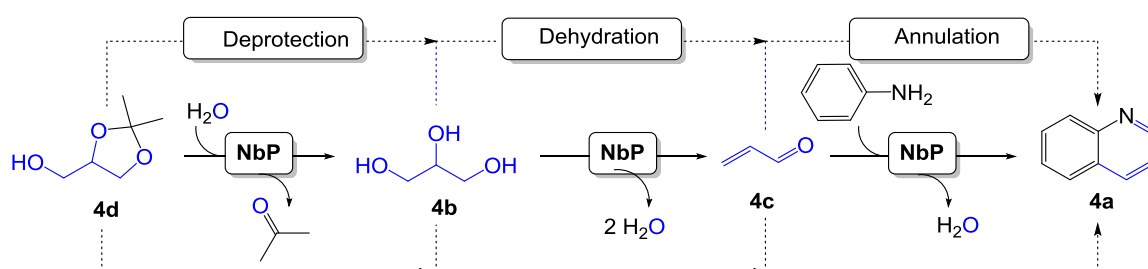
Although **4b** is fully miscible with water, aniline has only limited water solubility, to a maximum of *ca.* 0.4 M, and the solubility of the product, **4a**, is even lower *ca.* 0.05 M.^{200, 201} This suggests that water cannot transport the organic products through the catalyst bed efficiently, and may have led to coking, the formation of residue on the catalyst surface, which would impede the activity of the catalyst. This, coupled with the highly reactive nature of the intermediate product acrolein **4c**, is probably the origin of the poor yield in aqueous solutions.

As the high viscosity of neat **4b** prevents it from being directly pumped into the reactor on a lab scale, and the possible choice of the solvent is limited by solubility and unwanted side reactions, the use of an alternative starting reagent was investigated instead.

Solketal **4d** is the isopropylidene acetal protected form of **4b**; it is produced by the condensation of acetone with glycerol.^{202, 203} As two of its hydroxyl groups are protected, **4d** is less prone to hydrogen bonding than **4b**, and hence is soluble in a wider range of solvents.

It was envisaged that reaction with the acidic **NbP** catalyst would deprotect **4d** to generate **4b** in-situ, allowing its subsequent dehydration to **4c** (*Scheme 4.2.I*). It was

anticipated that this approach might avoid the large quantities of by-products observed in our preliminary experiments. With a larger choice of solvents available, the problem of poor AN solubility could also be overcome. To minimize potential alkylation reactions, protic solvents were avoided, and ultimately toluene was settled on as the solvent for this reaction.



*Scheme 4.2.1 The Multiple roles of **NbP** in the synthesis of **4a** from **4d**. The three-step transformation is envisaged as a single continuous process.*

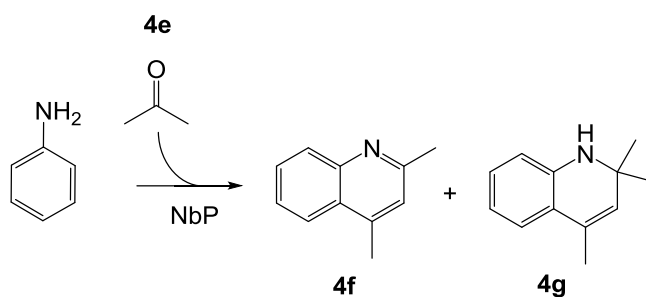
An initial temperature of 250 °C was chosen, as this had previously been identified as the best temperature for the dehydration of **4b**.²⁰⁴ The reaction was carried out at low pressure with a ratio AN to **4d** of 1:3, an excess of **4d** to allow for the possible loss of **4c** by polymerisation. Therefore, solutions of AN (0.275 M) and **4d** (0.825 M) were prepared in toluene and were separately introduced to the reactor at a flowrate of 0.1 mL/min, giving a total flowrate of 0.2 mL/min. The reaction was carried out for 20 hours at 250 °C, at a pressure of 100 bar and with 1.2 g untreated **NbP** catalyst. After 20 hours, the average conversion of AN was 60% and the selectivity for **4a** is around 50% (data based on GC analysis). Compared to **4b**, using **4d** as a starting material gave a higher yield of **4a** (30% versus 10%), even before the conditions were optimised.

Of course, the use of **4d** instead of **4b** represents potentially unnecessary derivatization step (contradicting to Green Chemistry Principle No.8)¹ but on a larger

scale the viscosity of neat **4b** would be less of a problem and replacement by **4d** would not be required. However, using **4d** does allow these continuous reactions to be explored on a laboratory scale.

4.3. Control Experiment and By-product Analysis

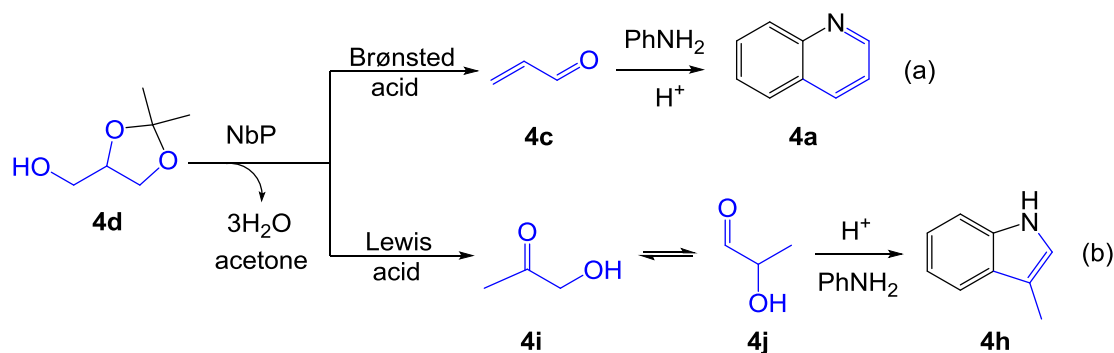
As shown in Scheme 4.2.1, acetone **4e** is generated during the deprotection of **4d**. According to the literature, **4e** can react with AN in the present of acid catalysts (such as heteropolyacids, zeolites and halide clusters).²⁰⁵⁻²⁰⁷ Therefore, a control experiment was carried out, to establish whether the **4e** liberated from the deprotection of **4d** could react with AN over a **NbP** catalyst.



*Scheme 4.3.1 Condensation of **4e** with aniline in the absence of **4d** over **NbP** to give compounds 2,4-dimethylquinoline **4f** and 2,2,4- trimethyl-1,2-dihydroquinoline **4g**. The same reaction products have been reported over a zeolite catalyst.²⁰⁶*

The control experiment was carried out supposing full conversion of the **4d** into **4b** and **4e**. Hence, a 0.275 M solution of **4e** in toluene was used instead of the **4d** solution. Then, a reaction was carried out under the conditions used previously of 250 °C and 100 bar, with a 0.275 M solution feed of **4e** in toluene and a 0.275 M solution feed of AN in toluene each at a flowrate of 0.1 mL/min. Less than 8% yield of two

products 2,4-dimethylquinoline **4f** and 2,2,4-trimethyl-1,2-dihydroquinoline **4g** was obtained (Scheme 4.3.1). The products were isolated and characterized by MS and NMR analysis (Section 4.12). However, these products were not detected in any of our reactions carried out with **4d**, demonstrating clearly that the **4e** does not take part in any side reactions in our system.



*Scheme 4.3.2 The main by-product observed from the continuous flow reaction of **4d** and AN over NbP. (a) Synthesis of **4a** through **4c** over Brønsted acid sites and (b) synthesis of **4h** through the **4i** intermediate over Lewis acid sites.*

The major by-product of the reaction between AN and **4d** was isolated by column chromatography and was identified via NMR and MS as 3-methylindole **4h**. (Section 4.12). Its formation can be understood as arising from the reaction of hydroxyacetone **4i** with aniline (Scheme 4.3.2).¹⁹⁸ **4i** has previously been reported as being formed from **4c** in the presence of Lewis acid sites.²⁰⁸⁻²¹⁰ Over Lewis acid sites, coordination of the **4b** intermediate takes place, leading to the removal of water from a primary OH group of **4b** as reported previously.²¹¹ This results in an unstable enol intermediate, which undergoes rapid tautomerisation to **4i**. Similar mechanisms have been observed over a La₂CuO₄ catalyst, explaining the occurrence of **4i**.²⁰⁸ Once **4b** is converted to **4i**, the latter is transformed to 2-hydroxy-1-propanal **4j** via a keto–enol tautomerism. The aldehyde undergoes condensation with AN to form a α -hydroxyimine

intermediate. Then, the loss of a second molecule of water generates a secondary carbocation, able to trigger a ring closure, which provides the final indole derivative.

The reaction carried out so far had demonstrated the successful synthesis of **4a** via a Skraup reaction over **NbP** catalyst. Therefore, the next step was to optimise the reaction conditions for the formation of **4a**. Four parameters were investigated, including the ratio of feedstocks, reagent flowrates, reaction temperature and pressure.

4.4. The Influence of the Ratio of Solketal to Aniline

The feedstock ratio is one of the key factors in chemistry, which could affect the conversion of the starting materials and even lead to the formation of different products. Therefore, the effect of altering the ratio of starting materials was first investigated.

Four different ratios of the two substrates were tested, with the limiting reagent held a concentration of 0.275 M: AN to **4d** 1:1 (0.275 M to 0.275 M), 1:2(0.275 M: 0.550 M), 1:3 (0.275 M: 0.825 M) and 2:1 (0.550 M to 0.275 M). All these experiments were carried out under the following conditions: **4d** 0.1 mL/min, AN 0.1 mL/min, at 250 °C and 100 bar with 1.2 g untreated **NbP** catalyst. Fresh **NbP** catalyst was used for each experiment. Since the **4d** could decompose on the catalyst bed, all the results discussed below were based on the conversion of AN.

The results depicted in Figure 4.4.1 show that with fresh **NbP** catalyst, the AN conversion increased when a higher concentration of **4d** was pumped into the system. For the first 6 hours, a high ratio of **4d** to AN (3:1) increased the AN conversion to above 80%. However, the catalysts activity decreased more rapidly with time, when higher concentrations of **4d** were used. For example, in the case of a 3:1 ratio of **4d** to

AN, the conversion of AN dropped from an initial value of 80% to 40% after 16 hours. Whereas, pumping a 1:1 ratio substrates gave a more stable activity for longer, with an AN conversion of 50% after the same 16 hour period. Increasing the ratio of **4d** to AN resulted in the formation of more **4c**, giving AN more chance to react with **4c** and leading a higher conversion. However, this also led to more coke being deposited on the catalyst surface, meaning that the deactivation of catalyst was faster with the increased feed concentration of **4d**.

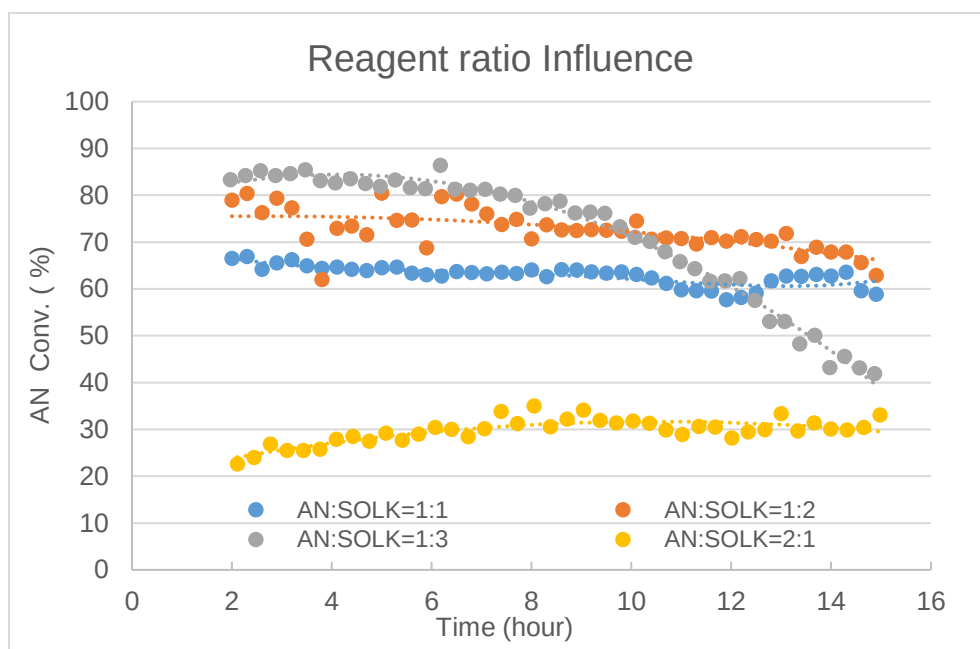


Figure 4.4.1 AN conversion against reaction length comparison based on different ratio of AN to SOLK (**4d**) (1:1, 1:2, 1:3 and 2:1). The reactions were under the conditions: 250 °C, AN 0.1mL/min, SOLK (**4d**) 0.1mL/min, at 100 bar with 1.2 g fresh **NbP** catalyst for each experiment. The dotted lines are purely to aid visualization.

In addition to the AN conversion, the selectivity for the desired product **4a** was also investigated (Figure 4.4.2). There was no obvious difference in selectivity observed among feed ratios tested. In fact, when a 2:1 ratio of AN to **4d** was used (AN 0.550 M to **4d** 0.275 M), over the 20 hour reaction the average **4a** selectivity was 52%. This is very similar to the 50% **4a** selectivity observed using a 1:2 ratio of AN to **4d**. The **4a**

selectivity also appeared to be quite stable with respect to reaction time in these experiments.

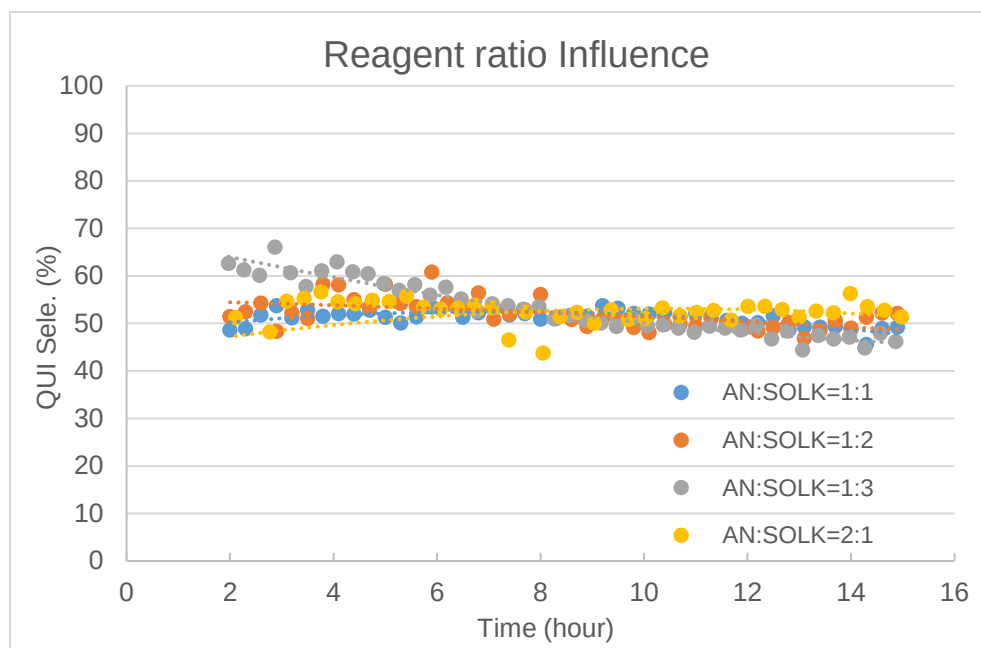


Figure 4.4.2 Effect of the reagents ratio on *QUI* (**4a**) selectivity over **NbP**. The different experiments were performed under the following conditions: 250 °C, 0.2 mL/min total flowrate and 100 bar, for 1:1, 1:2, 1:3 and 2:1 ratios of AN: SOLK (**4d**) with 1.2 g fresh **NbP** catalyst for each experiment.

Table 4.4.1 Influence of the reagents ratio on the conversion of AN, the selectivity and productivity of **4a** over **NbP** catalyst.

AN: SOLK	1:1	1:2	1:3	2:1
AN conversion ^a	63%	73%	72%	61%
QUI selectivity ^a	51%	52%	53%	52%
QUI productivity	0.068 g/h	0.08 g/h	0.08 g/h	0.065 g/h

^a The conversion, selectivity and productivity were averaged values of the reaction from 2nd to 15th hour and calculated based on GC analysis. Reaction conditions were at 250 °C, 100 bar with 1.2 g fresh **NbP** catalyst for 1:1, 1:2, 1:3 and 2:1 ratios of AN: SOLK (**4d**).

4.5. Temperature Influence

To investigate the effect of temperature on the **4a** synthesis, four sets of isothermal experiments were carried out at 200, 225, 250 and 275 °C. Each experiment was carried out at 100 bar with a constant reagent AN: **4d** ratio of 1:1 and 1.2 g fresh **NbP** catalyst was used for each experiment. Two 0.275 M solutions (in toluene) of **4d** and AN were prepared and the flowrate of each set to 0.1 mL/min.

The effect of temperature was more striking than that of the reagent ratio discussed previously. As shown in Figure 4.5.1, the conversion of AN increases with temperature from 53% at 225 °C up to 78% at 275 °C. Selectivity however drops from 52% at 250% to 20-30% at 275°C. This observation is possibly due to the different effects of temperature on the relative rates of generation of **4c** from **4d** and the subsequent polymerization of **4C**.

However, at higher temperature the selectivity for **4a** is not as good as expected. To be specific, the average conversion of AN of 13 hour reaction is 78 % at 275 °C, which is higher than 64 % at 250 °C. But the selectivity for **4a** at 275 °C is much lower than at 250 °C (24 % to 52 %). These results suggest that from 200 °C to 250 °C, the formation of **4a** increased with rising temperature. Nevertheless, when an even higher temperature was applied (275 °C) the **4a** selectivity dropped dramatically from 52 % to 24 %. According to the literature,⁷⁵ the probable cause for more **4a** formation at moderate temperatures might be the selective activation of the stronger adsorption mode of glycerol through the secondary OH group and the kinetically favoured subsequent consecutive steps resulting in a higher selectivity to **4c**.

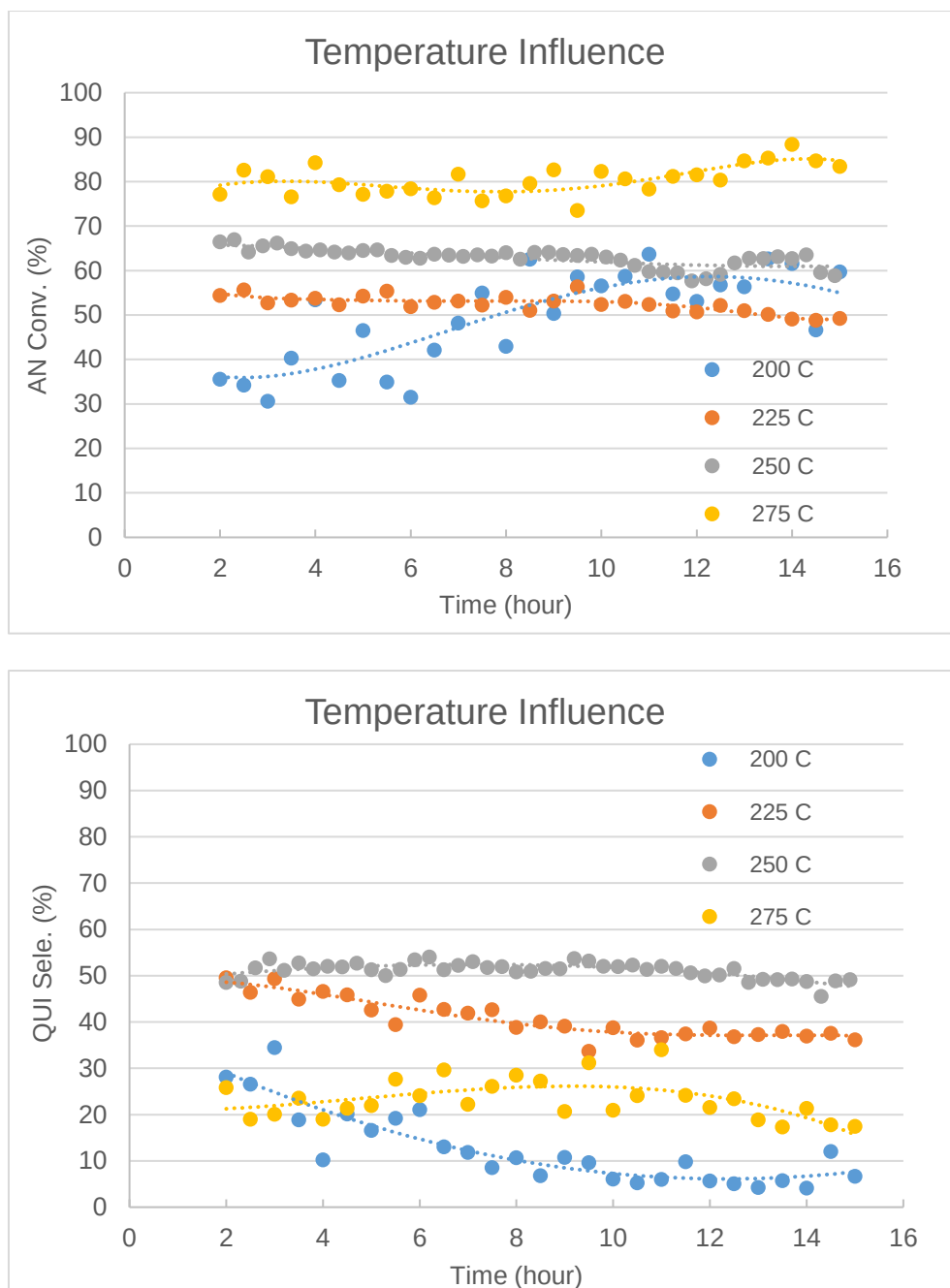


Figure 4.5.1 Effect of the temperature on AN conversion and QUI (**4a**) selectivity of four sets of experiments that were carried out isothermally at 200, 225, 250 and 275 °C at 100 bar with a constant reagent AN:**4d** ratio of 1:1 and 1.2 fresh **NbP** catalyst. Two 0.275 M solutions of **4d** and AN were each set to a flowrate of 0.1 mL/min.

Table 4.5.1 AN conversion, QUI (4a) selectivity and productivity measured as a function of temperature.

Temperature	200 °C	225 °C	250 °C	275 °C
AN conversion ^a	45 %	53 %	64 %	78 %
QUI selectivity ^a	16 %	42 %	52 %	24 %
QUI productivity	0.015g/h	0.049 g/h	0.068 g/h	0.040 g/h

^a The conversion, selectivity and productivity were averaged values of the reaction from 2nd to 15th hour and calculated based on GC analysis. Reactions were conducted under the conditions: 100 bar pressure with 1.2 g fresh **NbP** catalyst for each experiment. A 1:1 ratio of AN:4d (0.275 M in toluene) were separately pumped into the system, each at 0.1 mL/min.

4.6. Pressure Influence

Besides variation in the proportions of the starting materials and the reaction temperature, the influence of pressure on the synthesis of **4a** has also been considered. Five different conditions have been investigated, using pressure of 100 bar, 75 bar, 50 bar, 10 bar and atmospheric. With the exception of the experiment carried out at atmospheric pressure, which lasted for 4 hours, all other experiments were carried out for 16 hours. The reaction condition were at 250 °C with a 0.1 mL/min flowrate of aniline solution (0.275 M in toluene) and a 0.1 mL/min flowrate of **4d** (0.825 M in toluene) giving a 1:3 ratio of AN:**4d**.

From the results shown in Figure 4.6.1, it is clear that the conversion of AN decreased very rapidly with time at a 10 bar pressure, decreasing from 90% to 20%. As the pressure was increased, the rate of conversion drop off became slower. Increasing the pressure above 50 bar had no further effect. The selectivity for **4a** was never above 60% and reduced over time, with the reduction in selectivity appearing to be greater at lower pressure.

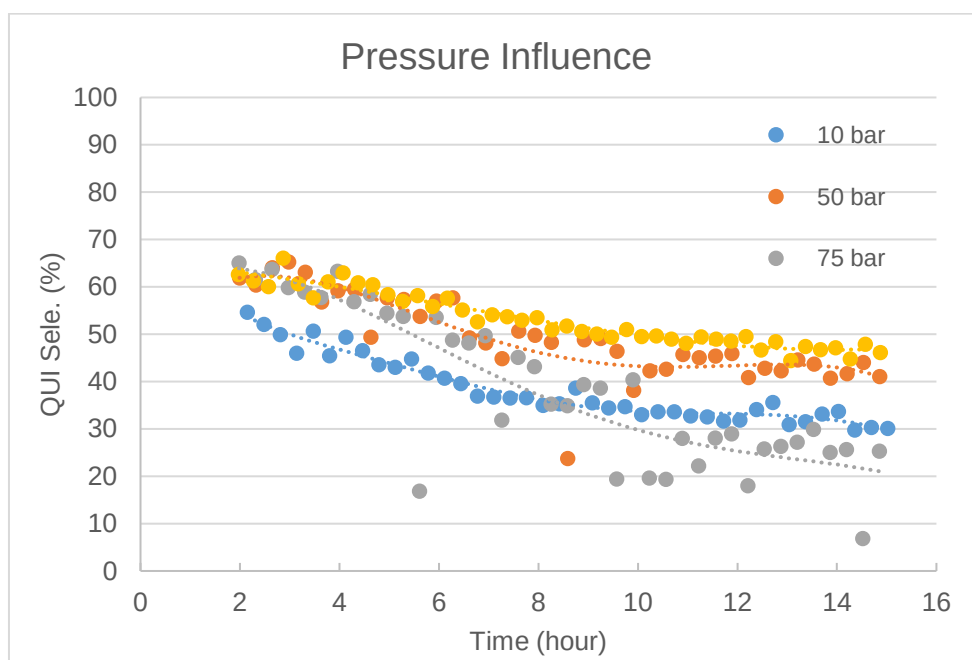
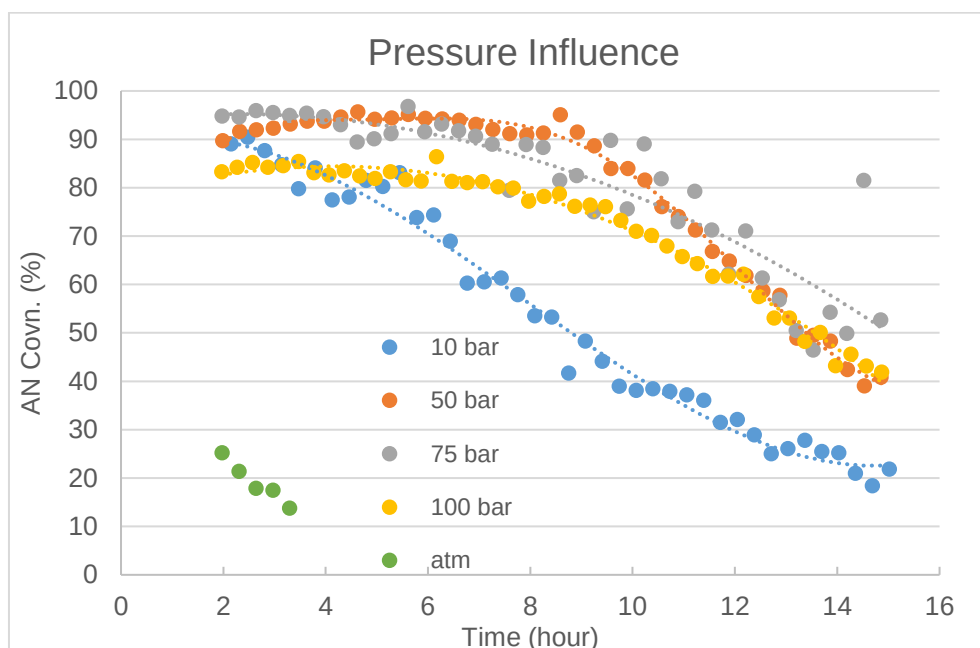


Figure 4.6.1 Effect of the system pressure on the AN conversion and QUI (4a) selectivity over NbP. The different experiments were performed under the following conditions: 250 °C, 1.2 g fresh NbP catalyst and 0.2 mL/min of total flowrate for 1:3 ratio of AN:4d in toluene (0.275 M: 0.825 M).

Table 4.6.1 Influence of the pressure on the conversion of AN, QUI selectivity and productivity over NbP.

Pressure	10 bar	50 bar	75 bar	100 bar
AN conversion ^a	68%	90%	90%	80%
QUI selectivity ^a	44%	53%	49%	57%
QUI productivity	0.067 g/h	0.100 g/h	0.093 g/h	0.100 g/h

^a The conversion, selectivity and productivity were averaged between the 2nd and 10th hour and calculated based on GC analysis. Reaction conditions were at 250 °C, 100 bar with 1.2 g **NbP** fresh catalyst and 1:3 ratio of AN:**4d** at a 0.2 mL/min total flowrate.

The effect of pressure on this reaction can be rationalised, at least qualitatively, by looking at the physical data in Table 4.6.2. Apart from glycerol, all the reaction components will be in the vapour phase at 250 °C and 10 bar pressure. Increasing the pressure will create a two-phase system, containing both liquids and vapours, and most probably the entire reactor will be filled with liquid at pressures greater than 50 bar. This switch from vapour to liquid phase will give higher volumetric concentrations of reactants within the reactor and longer residence times for a given flowrate of reactants into the system.

Table 4.6.2 Physical properties of the reagents and products involved in the reaction.

Compounds	Boiling point (°C)	T _c (°C)	P _c (bar)
Toluene	110.6	318.6	41.1
Glycerol (4b)	290.0	492.2	43.1
Solketal (4d)	188.0-190.0	-	-
Acrolein (4c)	53.0	254.0	50.7
Aniline	184.2	425.6	53.1
4-Methoxyaniline (4k) ^a	246.0	-	-
4,4'-methylenedianilin (4l) ^b	398.0	-	-
Quinoline (4a)	237.0	-	-
3-methylindole (4h)	265.5	-	-

^a Melting point 57 °C. ^b Melting point 89 °C.

4.7. Influence of Flowrate

As discussed in Section 4.4, with 1:1 ratio of AN to **4d**, a stable AN conversion (60 %) was obtained. Therefore, the same concentrations of AN and **4d** (0.275 M in toluene) were used in the following experiments. Three different total flowrates have been investigated (0.1 mL/min, 0.2 mL/min and 0.4 mL/min) under the conditions of 250 °C and 100 bar for 10 hours.

The results are shown in Figure 4.7.1. With total flowrates of 0.1 mL/min, 0.2 mL/min and 0.4 mL/min, the average aniline conversions are 65 %, 64 % and 62 % respectively. Therefore, in the range tested, changing the flowrate has little influence on the conversion of AN.

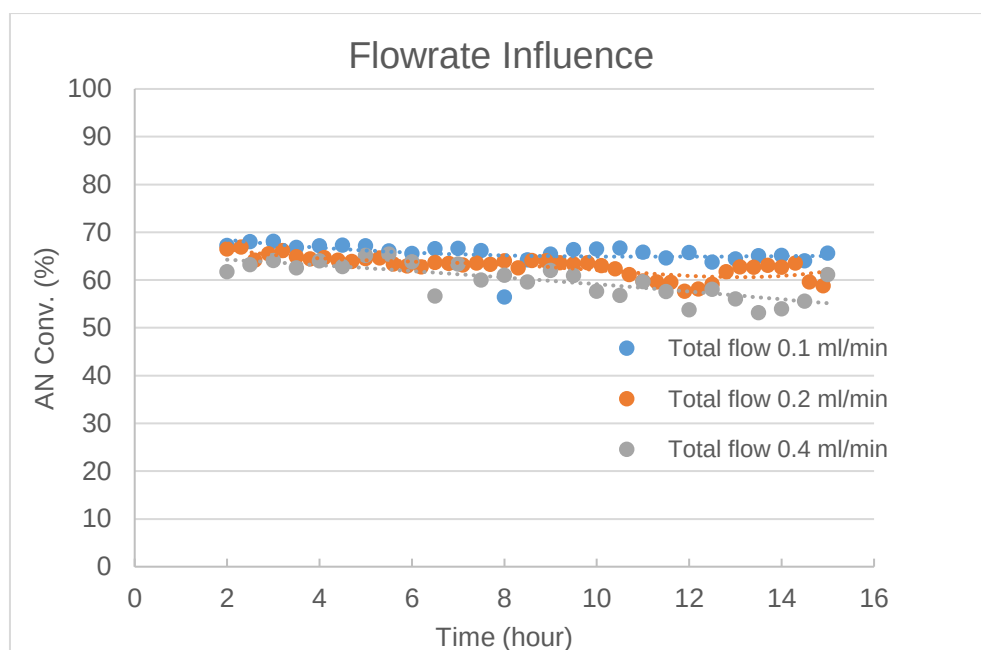


Figure 4.7.1 The influence of the total flowrate on AN conversion. The reactions were at 250 °C, under 100 bar with 1.2 g fresh **NbP** catalyst. The 1:1 ratio of AN and **4d** (0.275 M in toluene) were pumped into the system separately.

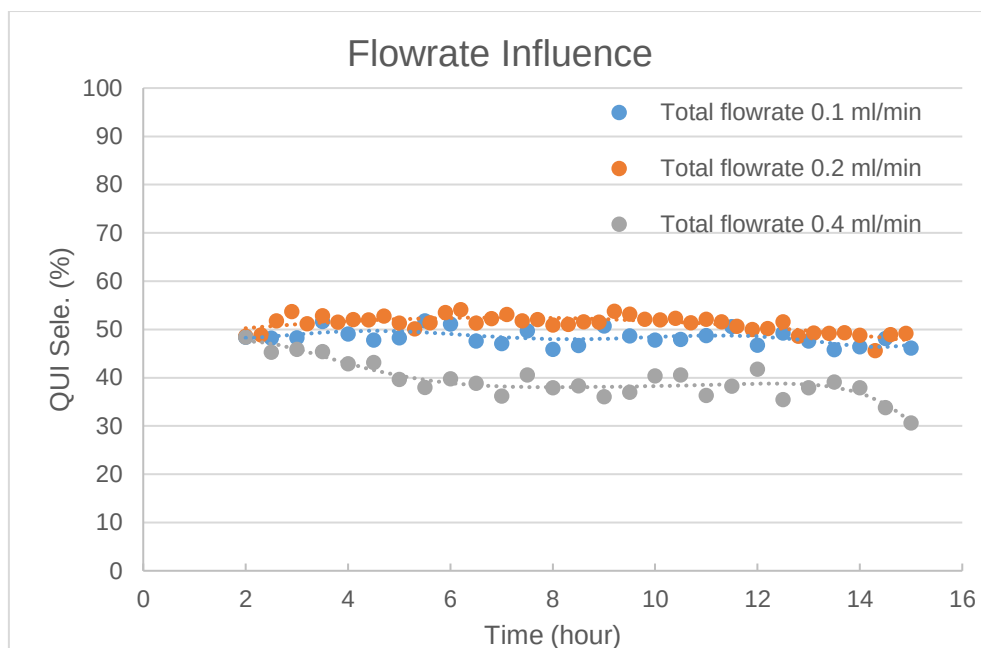


Figure 4.7.2 The influence of total flowrates on QUI **4a** selectivity. The reactions were at 250 °C, under 100 bar with 1.2 g fresh **NbP** catalyst. The 1:1 ratio of AN and **4d** (0.275 M in toluene) were pumped into the system separately.

Variations in the total flowrate did however effect the selectivity of the reaction towards to **4a** (Figure 4.7.2). In particular, with a 0.2 mL/min total flowrate the average selectivity for **4a** is 52 %, which is higher than with a 0.1 mL/min total flowrate (49%). Moreover, a 0.4 mL/min flowrate gave an even lower result selectivity of 41%.

Table 4.7.1 Influence of flowrate on the conversion of AN, QUI (**4a**) selectivity and productivity over **NbP**.

Total flow rate	0.1 mL/min	0.2 mL/min	0.4 mL/min
AN conversion. ^a	67 %	63 %	60 %
QUI selectivity. ^a	48 %	51 %	40 %
QUI productivity	0.034 g/h	0.068 g/h	0.100 g/h
TOF ^b	$0.30 \times 10^{-3} \text{ s}^{-1}$	$0.57 \times 10^{-3} \text{ s}^{-1}$	$1.09 \times 10^{-3} \text{ s}^{-1}$

^a The conversion, selectivity and productivity were averaged between the 2nd and 15th hour and calculated based on GC analysis. The different experiments were performed under the following conditions: 250 °C, 1.2 g fresh **NbP** catalyst and 0.2 mL/min of total flowrate for 1:1 ratio of AN:**4d** in toluene (0.275 M: 0.275 M). ^b 1) Turnover frequency (TOF) referred the limited starting reagent turnover that per acid site can achieve per second; 2) Calculated based on 13-hour reaction; 3) The number acid sites is calculated based on pyridine desorption.²¹²

Above 0.2 mL/min, increasing the flowrate appears to have a negative influence on the selectivity of **4a**. Increasing the flowrate does however improve the productivity and Turnover frequency (**TOF**) of the reaction as shown in Table 4.7.1. Due to limitations of the catalyst powder texture and the pipe size, higher flowrates cannot be tested in the current reactor. Instead, a scaled-up reactor was employed, and the details are discussed in Section 4.8.

4.8. Scale-up

A modest scale-up of this reaction was attempted using three reactors filled with **NbP** catalyst ($1.2\text{ g} \times 3$) in series with a fourth reactor placed upstream and filled with sand to act as pre-mixer as described in Section 2.2. Connecting three reactors in series could overcome the heat conduction and safety issues of using a single larger high pressure and high temperature reactor and is more suitable on a lab scale (Figure 4.8.1).

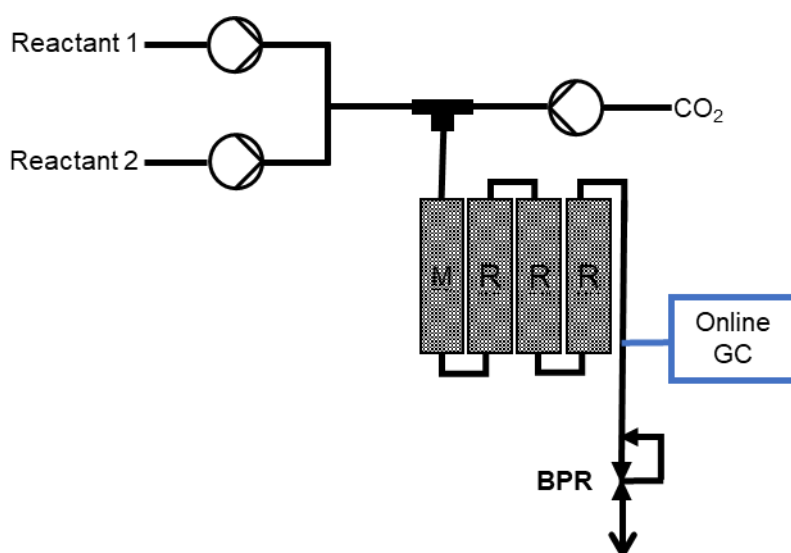


*Figure 4.8.1 A simplified schematic of scale-up high pressure and high temperature flow reactor; and more details were described in Section 2.2.1. M, mixer filled with sand; R, reactor filled with 1.2 g fresh **NbP** each.*

Initially reaction were carried out in the triple reactor using the same flowrate that had been used in the single reactor (0.1 mL/min of each reagent, giving a total flowrate of 0.2 mL/min). The triple reactor ran for 60 hours before any fall off in conversion was detected. By comparison, the single reactor showed significant fall off in less than 20 hours (one reactor **R**, 0.2 mL/min total flowrate). When the flowrate through the triple reactor (**3R**) was increased by a factor of three, its temporal behaviour was similar to that of the single reactor; although, the fall-off in both conversion and selectivity was more dramatic (Figure 4.8.2). This suggests that there may be a direct relationship between the amount of substrate passing through the reactor and the active lifetime of the **NbP**.

*Table 4.8.1 Scale-up continuous flow Skraup reaction productivity comparison for the single reactor **R** versus the triple reactor **3R** setup at various flow rates.*

Total Flowrate	1.2 g NbP for R				1.2 g $\times$ 3 NbP for 3R			
	AN Conv. ^a	QUI Sele. ^a	QUI Prod.	TON (TOF, s ⁻¹) ^b	AN Conv. ^a	QUI Sele. ^a	QUI Prod.	TON (TOF, s ⁻¹) ^b
0.2 mL/min	63%	51%	0.068 g/h	4.33 (0.57 $\times$ 10 ⁻³)	79%	41%	0.070 g/h	1.45 (0.24 $\times$ 10 ⁻³)
0.6 mL/min	-	-	-		74%	41%	0.190 g/h	4.09 (0.67 $\times$ 10 ⁻³)

^a The conversion, selectivity and productivity were averaged values of the reaction from 2nd to 15th hour and calculated based on GC analysis. The different experiments were performed under the following conditions: AN:SOLK ratio of 1:1 at 250°C and 100 bar.

^b 1) Turnover frequency (TOF) referred the limited starting reagent turnover that per acid site can achieve per second; 2) Calculated based on 13-hour reaction; 3) The number acid sites is calculated based on pyridine desorption.²¹²

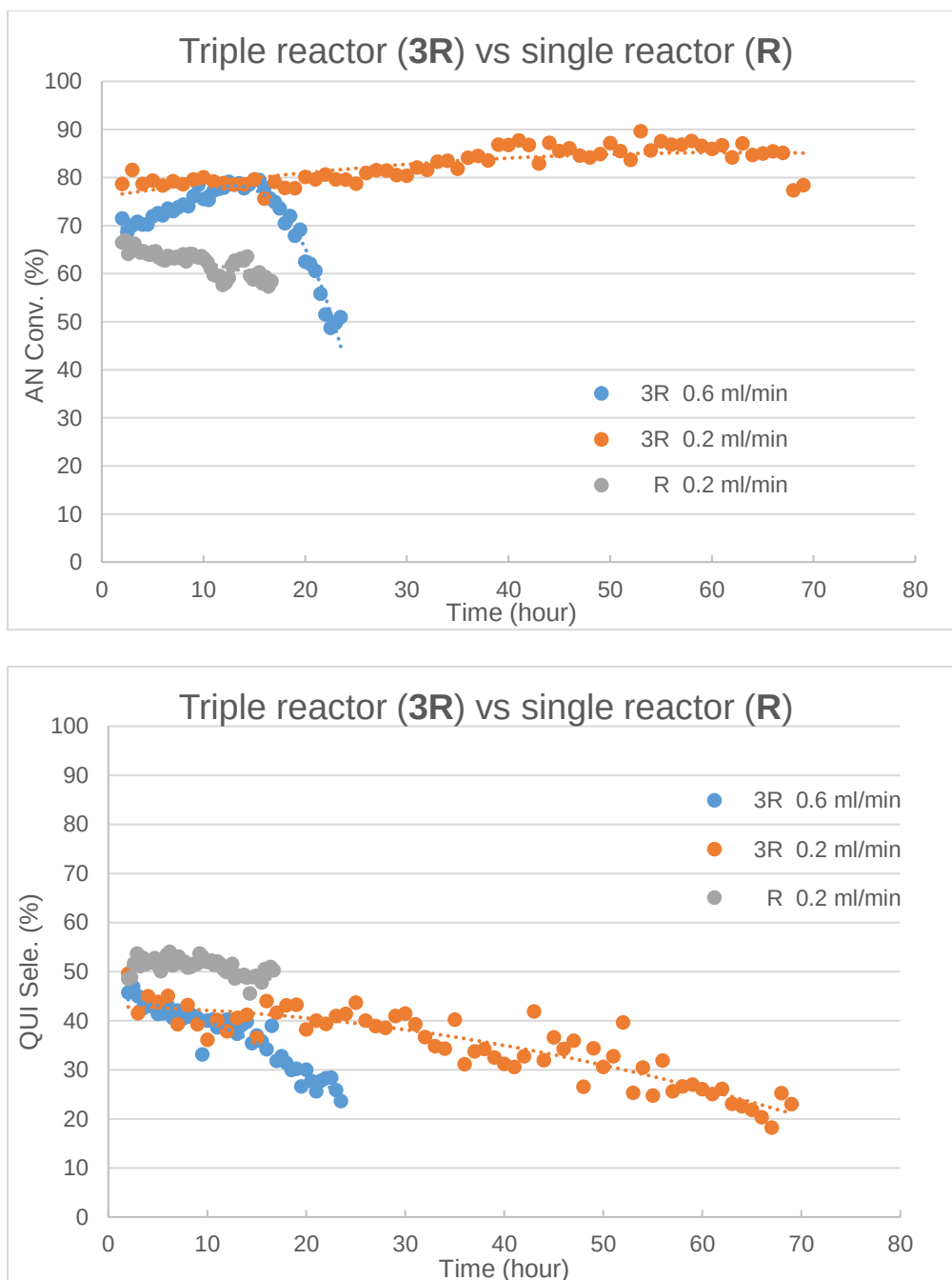
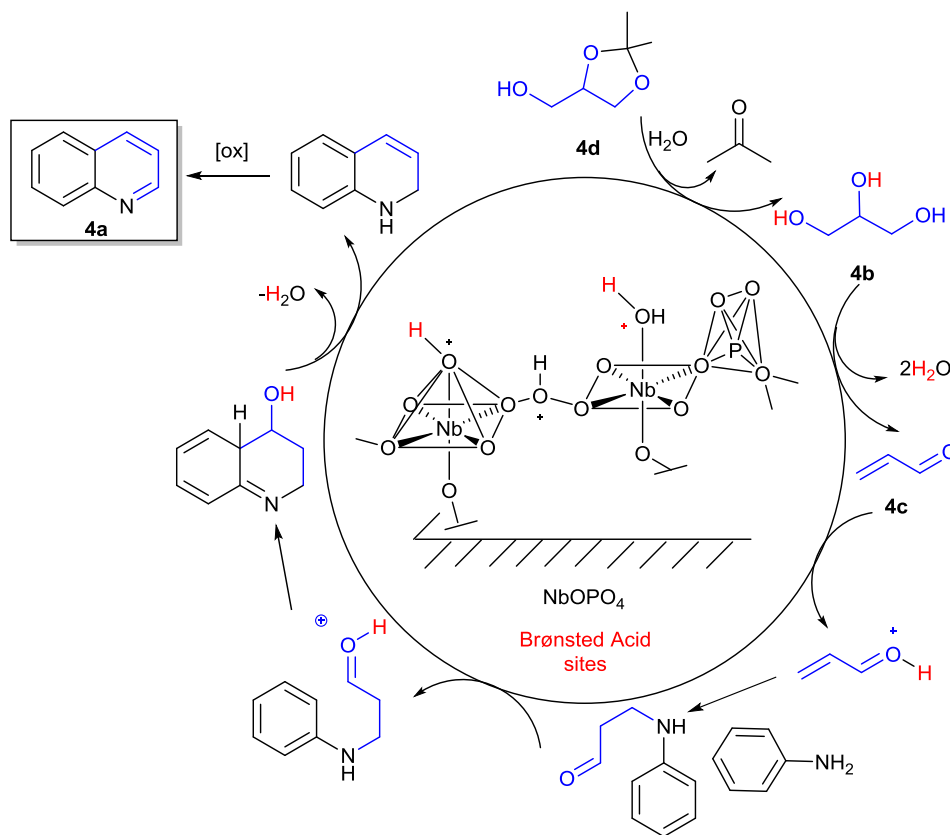


Figure 4.8.2 Scaled-up continuous flow QUI (**4a**) synthesis in series. (a) AN conversion and (b) selectivity to **4a**. Study under the same conditions of those in Section 4.7 (250 °C, 100 bar). Equimolar solutions (0.275 M in toluene) of both reactants AN and **4d** were fed at flow rates of 0.1 or 0.3 mL/min, separately, giving a total flowrate of either 0.2 mL/min or 0.6 mL/min. The result using a single reactor are the same as in Figure 4.7.1 & Figure 4.7.2 and are reported here for comparison.

4.9. Mechanism Conjecture



Scheme 4.9.1 . Possible acid-catalysed mechanism for the formation of **4a** starting from **4d** and AN over **NbP**.

Scheme 4.9.1 sketches a possible mechanism for the Skraup reaction catalysed by **NbP**. Even under the optimised conditions, the conversion of AN and the selectivity towards **4a** did not exceed 80% and 60%, respectively. The moderate yields can be understood by considering the overall reaction which occurs through three consecutive catalytic steps. Available data indicates that the dehydration of **4b** over **NbP** or mesoporous siliconiobium phosphate as (doped) catalysts proceeds with conversion and selectivity for **4c** from 68 to 100% and from 70 to 75%, respectively.^{74, 213, 214} It is therefore likely that, once the dehydration of **4b** is coupled to the other two catalytic

steps (*i.e.* the ketal deprotection and the condensation of **4c** with aniline), the overall yield will be low.

Two of the steps in Scheme 4.9.1 might be causing the decline in catalytic activity. The first is coking caused by polymerization of the free **4c**. The other is the final oxidation step leading to the formation of **4a**. The literature suggests that the acid strength of the most selective catalysts for the dehydration of **4b** to **4c** lies between $8.2 \leq H_0 \leq -3.0$.⁴⁰ Systems having very strong acid activities ($H_0 \leq -8.2$), such as **NbP** which contains 88% of strong acid sites as shown in Table 4.9.1, may offer low **4c** selectivity (40% - 50%) due to coke deposition during the reaction. The dehydration process usually requires high temperatures (250 °C – 300 °C) and **4c** can easily undergo undesired polymerization and coke formation under these conditions.²¹⁵ Various approaches have been proposed to limit the deactivation of dehydration catalysts. These include the suppression of the rate of coking by adding O₂ or H₂ to the feed flow^{216,217,218} and modifying the catalysts with promoters to change the acid properties of the catalysts. We have found that the deactivation of **NbP** is related to the amount of **4d** (and thus, of **4b**) used in the reaction. The more **4d** is delivered to the reactor, the more **4c** is formed, and consequently, the larger the coke deposition over the catalyst active phase.

Table 4.9.1 The acidic properties of **NbP** catalyst.⁶⁷

Sample	Total acid sites (meq/g)	Strong acid sites (meq/g)
NbP	0.403	0.353 (88%)

^a. Acidity was determined by liquid-solid titrations working with basic solution, which phenylethylamine was used a base probe and cyclohexane was used as apolar-aprotic solvent.

There seems to be no obvious reason why polymerization should give rise to the near stoichiometric behaviour which had been observed. On the other hand, the oxidation step must give rise to a corresponding reduction of the surface. Such reduction would be expected to be close to the stoichiometric. Whichever of the explanations is

correct, the route to regenerating the spent **NbP** may well be heating under a stream of air, which could either remove coking or deoxidise of the catalyst. We found that heating up to 300 °C for 20 hours was unsuccessful and, unfortunately our reactors could not be heated to higher temperature without compromising their pressure rating.

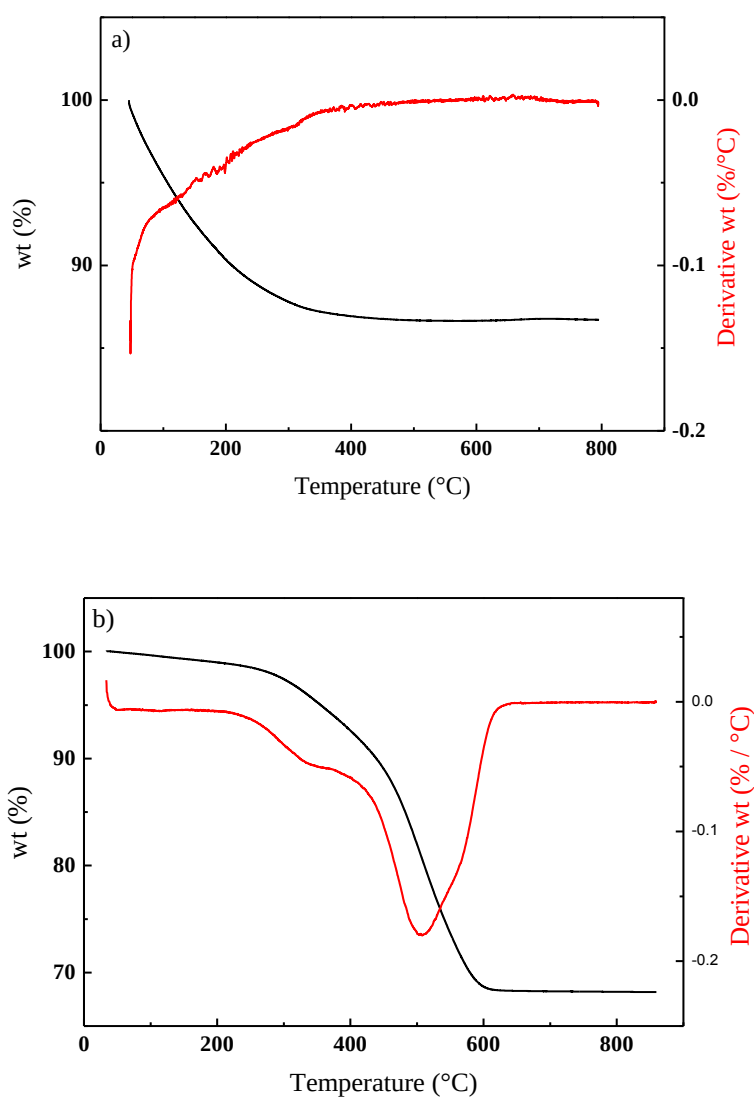


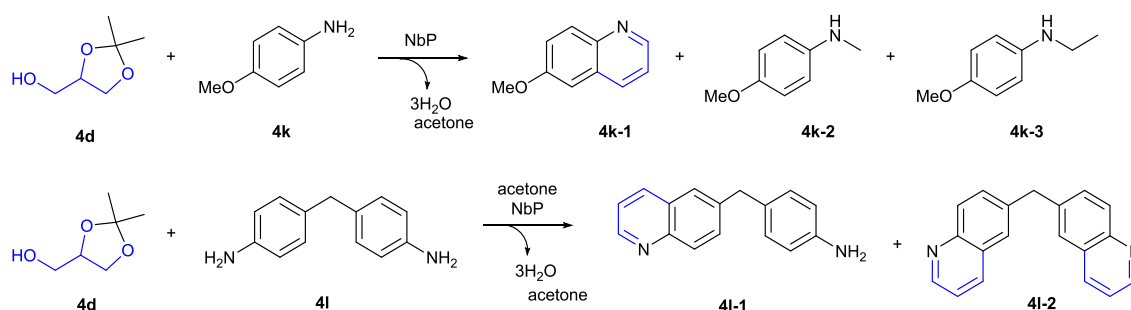
Figure 4.9.1 TGA analysis of the a) fresh **NbP** and b) used **NbP** catalyst.

The thermogravimetric analysis (**TGA**) traces shown in Figure 4.9.1 for the used catalyst are consistent with the presence of organic coking. As shown in Figure 4.9.1a),

for the fresh **NbP** catalyst, the total weight loss observed from 50 °C to 450 °C is about 13% , which probably corresponds to the loss of physically absorbed and hydrous water molecules. For the used **NbP** catalyst, the overall weight loss of 32 % occurs in two stages (Figure 4.9.1 b)). The initial weight loss around 13 % up to 420 °C is again attributed to water. The second weight loss around 19 % occurs between 450 – 600 °C and is attributed to coke burning off the surface. After the thermogravimetric analysis, the used dark brown **NbP** catalyst returned to white colour of unused **NbP**. This may also provide evidence that coking caused the deactivation, and coking can be burned at higher temperature above 450 °C.

4.10. Using Different Anilines in Skraup Reaction

Two other anilines 4-methoxyaniline **4k** and 4,4'-methylenedianiline **4l** were used to react with **4d** in order to demonstrate that **NbP** can be extended to catalyse the Skraup reaction more widely. In both the cases, the expected heterocyclic quinoline product was formed as the major component.



*Scheme 4.10.1 Products observed from the continuous flow reaction of 4-methoxyaniline **4k** and 4,4'-methylenedianiline **4l** with **4d** over **NbP**.*

We began with best reaction conditions found for aniline itself, i.e. 1:1 ratio of reactants, 250°C and 100 bar. With **4k**, the 6-methoxyquinoline **4k-1** was obtained with a GC-yield of 30%. The two main by-products observed were 4-methoxy-N-methylaniline **4k-2** and N-ethyl-4-methoxyaniline **4k-3** (total amount less than 10 %). All these compounds were isolated and characterized by NMR and MS (see Section 4.12). The process was not further optimised.

For the toxic 4,4'-methylenedianiline **4l** (MDA), a higher temperature of 300 °C was necessary to increase the **4l** conversion with a 1:1 feedstock mixture. Both the asymmetric 4-(quinolin-6-yl methyl)aniline **4l-1** and symmetric di(quinolin-6-yl)methane **4l-2** products were observed with a GC-yield of 20% and 12% respectively.

A crystal of compound **4l-1** was grown and the structure determined by crystallographic analysis for the first time. The compounds were isolated and characterized by MS and NMR analysis (Section 4.12). It is interesting that the major product is the asymmetric compound **4l-1**.

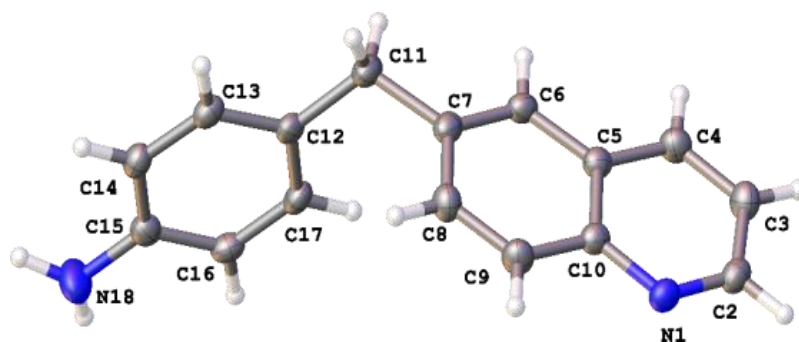


Figure 4.10.1 Crystallographic structure of compound 4-(quinoline-6-yl methyl)aniline **4l-1**.

4.11. Conclusions

The experiments described here are a useful proof of concept. **4d** can be used as a feedstock for the continuous Skraup reaction promoted by a **NbP** solid acid catalyst. No liquid acids or added oxidants are needed. This therefore adds to the range of transformations that can be carried out using glycerol, a by-product of the energy industry. Although the reaction contravenes the sixth Principle of Green Chemistry¹ in which it requires high temperatures and pressures, it should be noted that : (i) the high pressure may not be a substantial hindrance since the reactants are liquids and therefore relatively incompressible requiring little energy to be pressurized; and (ii) technologies for the integrated heat recovery in modern biorefineries allow cheap access to temperatures up to 300 °C.

The major problem still to be addressed is how best the **NbP** can be regenerated. Heating the catalyst to 300 °C in air had little effect. The TGA experiment suggests that at much higher temperatures calcination may be effective. Even at the current stage of development, however, the reaction could provide a convenient route to less common quinolines such as the desymmetrized **4l-1**.

From a sustainability point of view, the key points are that a continuous Skraup reaction is possible and can be catalysed by **NbP** a relatively inexpensive and abundant metal in a continuous flow process.

As explained above, the using (solketal) **4d** because the limitations of the small-scale equipment prevent the efficient pumping of glycerol. Those experiments that were performed with glycerol gave poor selectivity. The improved selectivity that was

observed with **4d** was attributed as being due to the better control of the reaction conditions that could be obtained using the available equipment when using this substrate. However, there remains the intriguing possibility that **4d** may give inherently better selectivity than glycerol itself under these reaction conditions. If this were the case, **4d** would be the preferred starting material for this process of valorisation of the glycerol by-product. Unfortunately, we have insufficient data to test this possibility. Nevertheless, the point should be explored before dismissing the use of **4d** as unnecessary derivatization, in contravention of the eighth Principle of Green Chemistry¹ (i.e. “unnecessary derivatization [blocking group, protection/deprotection, temporary modification of physical/chemical processes] should be avoided whenever possible”). For the moment, it is clear that **4d** is potentially an alternative to glycerol for smaller scale reactions, even if glycerol may eventually turn out to be preferable from a Green Chemistry point of view for larger scale processes.

4.12. Products characterization

Synthesis of quinoline (**4a**)

The reaction was carried out according to the general procedure described in Section 4.4. The purification of quinoline **4a** was undertaken with 85:15 (v/v) of CyHex:AcOEt as eluent. **¹H NMR** (400 MHz, CDCl₃) δ ppm: 8.92 (dd, $J=4.2, 1.7$ Hz, 1H), 8.19 – 8.09 (m, 2H), 7.85-7.80 (m, 1H), 7.72 (ddd, $J=8.5, 6.9, 1.5$ Hz, 1H), 7.55 (ddd, $J=8.1, 6.9, 1.2$ Hz, 1H), 7.40 (dd, $J=8.3, 4.2$ Hz, 1H). **¹³C NMR** (100 MHz, CDCl₃) δ ppm: 150.5, 148.4, 136.2, 129.6, 129.6, 128.4, 127.9, 126.7, 121.2. **HRMS-ESI** for C₉H₈N [M]⁺ calculated 130.0657, found: 130.0653.

Synthesis of 3-methyl-1H-indole (4h)

The reaction was carried out according to the general procedure described in Section 4.4. The purification of 3-methyl-1H-indole **4h** was carried out with 80:20 (v/v) of CyHex:AcOEt as eluent. **¹H NMR** (500 MHz, CDCl₃) δ ppm: 7.59 (dd, *J*=7.8, 1.1 Hz, 1H), 7.35 (dd, *J*=8.0, 0.9 Hz, 1H), 7.19 (ddd, *J*=8.2, 7.0, 1.3 Hz, 1H), 7.12 (ddd, *J*=7.9, 7.0, 1.0 Hz, 1H), 6.97 (dd, *J*=2.3, 1.2 Hz, 1H), 2.34 (d, *J*=1.1 Hz, 3H). **¹³C NMR** (125 MHz, CDCl₃) δ ppm: 136.4, 128.4, 122.0, 121.7, 119.2, 119.0, 111.9, 111.1, 9.8. **HRMS-ESI** for C₉H₉N M⁺ calculated 130.0813, found 130.0654.

Synthesis of 2,4-dimethylquinoline (4f)

The reaction was carried out according to the general procedure described in Section 4.3. The purification of 2,4-dimethylquinoline **4f** was carried out with 50:50 (v/v) of CyHex:AcOEt as eluent. **¹H NMR** (500 MHz, CDCl₃) δ ppm: 8.02 (d, *J*=8.5, 1H), 7.95 (dd, *J*=8.3, 1.4 Hz, 1H), 7.67 (ddd, *J*=8.4, 6.8, 1.4 Hz, 1H), 7.50 (ddd, *J*=8.2, 6.9, 1.3 Hz, 1H), 7.14 (d, *J*=1.1 Hz, 1H), 2.70 (s, 3H), 2.67 (d, 3H). **¹³C NMR** (126 MHz, CDCl₃) δ ppm: 158.8, 147.8, 144.3, 129.3, 129.2, 126.7, 125.5, 123.7, 122.9, 25.4, 18.7. **HRMS-ESI** for C₁₁H₁₂N [M+H]⁺ calculated 158.0970, found 158.0961.

Synthesis of 2,2,4-trimethyl-1,2-dihydroquinoline (4g)

The reaction was carried out according to the general procedure described in Section 4.3. The purification of 2,2,4-trimethyl-1,2-dihydroquinoline **4g** was carried out with 50:50 (v/v) of CyHex:AcOEt as eluent. **¹H NMR** (500 MHz, CDCl₃) δ ppm: 7.07 (dd, *J*=7.6, 1.5 Hz, 1H), 6.99 (td, *J*=7.6, 1.5 Hz, 1H), 6.67 (td, *J*=7.5, 1.3 Hz, 1H), 6.53–6.49 (d, 1H), 5.32 (d, *J*=1.5 Hz, 1H), 1.99 (d, *J*=1.4 Hz, 3H), 1.30 (s, 6H). **¹³C NMR**

(125 MHz, CDCl₃) δ ppm: 142.6, 128.8, 128.5, 128.5, 123.9, 122.1, 117.9, 113.6, 52.2, 30.8, 18.7. **HRMS-ESI** for C₁₂H₁₆N [M+H]⁺ calculated 174.1283, found 174.1287.

Synthesis of 6-methoxyquinoline (**4k-1**)

The reaction was carried out according to the general procedure described in Section 4.10. The purification of 6-methoxyquinoline **4k-1** was carried out with a gradient of polarity from 85:15 to 50:50 (v/v) of CyHex:AcOEt as eluent. **¹H NMR** (300 MHz, CDCl₃) δ ppm: 8.78 (dd, J =4.3, 1.7 Hz, 1H), 8.12–8.07 (m, 1H), 8.07–8.02 (m, 1H), 7.43–7.36 (m, 2H), 7.09 (d, J =2.8 Hz, 1H), 3.95 (s, 3H). **¹³C NMR** (75 MHz, CDCl₃) δ ppm: 157.9, 147.7, 144.2, 135.3, 130.7, 129.5, 122.6, 121.5, 105.2, 55.7. **HRMS-ESI** for C₁₀H₁₀NO [M+H]⁺ calculated 160.0762, found 160.0766.

Synthesis of 4-methoxy-N-methylaniline (**4k-2**)

The reaction was carried out accordingly to the general procedure described in Section 4.10. The purification of 4-methoxy-N-methylaniline **4k-2** was carried out with a gradient of polarity from 85:15 to 50:50 (v/v) of CyHex: AcOEt as eluent. **¹H NMR** (300 MHz, CDCl₃) δ ppm: 6.84–6.78 (m, 2H), 6.69–6.62 (m, 2H), 3.76 (s, 3H), 2.82 (s, 3H). **¹³C NMR** (75 MHz, CDCl₃) δ ppm: 152.7, 142.9, 115.1, 114.4, 55.9, 32.2. **HRMS-ESI** for C₈H₁₂NO [M+H]⁺ calculated 138.0919, found 138.0919.

Synthesis of N-ethyl-4-methoxyaniline (**4k-3**)²¹⁹

The reaction was carried out accordingly to the general procedure described in Section 4.10. The purification of N-ethyl-4-methoxyaniline **4k-3** was carried out with a gradient of polarity from 85:15 to 50:50 (v/v) of CyHex:AcOEt as eluent. **¹H NMR** (300 MHz, CDCl₃) δ ppm: 6.78 (m, 2H), 6.62–6.55 (m, 2H), 3.75 (s, 3H), 3.11 (q, J =7.1 Hz, 2H), 1.24 (t, J =7.1 Hz, 3H). **¹³C NMR** (75 MHz, CDCl₃) δ ppm: 152.2, 142.9,

115.0, 114.2, 55.98, 39.6, 15.16. **HRMS-ESI** for $C_{19}H_{14}NO$ $[M+H]^+$ calculated 152.1075, found 152.1077.

Synthesis of 4-(quinolin-6-yl methyl)aniline (**4l-1**)

The reaction was carried out according to the general procedure described in Section 4.10. The purification of 4-(quinoline-6-yl methyl)aniline **4l-1** was carried out with a gradient of polarity from 80:20 to 30:70 (v/v) of CyHex:AcOEt as eluent. **¹H NMR** (400 MHz, $CDCl_3$) δ ppm: 8.85 (dd, $J=4.3, 1.7$ Hz, 1H), 8.07 (dd, $J=8.3, 1.8$ Hz, 1H), 8.01 (d, $J=9.2$ Hz, 1H), 7.58–7.54 (m, 2H), 7.36 (dd, $J=8.3, 4.2$ Hz, 1H), 7.02 (d, $J=8.3$ Hz, 2H), 6.67–6.63 (m, 2H), 4.06 (s, 2H). **¹³C NMR** (100 MHz, $CDCl_3$) δ ppm: 149.9, 147.3, 144.9, 140.7, 135.9, 131.4, 130.6, 130.1, 129.5, 128.5, 126.6, 121.2, 115.5, 41.2. **HRMS-ESI** for $C_{16}H_{15}N_2$ $[M+H]^+$ calculated 235.1235, found 235.1245.

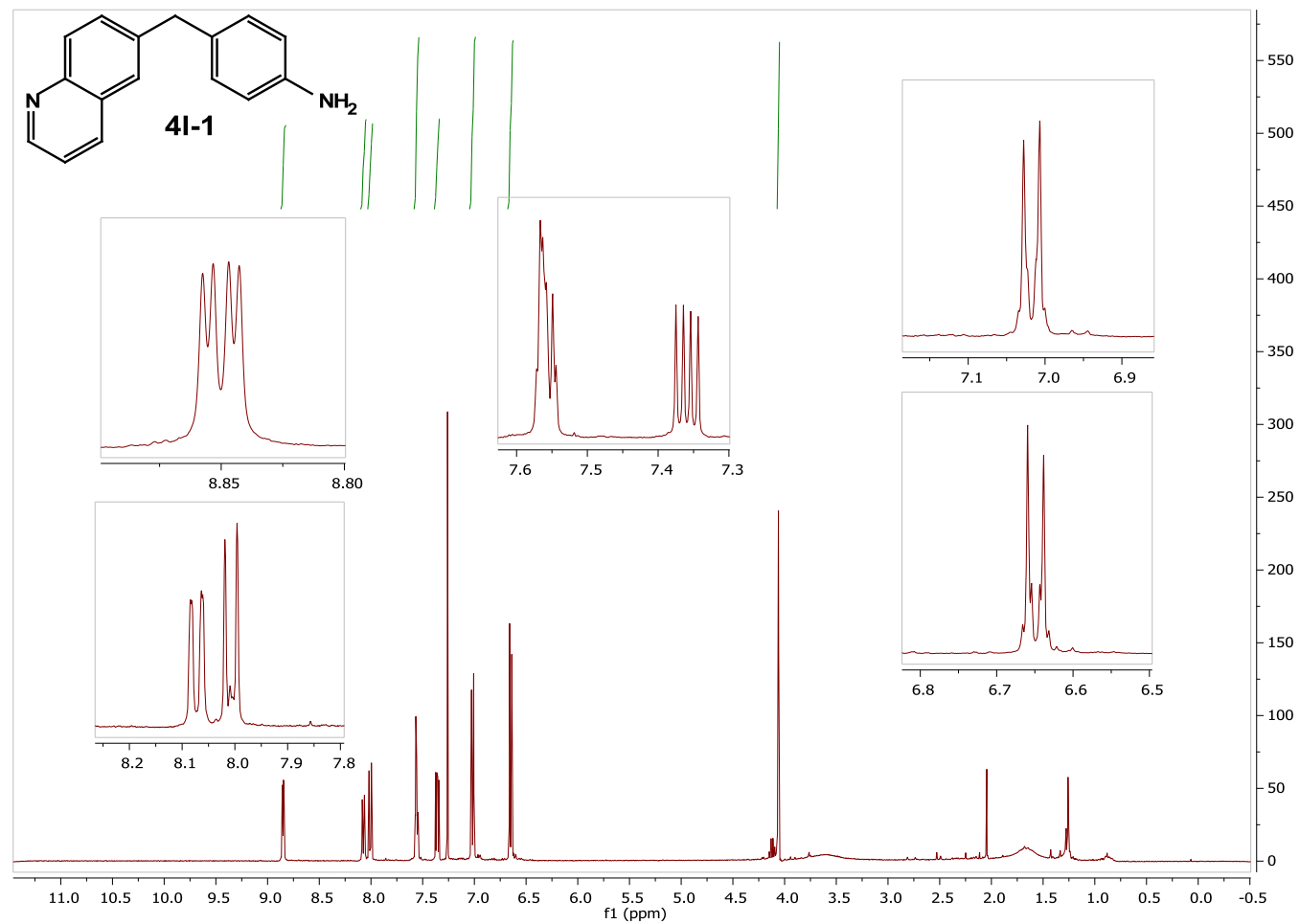


Figure 4.12.1. ^1H NMR spectra of **4I-1**

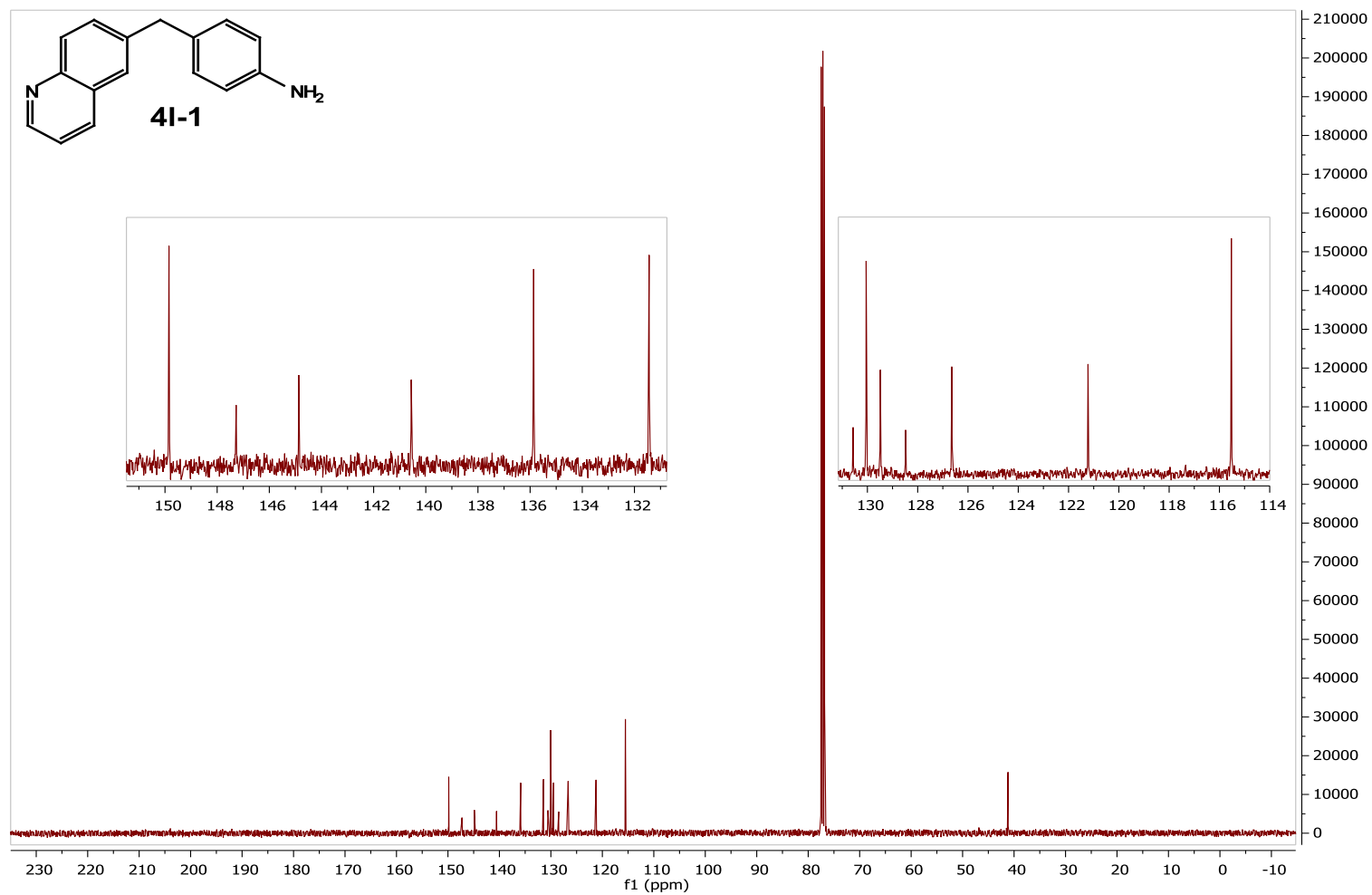


Figure 4.12.2. ^{13}C NMR spectra of **4I-1**

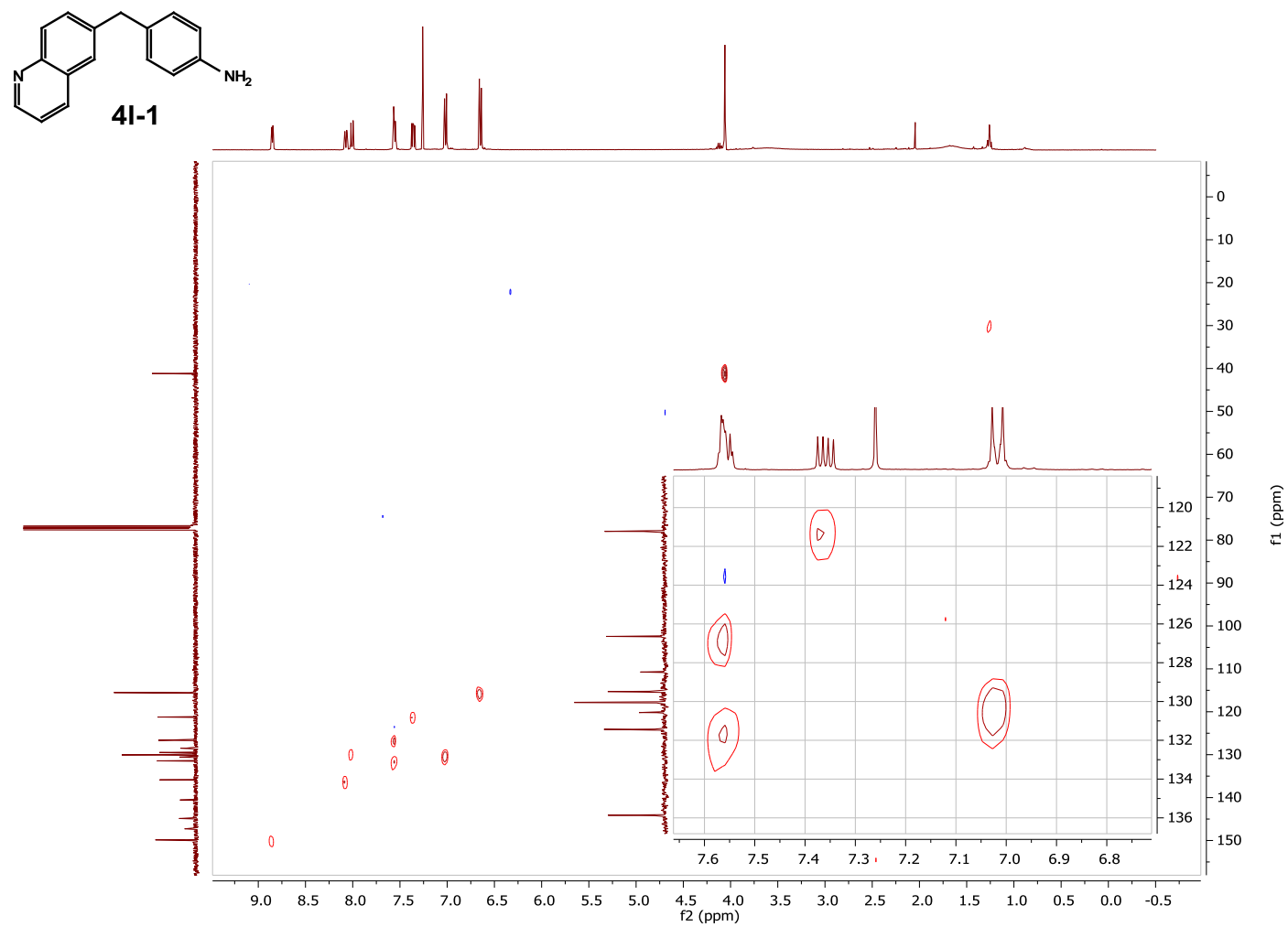


Figure 4.12.3. HMQC spectra of **4I-1**

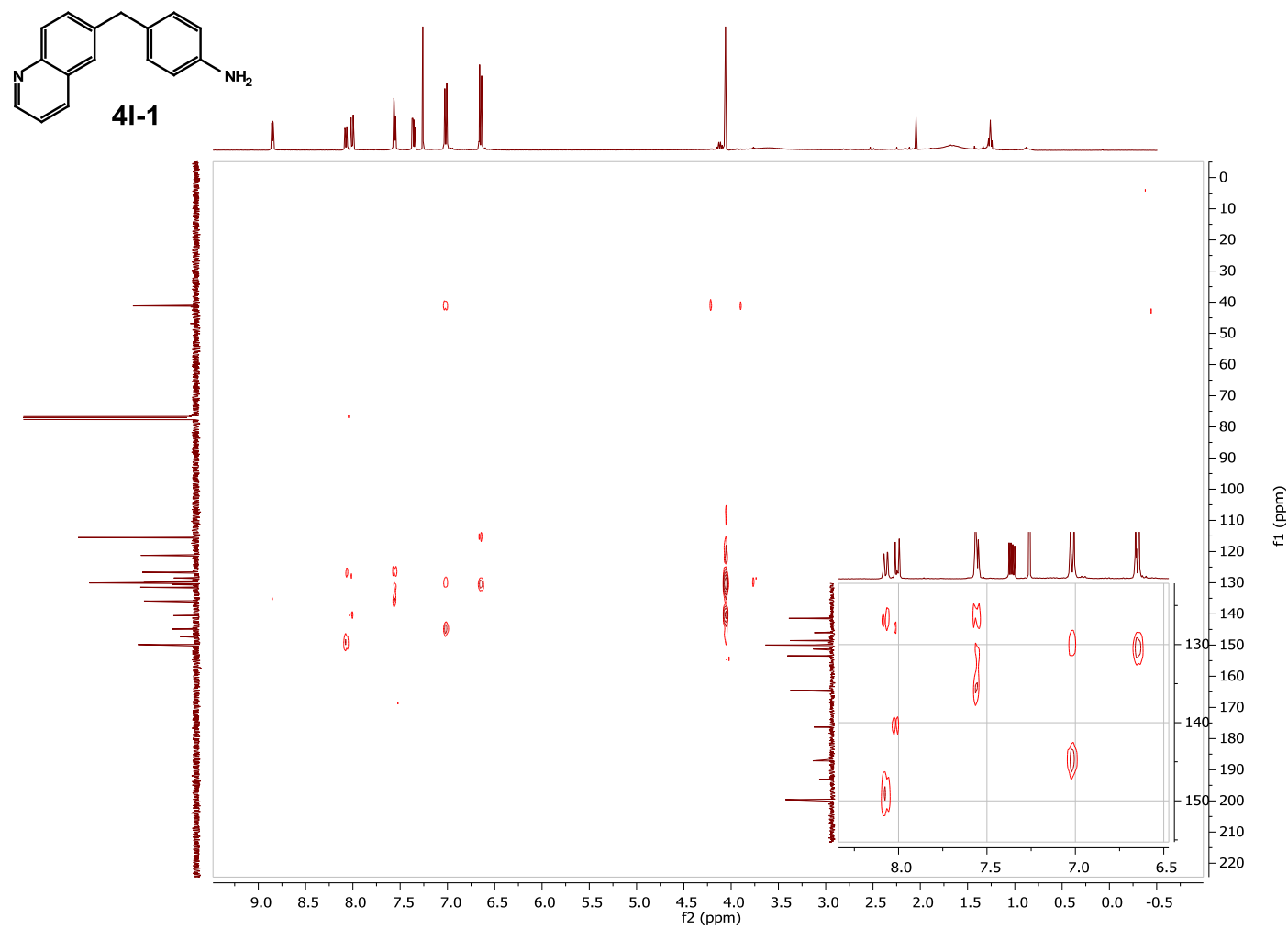


Figure 4.12.4. HMBC spectra of **4l-1**

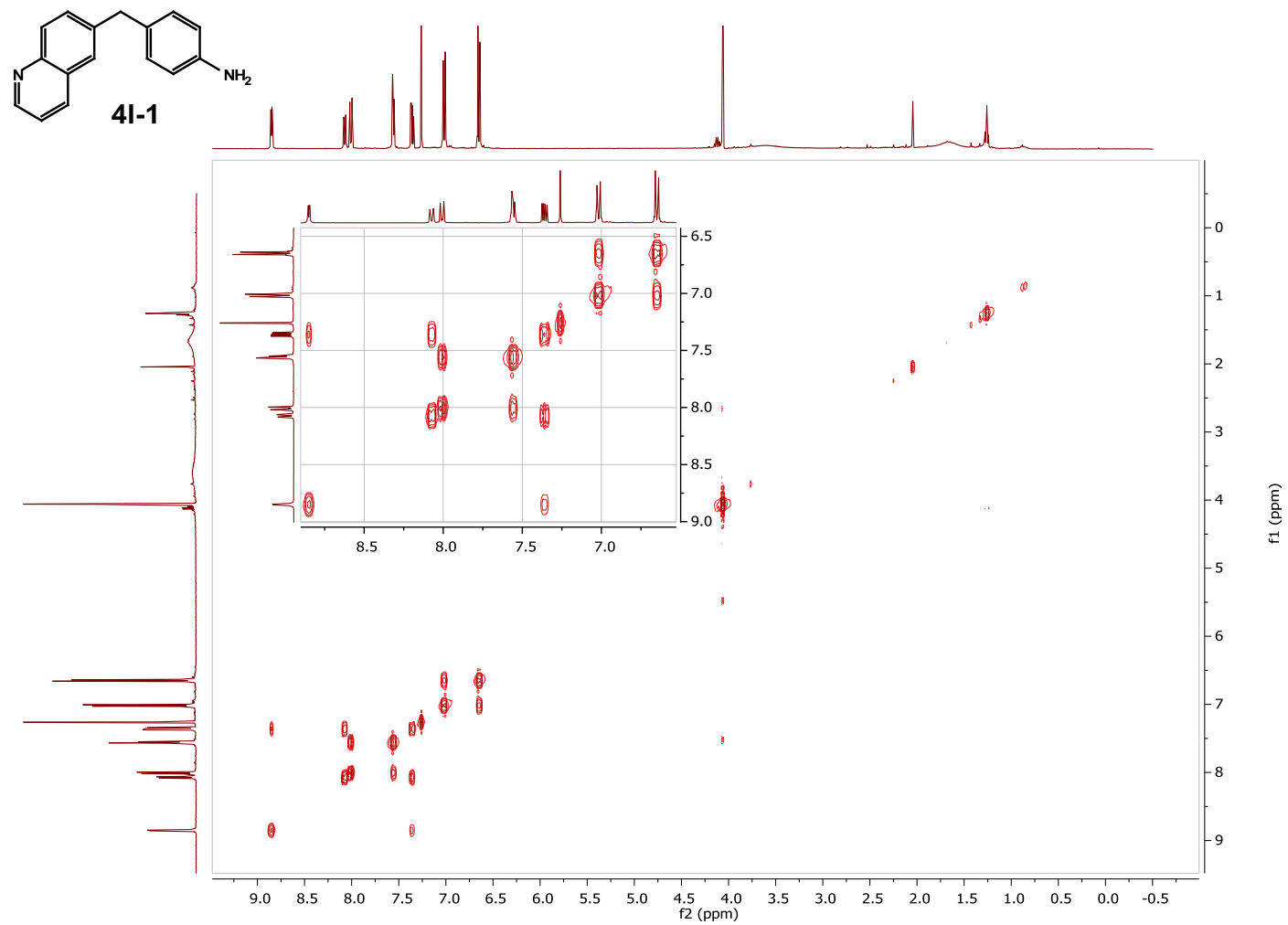
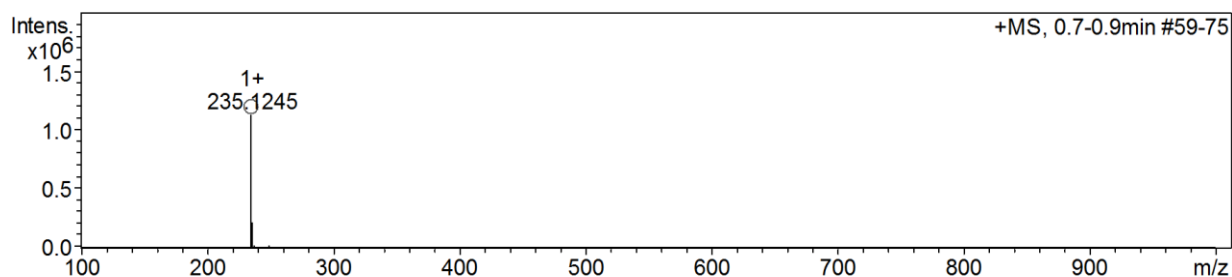


Figure 4.12.5. COSY spectra of **4I-1**



Generate Molecular Formula Parameters

Charge	Tolerance	sigma limit	H/C Ratio	Electron Conf.	Nitrogen Rule	Chrom.BackGround	Calibration
+1	12 ppm	0.08	3 - 0	both	false	false	TRUE
Expected Formula		C16 H14 N2		Adduct(s):		H, Na, NH4, radical	
#	meas. m/z	theo. m/z	Err [ppm]	Sigma	Formula	Adduct	Adduct Mass
1	235.1245	235.1230	6.30	0.0034	C16H15N2	M+H	1.0078

Note: Sigma fits < 0.05 indicates high probability of correct MF

Figure 4.12.6. HRMS-ESI of 4I-1

X-ray crystallographic structure of compound 4I-1

Single crystals of C₁₆H₁₄N₂ 4-(quinolin-6-yl methyl)aniline **4I-1** were grown. A suitable crystal was selected and mounted in fomblin film on a micromount on a GV1000, Atlas diffractometer giving the crystal structure shown in Figure 4.12.7.

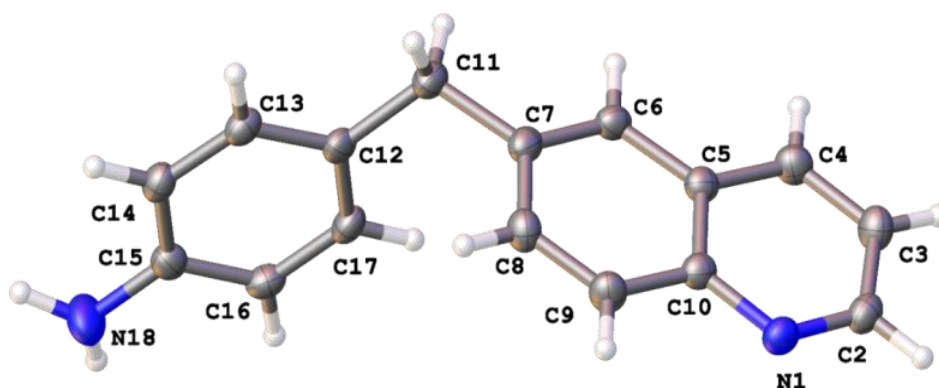


Figure 4.12.7. X-ray crystallographic structure of compound 4I-1.

Table 4.12.1. Crystal data and structure refinement for compound **4I-1**

Empirical formula	C ₁₆ H ₁₄ N ₂
Formula weight	234.29
Temperature/K	120(2)
Crystal system	monoclinic
Space group	P2 ₁ /n
a/Å	10.0024(9)
b/Å	6.9487(7)
c/Å	17.5896(15)
α /°	90
β /°	98.794(9)
γ /°	90
Volume/Å ³	1208.2(2)
Z	4
ρ_{calc} /g/cm ³	1.288
μ /mm ⁻¹	0.594
F(000)	496.0
Crystal size/mm ³	0.354 × 0.17 × 0.164
Radiation	CuK α (λ = 1.54184)
2 Θ range for data collection/°	10.178 to 147.092
Index ranges	-12 ≤ h ≤ 12, -8 ≤ k ≤ 8, -11 ≤ l ≤ 21
Reflections collected	4597
Independent reflections	2356 [R_{int} = 0.0226, R_{sigma} = 0.0265]
Data/restraints/parameters	2356/0/169
Goodness-of-fit on F ²	1.026
Final R indexes [$I \geq 2\sigma(I)$]	R_1 = 0.0395, wR_2 = 0.1042
Final R indexes [all data]	R_1 = 0.0451, wR_2 = 0.1091
Largest diff. peak/hole / e Å ⁻³	0.19/-0.20

Synthesis of di(quinolin-6-yl)methane (**4l-2**)

The reaction was carried out according to the general procedure described in Section 4.10. The purification of di(quinolin-6-yl)methane **4l-2** was carried out with a gradient of polarity from 80:20 to 30:70 (v/v) of CyHex:AcOEt as eluent. **¹H NMR** (300 MHz, CDCl₃) δ ppm: 8.91 (dd, *J*=4.3,1.7Hz, 2H), 8.09 (m, 4H), 7.70-7.57 (m, 4H), 7.41 (dd, *J*=8.3,4.2Hz, 2H), 4.39 (s, 2H). **¹³C NMR** (100 MHz, CDCl₃) δ ppm: 150.1, 147.3, 138.9, 135.7, 131.2, 129.8, 128.4, 127.1, 121.3, 41.8. **HRMS-ESI** for C₁₉H₁₅N₂ as [M+H]⁺ calculated 271.1235, found 271.1245 calculated.

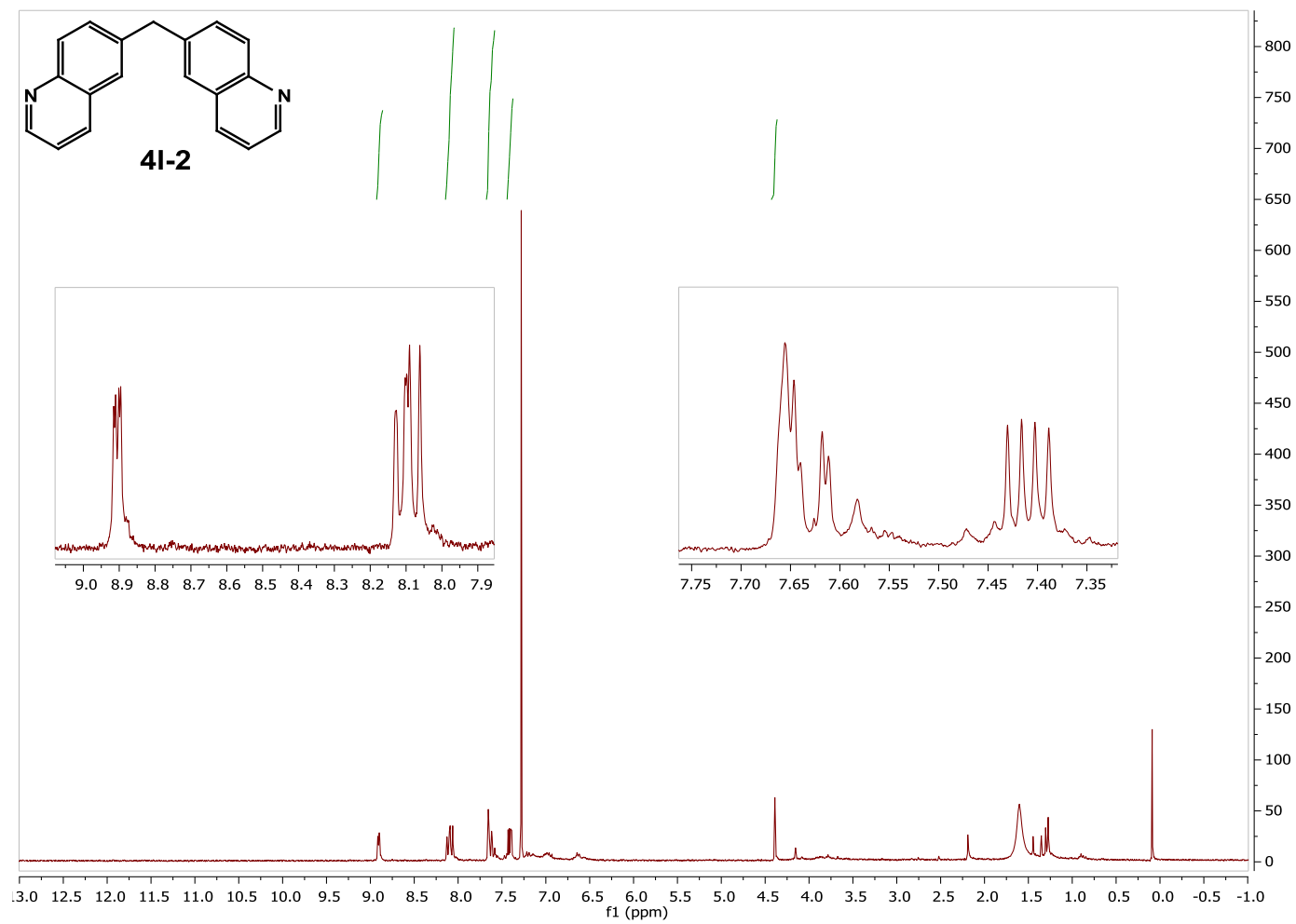


Figure 4.12.8. ^1H NMR spectra of **4I-2**

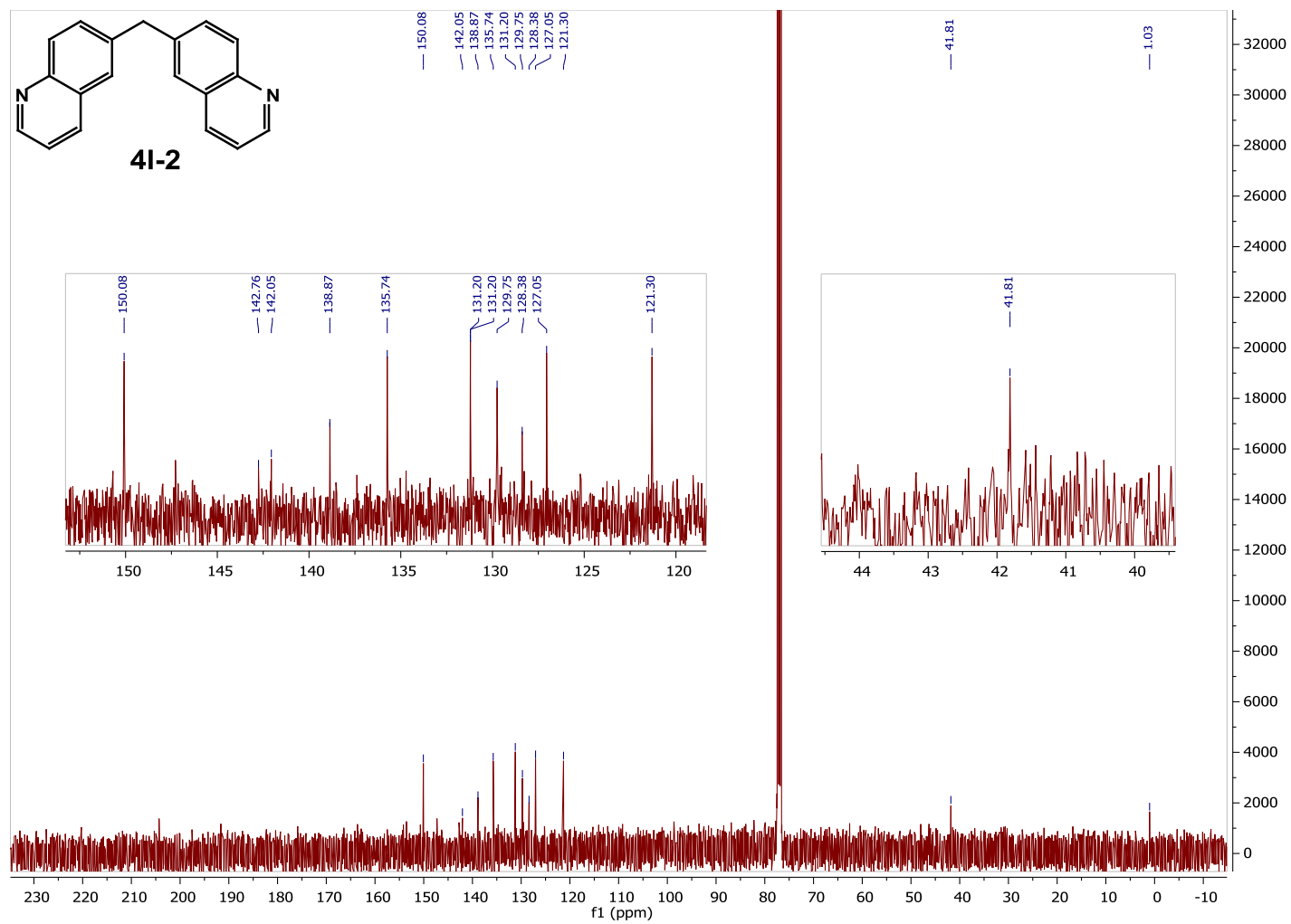


Figure 4.12.9. ¹³C NMR spectra of **4I-2**

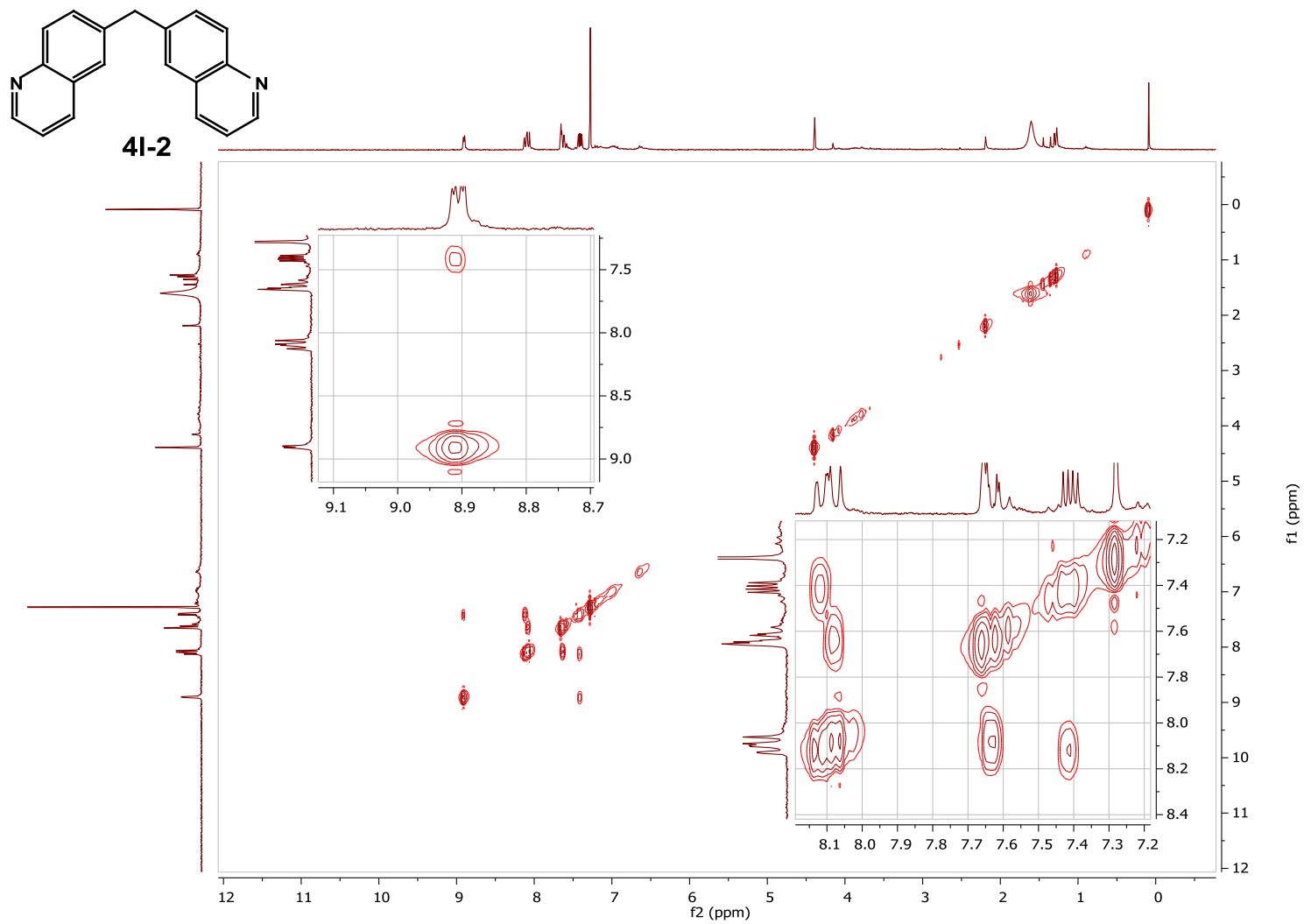
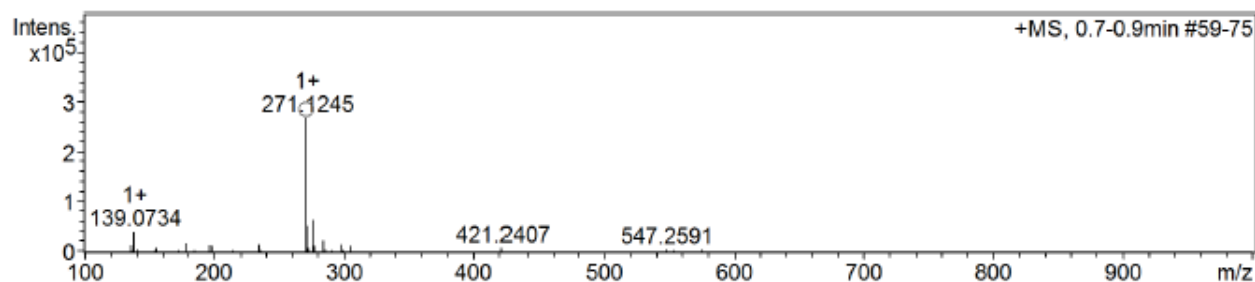


Figure 4.12.10. COSY spectra of **4I-2**

+MS, 0.7-0.9min #59-75



Generate Molecular Formula Parameters

Charge	Tolerance	sigma limit	H/C Ratio	Electron Conf.	Nitrogen Rule	Chrom.BackGround	Calibration
+1	6 ppm	0.08	3 - 0	both	false	false	TRUE
Expected Formula		C19 H14 N2				Adduct(s):	H, Na, NH4, radical
#	meas. m/z	theo. m/z	Err [ppm]	Sigma	Formula	Adduct	Adduct Mass
1	271.1245	271.1230	5.50	0.0153	C19H15N2	M+H	1.0078

Note: Sigma fits < 0.05 indicates high probability of correct MF

Figure 4.12.11. HRMS-ESI of **4I-2**

Chapter 5. Niobium Compounds as Supports for Immobilised Photosensitiser

As described in Chapter 1, the advantages of continuous flow processes such as efficient irradiation, good mixing and fast heat exchange are beneficial to photochemistry. This Chapter will describe an exploration of the application of Nb catalysts in continuous photochemical processes, where niobium solid acids (**NbP** and **NbO**) will be used as supports to immobilise a photosensitiser, forming bifunctional heterogeneous catalysts, for continuous photo-oxidation reactions using singlet oxygen.

First, a brief review of photochemistry and singlet oxygen is presented in Section 5.1, where previous studies on photo-oxidation reactions with singlet oxygen conducted at the University of Nottingham are also summarised. Building on these previous studies, the initial aim of the work presented in this Chapter was to improve the stability and activity of bifunctional photocatalysts for the synthesis of an antimalarial drug, artemisinin ART, in a continuous flow processes.

Initial results obtained for the immobilisation of the photosensitiser meso-tetraphenylporphyrin TPP on **NbP** solid acid, are described in Section 5.2. The effects of varying parameters, such as the choice of solvent, amount of TPP and immobilisation

time, on the stability of TPP@NbP were investigated. Following this, the catalytic activity of TPP@NbP was investigated, both for the photo-oxidation of α -terpinene to ascaridole in a batch reactor, and for the photochemical synthesis of ART in a high pressure continuous photoreactor.

The loading of photosensitises TPP onto several forms of NbO, including powder and graphite bound pellets, was also tested, as described in Section 5.3. The activity of NbO supported TPP in the synthesis of ART, via photo-oxidation with singlet oxygen, was then investigated, as outlined in Section 5.3.

The results presented in this Chapter are summarised in Section 5.4.

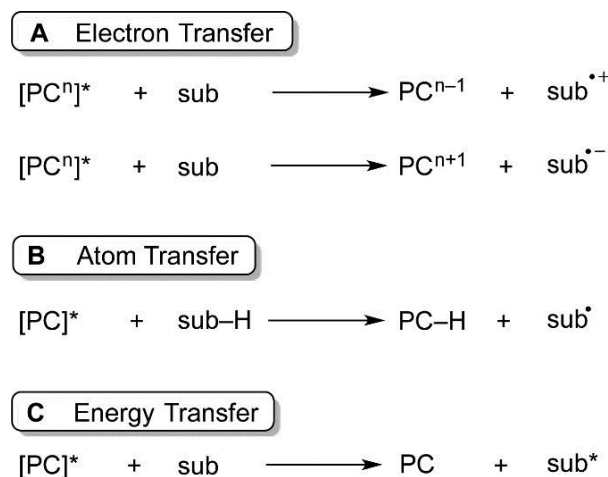
5.1. Background

Developing clean energy and reducing environmental pollution has always been a goal for green and sustainable chemistry. Solar energy, which is clean, abundant and renewable, has received extensive attention. Scientists have made great efforts to utilize solar energy, through a variety of areas, such as solar thermal conversion, solar electrical energy generation and solar fuels production.²²⁰⁻²²³

Photochemistry, which utilizes light to activate organic reactions, is considered an environmentally benign way to perform organic synthesis, particularly when using solar energy. The great potential of organic synthetic photochemistry was firstly pointed out by the Italian scientist Giacomo Ciamician over 100 years ago but significant interest in this area has only developed with the last few decades.²²⁴ Most organic molecules tend to only absorb light in the ultraviolet (UV) region, a limited section of the solar spectrum. However, high energy of UV photons can also cause uncontrolled

photodecomposition to occur, which was particularly challenge in the early days of photochemistry.²²⁵

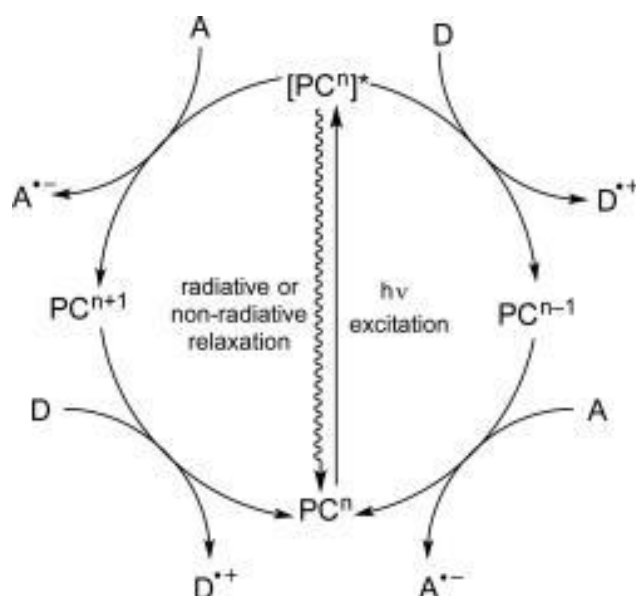
Investigations into the possible applications of transition metal complexes initially focused on the conversion of sunlight to electrochemical potential. However, scientists then began to discover the activity of these visible light-absorbing species could be used as catalysts in the photochemical synthesis.^{93, 226} Transition metal photocatalysts can absorb light highly efficiently, at wavelengths longer than those absorbed by organic molecules can. When a photo catalyst absorbs a photon of light, it is excited to a higher electronic state. In excited state, the photocatalyst can then activate an organic reaction via several mechanisms. Yoon *et al.* summarised the possible mechanisms, and divided them into three types: electron transfer, atom transfer and energy transfer (Scheme 5.1.1).²²⁷



Scheme 5.1.1 Homogeneous photocatalytic mechanisms. The scheme is adapted from reference²²⁷. PC: photocatalyst; sub: substrate.

The first possible mechanism for the photocatalysis is electron transfer (Scheme 5.1.2). This mechanism is based on the photoexcited photocatalyst (PC) being either a stronger reducing or oxidising agent of organic substrates than its ground state. This can

lead to the transfer of an electron between the PC and the organic substrate, resulting in change in the charge on the photocatalyst and generation of an organic radical ion. The radical ion then can undergo a number of reactions. Regeneration of the photocatalyst requires a second electron-transfer process from a complementary donor or acceptor species. So formally, the electron is transferred from one substrate to another.



Scheme 5.1.2 Photoinduced electron transfer (adapted from reference.²²⁷) PC: photocatalyst; A: electron acceptors; D: electron donors.

The second type of photocatalytic mechanism is atom transfer. The excited-state photocatalyst can react directly with the substrate via hydrogen atom abstraction, which avoids stepwise electron transfer. This reaction mechanism is typical of photoexcited aromatic ketones.²²⁸

The third type of photocatalysis is energy transfer, in which energy is transferred from the excited-state photocatalyst to a substrate by the generation of an excited-state of the organic substrate. One example of this mechanism is the photosensitised generation of singlet oxygen ($^1\text{O}_2$) (Figure 5.1.1). Firstly, the photosensitiser is excited

via a photon transition ($h\nu$) from the ground state, S_0 , to a singlet excited state S_n . Then the S_n state relaxes to the lowest excited singlet state of the photosensitiser S_1 . Intersystem crossing **ISC** generates a triplet excited state (T_1) of the photosensitiser. The lifetime of the T_1 state is longer (typically microseconds) than that of the S_1 state (typically nanoseconds), which allows this excited state of the photosensitiser to react with the substrate in two ways. The first proceeds via hydrogen-atom abstraction or electron-transfer between the excited photosensitiser and the substrate, yielding free radicals that react with oxygen to form active oxygen species, such as the superoxide radical anion. The other way is via an energy transfer process during a collision of the excited photosensitiser with triplet oxygen ($^3O_2$), generating singlet oxygen ($^1O_2$).

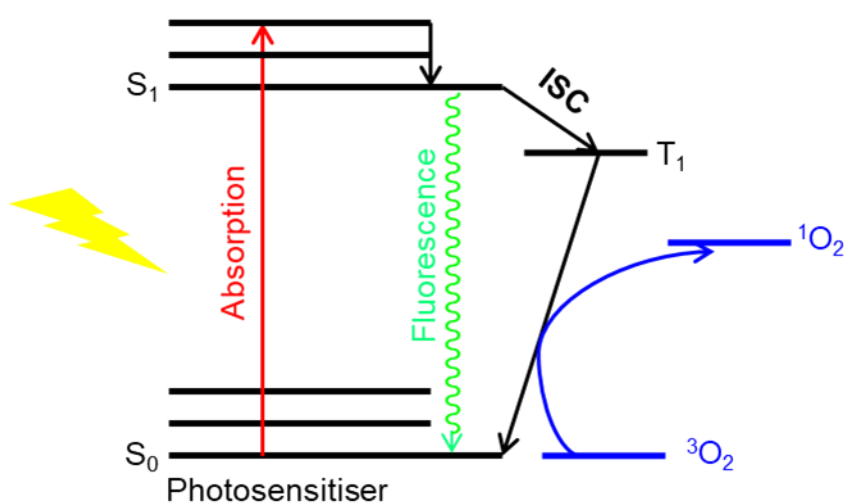


Figure 5.1.1 Photosensitised generation of singlet oxygen $^1O_2$.

Singlet oxygen is an excited state of molecular oxygen. The ground state of molecular oxygen has two electrons with parallel spin in two separate π 2p* orbitals. When molecular oxygen (triplet oxygen) is excited, the two electrons can either occupy one π 2p* orbital simultaneously with opposite spin, or occupy two separate π 2p* orbitals, again with opposite spins. This generates two singlet excited states (Figure

5.1.2).²²⁹ Two kinds of excited singlet states, $^1\Sigma_g^+$ ($158 \text{ kJ}\cdot\text{mol}^{-1}$) and $^1\Delta_g^+$ ($92 \text{ kJ}\cdot\text{mol}^{-1}$) both of which have higher energy than that of the triplet ground state.²³⁰

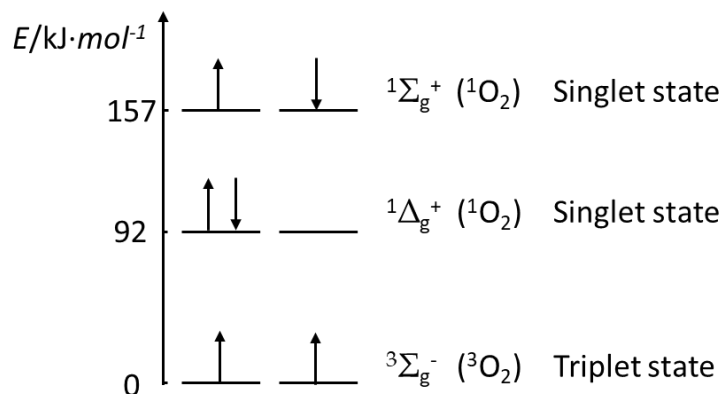


Figure 5.1.2 The triplet state and singlet states of molecular oxygen.²³⁰

Singlet oxygen is found to be *ca.* 1 V more oxidizing than molecular oxygen, and can oxidize substrates that are unaffected by oxygen in its ground state.^{229, 230} Therefore singlet oxygen is significantly more electrophilic than triplet oxygen, reacting rapidly with unsaturated bonds to form carbon-oxygen or heteroatom-oxygen bonds. This makes singlet oxygen a versatile synthetic reagent and several reviews have summarised the applications of singlet oxygen in organic synthesis.^{82, 92, 231}

For organic reactions involving singlet oxygen, there are several issues that need to be considered: (i) How to generate sufficient singlet oxygen? (ii) The lifetime of singlet oxygen varies in different solvents. (iii) Safety concerns when operating a reaction involving organic reagents and an excess of oxygen.

To improve the production of singlet oxygen, the key issue is to maximise the absorption of photons. As discussed in Section 1.2.3, continuous flow processes have unique advantages to improve the efficiency of irradiation. According to the Bouguer-Lambert-Beer law, the radiation intensity will decrease in solution further away from

the light source due to the absorption of light by molecules close to the light source. This means that for a batch reaction, the light intensity rapidly decreases from the outside surface towards to the centre. However, for a flow reactor, especially a microflow reactor, the diameter of reactor is much smaller than a batch reactor, which should keep the radiation distribution more uniform, and thus improve the absorption of photons through the reactor. Moreover, as singlet oxygen is a strong oxidizing agent, continuous transfer of reagents and products through a flow process could reduce the chance of overreaction and side products generation.

As an excited state of molecular oxygen, the lifetime of singlet oxygen is quite short (usually on a μs scale) and depends significantly on both temperature and solvent. Ogilby *et al.* carried out detailed research into the influence of temperature on the deactivation of singlet oxygen in a number of common solvents.²³² This study indicated that the lifetime of singlet oxygen is longer at low temperature, and decreases with an increase in temperature. The temperature effect is especially obvious in D_2O , toluene- d_8 , benzene- d_6 . In toluene- d_6 , the lifetime of singlet oxygen is 303 μs at 10 $^\circ\text{C}$, decreasing dramatically to 127 μs when the temperature is raised to 80 $^\circ\text{C}$. Therefore, to keep the desired singlet oxygen reactivity, reactions need to be carried out at stable low temperatures. However, for a photoreaction, the light irradiation can generate a lot of heat during the reaction which needs to be removed. Thus efficient heat transfer is important for photo-oxidation reactions with singlet oxygen. As discussed in Section 1.2.2, heat transfer in a continuous flow process is more efficient than in a batch reactor. This is because the reagents and products which are flowing through the reactor can continuously remove some of the heat during reaction, and the diameter of a flow reactor is relatively smaller than a batch reactor, creating a large surface area to volume ratio and avoiding local overheating to keep a uniform and stable temperature.

Beside of the temperature influence, the lifetime of singlet oxygen is also significantly solvent dependent. Table 5.1.1 summarises the lifetime of singlet oxygen in different solvents, where the lifetime of singlet oxygen varied from 59 ms in carbon tetrachloride CCl₄ to 3 μ s in water.^{233, 234}

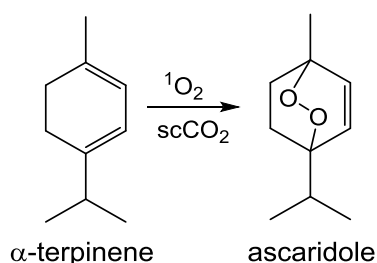
Table 5.1.1 The lifetime of singlet oxygen in different solvent.²³³⁻²³⁵

Solvent	Lifetime of ¹ O ₂ (μ s)
carbon tetrachloride	59000
hexafluorobenzene	21000
chloroform-d	7000
acetone-d ₆	992
benzene-d ₆	681
chloroform	229
dichloromethane	99
acetonitrile	77
deuterium oxide	68
acetone	51
ethyl acetate	45
benzene	30
toluene	29
methanol	10
water	3

In addition to the common solvents mentioned above, Wilkinson *et al.*²³⁶ have investigated the lifetime of singlet oxygen in supercritical carbon dioxide (scCO₂). These results showed that singlet oxygen can be efficiently sensitized in scCO₂, and that it has a reasonably long lifetime of 5.1 ms at 41 °C and 147 bar. This means that scCO₂ is a good solvent for the generation of singlet oxygen. Supercritical CO₂, is a fluid state of CO₂ when it is compressed to higher than its critical pressure (73.9 bar) while also being above the critical temperature of 31.1 °C, and it displays properties

which are a mixture of those normally associated with gases (high diffusivity) and liquids (solvent power of a light liquid alkane).^{133, 237, 238} Such properties could overcome the mass-transfer limitation between gaseous oxygen and the organic reagents, improving the reaction processing.

In addition, CO₂ is fully oxidised and hence is a safe and inert solvent for oxidative reactions with high concentrations of oxygen and organic reagents, where scCO₂ can dilute the reagent mixture and keep the system below explosion limits. Thus, scCO₂ is considered to be a promising solvent for singlet oxygen reaction.



Scheme 5.1.3 Photo-oxidation of α -terpinene to ascaridole with singlet oxygen in scCO₂.²³⁹

Previous work carried out at Nottingham the into singlet oxygen syntheses in scCO₂ has included homogeneous and heterogeneous reactions in both batch reactors and continuous flow processes. The initial investigation was done by Bourne *et al.*,²³⁹ who explored the photo-oxidation of α -terpinene to ascaridole with singlet oxygen in scCO₂. This study was carried out in a high pressure spectroscopic cell (total volume 2 cm³) with calcium fluoride windows, using a perfluorinated porphyrin which is soluble in high pressures of scCO₂ as a photosensitiser. Quantitative photochemical oxygenation of α -terpinene was achieved in less than 3 min.

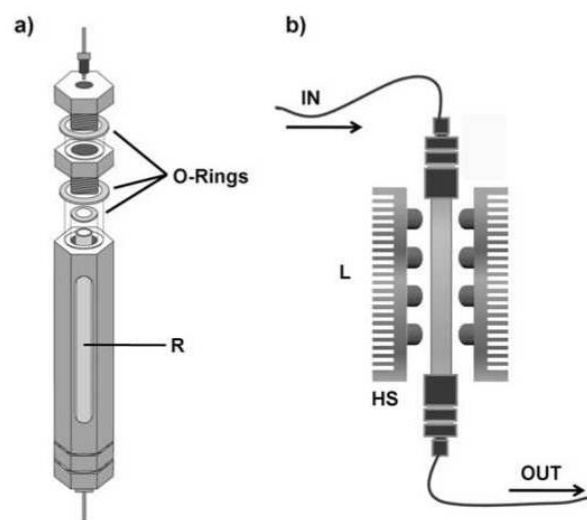
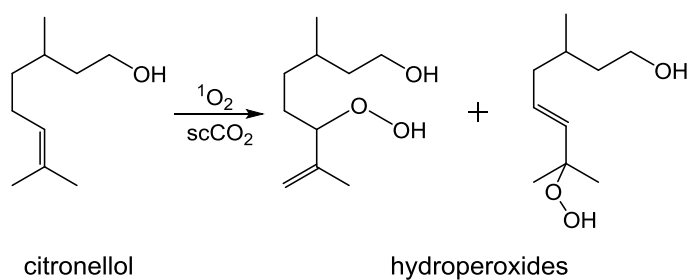


Figure 5.1.3 Schematic diagram of the first generation continuous photoreactor designed in the University of Nottingham. a) Sapphire tube reactor **R**, which is held in place by a pair of EPDM rubber O rings and connected to the apparatus by a 1/8 inch Autoclave Engineering fittings. b) Irradiation of the sapphire tube reactor with two LED arrays **L**. Picture is adapted from reference.²⁴⁰

This success encouraged further study of this reaction, including scaling-up to a continuous flow process.²⁴⁰ The first generation of an in-house designed continuous reactor (total volume 5.7 mL and the irradiated volume 4.1 mL), illuminated by high-power visible-light-emitting diodes (LEDs), as shown in Figure 5.1.3, was used to perform the photo-oxidation of α -terpinene to ascaridole in scCO₂. The reaction was carried out over 8 hours without a change in efficiency and yielded 96 mL of ascaridole. This demonstrated a successful 3000-times scale-up, compared to the previous work carried out in a high pressure spectroscopic cell. This flow reactor was then applied to the photo-oxidation of citronellol (Scheme 5.1.4), the first stage in the synthesis of Rose Oxide, a fragrance of commercial value. Compared to a continuous microreactor with a tungsten lamp or a conventional Schlenk reactor under LED irradiation,²⁴¹ the combination of millilitre-scale flow reactor and LED irradiation can provide a substantial improvement in efficiency.



*Scheme 5.1.4 Photo-oxidation of citronellol to hydroperoxide products with singlet oxygen in scCO₂.*²⁴⁰

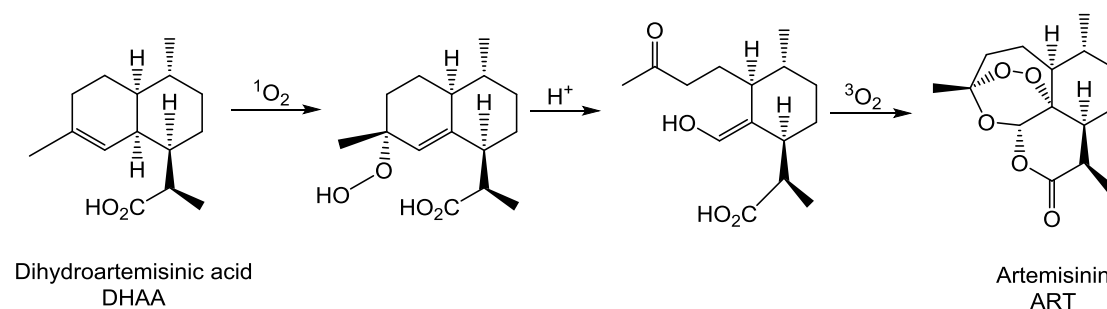
Despite the success of photo-oxidation in scCO₂, there remains the challenge of how to recycle expensive photosensitisers. Two different recycling strategies have previously been investigated at Nottingham. The first strategy was adapting a fluorous biphasic system to continuously recycle the homogeneous photosensitiser.¹¹³ Further details has been described in Section 1.2.4 of the Introduction Chapter of this Thesis, as an example to demonstrate the recycling of homogeneous catalysts in a continuous flow process. With this method, the solution of photosensitiser can be recycled 10 times and maintain 75% of its catalytic activity compared with fresh catalyst.

Another method of photocatalyst recycling is to immobilize the photosensitiser on solid supports, such as boehmite,^{242, 243} polystyrene,²⁴⁴ and silica,^{245, 246} to form heterogeneous photocatalysts to allow easy catalyst recovery and recycling. The combination of continuous flow processes with heterogeneous photocatalysts could not only avoid the need to the separate the photosensitiser from products that are usually thermally sensitive, but also reduce the amounts of photosensitiser required for scale-up.

Han *et al.* have demonstrated the immobilisation of several photosensitisers onto both polymer and aerogel supports, for the photochemical generation of singlet oxygen in scCO₂.²⁴⁷ The immobilized photosensitisers showed high activity and an acceptable

lifetime (at least 5 hours) for the photo-oxidation of α -terpinene to ascaridole (Scheme 5.1.3), and of citronellol to hydroperoxide products (Scheme 5.1.4) in continuous flow processes. The most effective photosensitiser was a covalently coupled analogue of tetradi(2,6)chloro-phenylporphyrin (TDCPP) on polyvinyl chloride (PVC).

With the success of singlet oxygen reactions, carried out in continuous flow processes in scCO_2 with either homogeneous or immobilized heterogeneous photosensitisers, this approach was then applied to the synthesis of artemisinin (ART) which is an important antimalarial drug.



Scheme 5.1.5 Semi-synthesis of artemisinin (ART) from dihydroartemisinic acid (DHAA).¹⁴⁴

Artemisinin was first discovered by a Chinese chemist, Tu Youyou, who was awarded half of the 2015 Nobel Prize in Medicine for her discovery.²⁴⁸ Currently the supply of ART is still obtained by isolation from the plant *artemisia annua*, which is low yielding and does not always meet demand. A semi-synthetic manufacturing process from a much-less complex molecular precursor, dihydroartemisinic acid (DHAA), which can be extracted from the same plant in higher yields or produced by engineered yeast, could become a promising alternate route for ART production (as shown in Scheme 5.1.5).^{249-252.}

This semi-synthesis of ART has been performed by Amara *et al.* at the University of Nottingham, by using the second generation of a high pressure continuous

flow reactor, designed in-house by Dr Jessica Bellamy and Dr Richard Bourne, which was described in Section 2.2 of the Experimental Chapter. This new photoreactor has a small footprint and allows for the incorporation of different lengths of sapphire tubing and, hence, different reactor volumes, which increases the versatility of the reactor.

The comparison of the second-generation high-pressure continuous photoreactor *versus* the original design was carried out by conducting the model photo-oxidation reaction of α -terpinene to ascaridole. With the original reactor, a full conversion of α -terpinene was obtained at a CO₂ flowrate of 0.80 mL/min and an organic flow rate of 0.08 mL/min, which gave a yield of ascaridole of 96%. Increasing the flowrates of the CO₂ to 1 mL/min and organic reagent to 0.1 mL/min, the conversion of α -terpinene decreased due to the shorten of the resident time. Same reaction was carried out in the new photoreactor, which achieved a 100% yield of ascaridole under the same conditions. Besides, with threefold flowrates, such as the CO₂ flowrate was 3.0 mL/min⁻¹ and the organic flowrate was 0.3 mL/min, the reaction conversion only dropped to ca. 95% with a yield of ascaridole of 90%, which indicated that the new design was ca 3.5 times higher than the first generation.¹⁴⁵ The same, second generation photoreactor was used in this chapter to test the activity of immobilised photosensitisers.

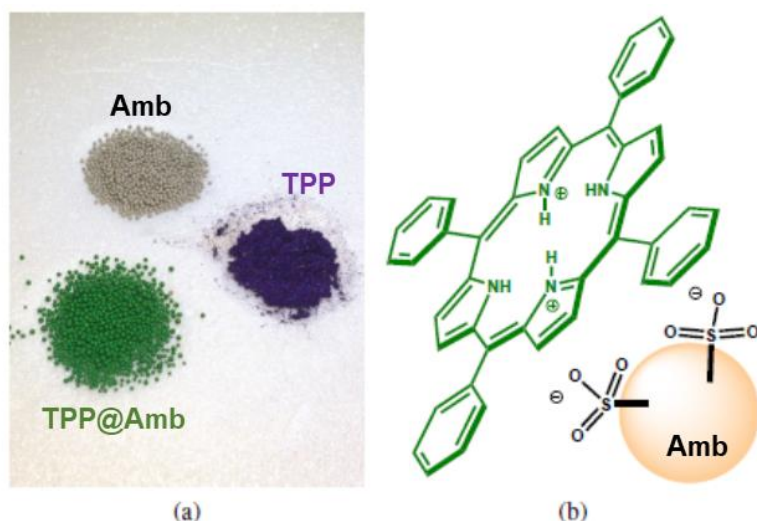


Figure 5.1.4 Photograph (a) and scheme(b) of a porphyrin TPP immobilised on Amberlyst-15. (a): Amberlyst-15 beads are a beige colour and the neutral porphyrin TPP is purple, but after immobilisation on the Amberlyst-15 beads the porphyrin becomes green (the colour of the protonated porphyrin). (b): A schematic showing the acid-base interaction which is presumed to result in the binding of porphyrins, such as TPP, to the Amberlyst-15 beads. Reproduced from reference.¹⁴⁵

In addition to the improved photoreactor, a novel heterogeneous dual-function photocatalysts was developed by immobilising the photosensitiser meso-tetraphenylporphyrin (TPP) on Amberlyst-15 (Amb) beads as shown in Figure 5.1.4. The immobilised porphyrin has both the Brønsted acidic and photo-catalytic function and can readily convert DHAA to ART in one step, without the need for further heating of the solution under an atmosphere of O₂.¹⁴⁴

A number of different conditions were investigated using this bifunctional catalyst TPP@Amb for the semi-synthesis of ART from DHAA, in the new high pressure continuous photoreactor. A near 100% conversion of DHAA and around 50% yields of ART were obtained. It is noted that the nature of this bifunctional TPP@Amb, which performs the photo-oxidation step under acidic conditions, could minimize the formation of by-products arising from elimination of H₂O₂ from reaction intermediates and hence improve the selectivity for the ART.¹⁴⁴

This continuous photochemical process, using dual-function heterogeneous photocatalysts, which can achieve the formation of ART in a single flow process, is likely to be a promising route for the green and sustainable synthesis of ART in the future. However, when using an immobilised catalyst, leaching of the catalyst support is an essential issue. In the continuous flow process described above, there was obvious TPP leaching, as a pink solution (colour of free TPP) was collected after the colourless reagent mixture passed through the fixed catalyst bed of Amberlyst-15 supported TPP.

In an attempt to reduce the chance of leaching, in this work, Nb solid acids (**NbP** and **NbO**), which show stronger acid activity than Amberlyst-15, were used as alternative acid supports to immobilise the photosensitiser TPP. The stability and activity of the Nb solid acid supported TPP catalysts were then tested in continuous photo-oxidation reactions.

5.2. NbP-Supported Photosensitiser TPP

The exploratory immobilisation of photosensitiser meso-tetraphenylporphyrin TPP on solid acid **NbP** was carried out at room temperature. The support, **NbP** (1 g) was put into a TPP solution (30 mg TPP in 15 mL ethyl acetate EtOAc) and the mixture was stirred for 24 hours. The powder was then separated from the solution by filtration and washed with 20 mL EtOAc. After that, the TPP@**NbP** powder was dried in a fume hood overnight.

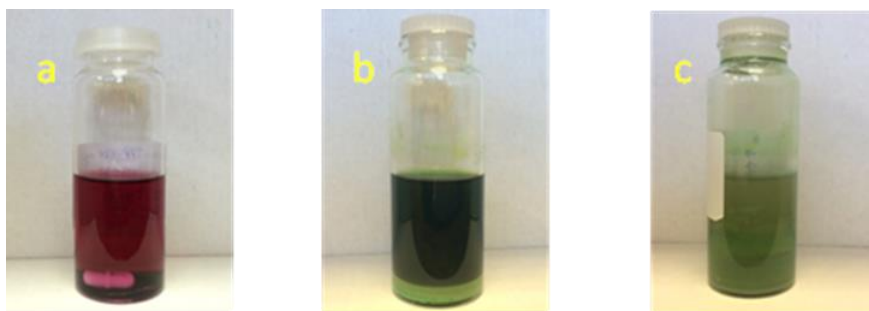


Figure 5.2.1 The immobilisation of TPP on **NbP** catalyst. a) 30 mg TPP in 15 mL EtOAc (not completely dissolved); b) 1 g **NbP** was added into the TPP solution, and the solution becomes green immediately; c) After being stirred for 24 hours the **NbP** powder becomes green and no undissolved TPP was left.

Figure 5.2.1 shows the immobilisation process for TPP on **NbP** catalyst. *Picture a* shows the TPP solution in ethyl acetate, which was a purple colour and still had undissolved TPP on the bottom of the vial. After adding 1 g **NbP** catalyst (white powder), the solution immediately turned to dark green (the colour of protonated TPP) (*Picture b*). Stirring for 24 hours (*Picture c*), the white **NbP** powder became green, indicating that TPP had successfully loaded onto the **NbP** catalyst. In addition, the supernatant layer had become much lighter in colour than before and there was no solid TPP was left in the vial, which suggests that most of the TPP had been immobilised on the **NbP**. The TPP and **NbP** before and after this successfully immobilisation are shown in Figure 5.2.2



Figure 5.2.2 Photosensitiser TPP (purple), **NbP** solid acid (white) and bifunctional catalyst TPP@**NbP** (green).

In addition to recovering the catalyst, The EtOAc filtrate from immobilisation and the EtOAc used to wash the catalyst were retained, and as can be seen in Figure 5.2.3 were coloured. The filtrate colour indicated that, when using EtOAc as the immobilisation solvent, not all the TPP (30 mg) had been immobilised on the **NbP** (1 g) and that the loaded TPP was not stable to leaching. Given this, the next steps are to optimise the immobilisation conditions, and to test the activity of TPP@**NbP** for photo-oxidation reactions.



*Figure 5.2.3 The collection of filtrate and of washing EtOAc solution after the immobilisation process, The coloured solution indicated that not all the TPP was immobilised on the **NbP** catalyst and that there was TPP leaching from the **NbP** support.*

5.2.1 Comparison of Immobilisation Solvents

Five different solvents were investigated, methanol (MeOH), ethanol (EtOH), ethyl acetate (EtOAc), toluene (Tol) and dimethyl carbonate (DMC). The TPP solutions were first made by adding 30 mg TPP to 5 mL of each solvent (Figure 5.2.4). From the colour of the solution, TPP showed higher solubility in Tol than the other four solvents. Among these solutions, TPP in MeOH solution presented a brown colour indicated MeOH was not a suitable solvent for the immobilisation, so it was not used in the further study.



Figure 5.2.4. 30 mg TPP in 5 mL of different solvents (methanol (MeOH), ethanol (EtOH), ethyl acetate (EtOAc), toluene (Tol) and dimethyl carbonate (DMC)). TPP has highest solubility in Tol, and the brown MeOH solution is not ideal solution for further investigation.

The other four solutions (Tol, EtOAc, DMC and EtOH) were then topped up to 15 mL separately, but there was still undissolved TPP in the vials. **NbP** (1 g) was then put into each solution (30 mg TPP in 15 mL of each solution), and the mixture was started to be stirred. Figure 5.2.5 shows the process of TPP immobilisation in different solvents. Pictures in [Column A](#) displays the colour just after the **NbP** catalyst had been added into the solutions. The white **NbP** powder in Tol solution became dark green immediately. By contrast, it was less coloured in both DMC and EtOAc than in Tol. The EtOH solution turned to light green but the colour of **NbP** catalyst did not change.



*Figure 5.2.5 The immobilisation process of TPP on **NbP** catalyst in different solvents (30 mg TPP and 1g **NbP** catalyst mixed in 15 mL of each solvent separately: Tol, EtOH, DMC and EtOAc. Column A: just adding **NbP** catalysts; Column B: stirred for 5 min; Column C: stirred for 2 hour; Column D: stirred for 24 hour. The immobilisation processed in Tol finished quickest among these four solvents. And the immobilisation did not accomplish in EtOH after 24 hour.*

After being stirred for 5 min (**Column B**), the Tol solution became green, and the **NbP** catalyst turned to much darker than before. The solutions in DMC and EtOAc turned from dark green to purple, the original colour of TPP solution, while the **NbP** catalyst became darker. The EtOH solution did not undergo any obvious change. Two hours later (**Column C**), the immobilisation of TPP in Tol solution was almost done, as the colour of the solution became quite clear and the **NbP** powder was dark green. However, the EtOH solution was unchanged, and there was still undissolved TPP in the solution. After 24 hours immobilisation (**Column D**), both DMC and EtOAc solution

turned from purple to light yellow, and the **NbP** catalyst assumed a green colour. However, in EtOH there was still undissolved TPP, and the immobilisation did not succeed.

After the immobilisation, all of the TPP@**NbP** powders were filtered and then washed with 20 mL of the appropriate solvent. The filtrate and washing liquid were collected for UV-vis analysis (Figure 5.2.6).

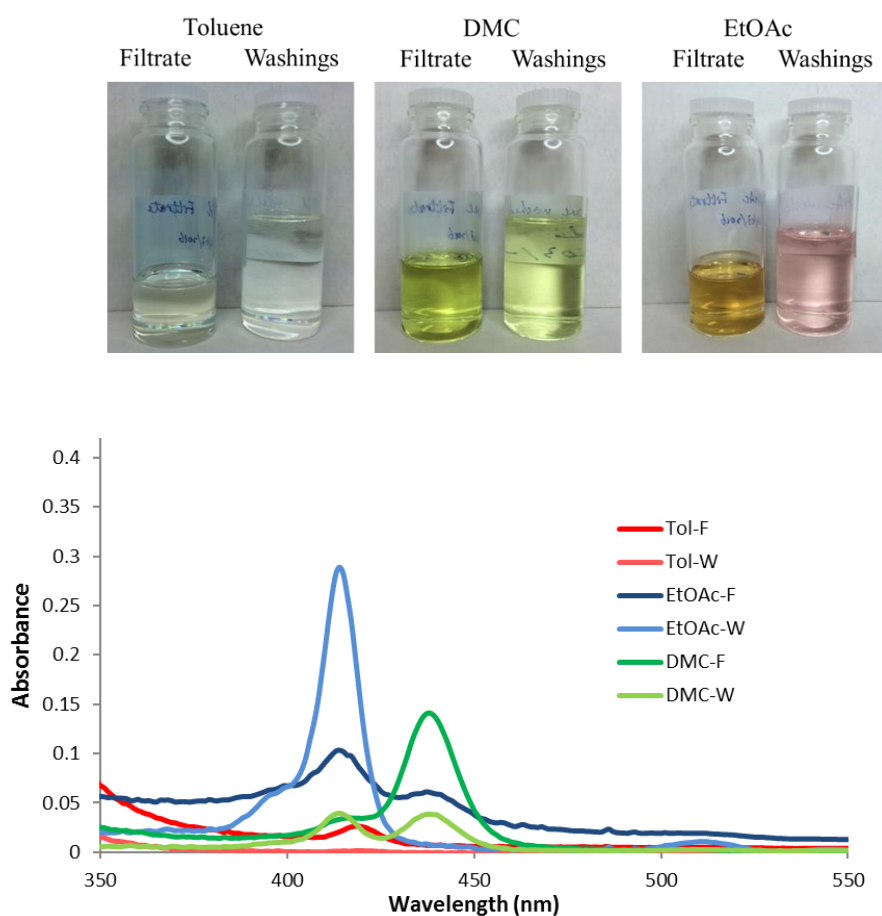


Figure 5.2.6. The filtrates and washing liquids after the immobilisation in different solvents (toluene (Tol), dimethyl carbonate (DMC) and ethyl acetate (EtOAc)) and UV-vis absorbance spectrum of each solution. F: filtrate; W: washing

The catalyst powder in EtOH powder was quite pale and formed a suspension which passed through the filter and cannot be filtered. This might be due to the interaction between the **NbP** solid acid and the EtOH is stronger than the photosensitiser TPP,

resulting in the failure of TPP immobilisation in EtOH. As the EtOH is not an ideal solvent for the TPP immobilisation, the further study focused on Tol, EtOAc and DMC.

As shown in Figure 5.2.6 (a), both Tol filtrate and washing liquid were colourless, the UV-vis spectrum (d, red line and light red line) that confirmed trace amounts of TPP were found in the UV spectrum indicating that almost all the TPP (30 mg) had been immobilised on 1 g **NbP** in Tol.

By contrast, both DMC and EtOAc filtrates were coloured in green (i.e. they contained protonated TPP) or yellow (a mixture of pink free TPP and green protonated TPP), which are also observed in the corresponding UV-vis spectrum that the B-band of the free base TPP at 417 nm and protonated TPP at 438 nm. This means that when using DMC and EtOAc as solvents after 24 hours immobilisation there is still some TPP (free or protonated) can not be loaded on the 1g **NbP**. This might be due to the polarity of solvent and strong hydrogen bonding between the solvent and **NbP** acid sites. This was more obvious when using the high polarity solvent EtOH with a stronger hydrogen bonding ability, the strong interaction between **NbP** and EtOH possibly impeded the TPP immobilisation being achieved and furthermore the **NbP** can not be filtered from EtOH.

Table 5.2.1 Solubility parameter²⁵³

Solvents	Nonpolarity	Polarity	Hydrogen Bonding
	$MPa^{1/2}$		
Toluene	36.8	2.9	4.3
Dimethyl carbonate	35.6	19.6	10.4
Ethyl acetate	32.3	10.8	14.7

Table 5.2.1 shows the properties of solvents used in the immobilisation processes.²⁵³ The polarity and hydrogen bonding ability of either DMC or EtOAc is

higher than Tol, which results in the lower efficiency of TPP immobilisation in either DMC or EtOAc than in Tol. This also been shown in the final products.

The **NbP** supported TPP that made in different solvents are shown in Figure 5.2.7. After 24 hour immobilisation, TPP@**NbP** powder appears dark brown when the immobilisation was carried out in Tol. In contrast, using EtOAc and DMC as solvents, the **NbP** supported TPP shows green colour, colour of protonated TPP.

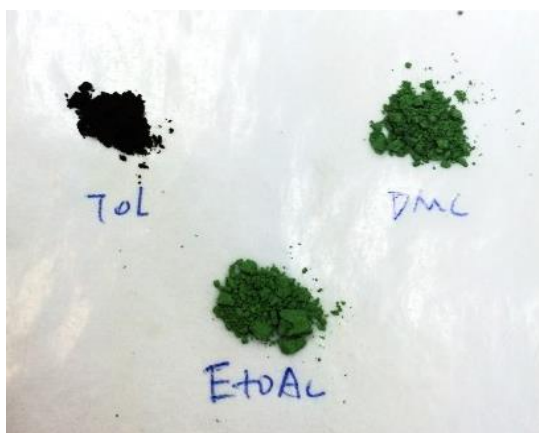


*Figure 5.2.7 TPP@**NbP** made in different solvents (Tol, DMC and EtOAc).*

To identify the photocatalytic property of supported TPP, UV–Visible diffuse reflectance spectrum (UV–Vis DRS) of TPP@**NbP** synthesised in different solvents have been recorded (Figure 5.2.8). All the samples exhibit strong absorption band at around 438 nm ascribed to the di-protonated TPP, which indicated that the TPP immobilisation processes has succeeded. By comparison, using Tol as solvent, the TPP@**NbP** exhibited a stronger di-protonated TPP absorbance (438 nm) than using EtOAc or DMC. This confirmed that there was more TPP loaded onto **NbP** in Tol than in either EtOAc or DMC, and that the immobilisation that carried out in Tol is more efficient than in either EtOAc or DMC.

Besides, a new absorption around 516 nm was observed in the spectrum TPP@NbP made in Tol. According to the literature, this strong absorption band at 516 nm could be due to the formation of a complex of TPP dimer with metal.²⁵⁴ It has been reported that the mono-protonated TPP dimer did coordinate with transition metal ions such as Mn^{2+} or Rh^{3+} , and the complexes exhibited absorption around 500 nm.²⁵⁵ In addition, for TPP@NbP made in EtOAc and DMC, the spectrum exhibit a band at 475 nm, which is proposed to be mono-protonated TPP dimers.

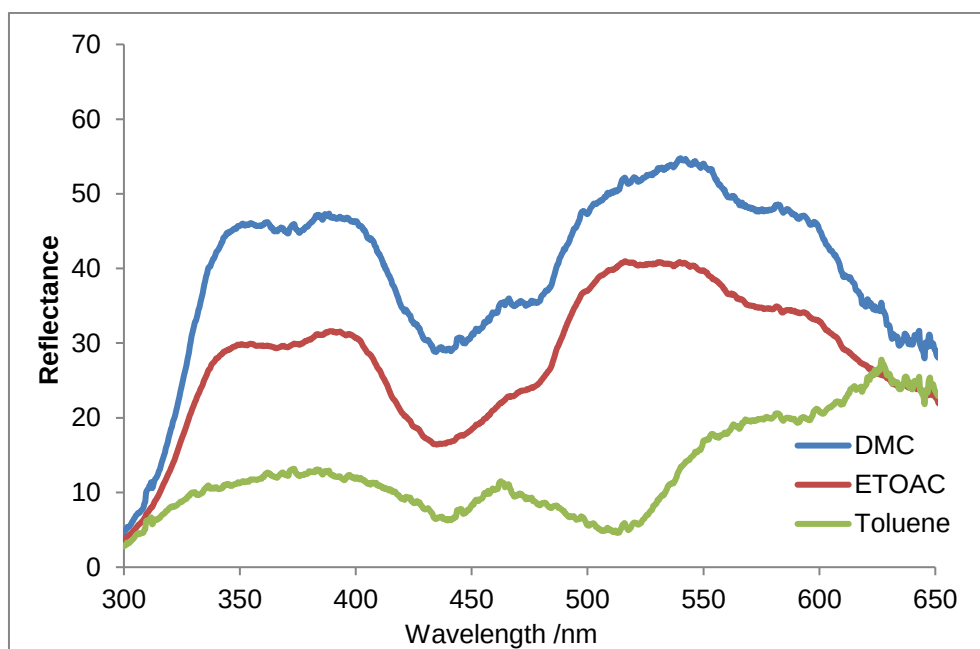


Figure 5.2.8 The UV-Visible diffuse reflectance spectrum of NbP supported TPP. The immobilisations were carried out with 30 mg TPP mixed with 1g NbP catalyst in different solvents for 24 hour.

5.2.2 The Amount of TPP for Immobilisation

As discussed above, Tol showed a better performance for the TPP immobilisation process than EtOAc and DMC. With a view to investigating the maximum amount of TPP that could be immobilised on NbP, different amounts (15 mg, 30 mg, 45 mg and 60 mg) of TPP were used to load onto 0.5 g NbP in 7.5 mL Tol. After

the immobilisation, the filtrates were collected (Figure 5.2.9) and analysed by UV-vis spectroscopy (Figure 5.2.10).

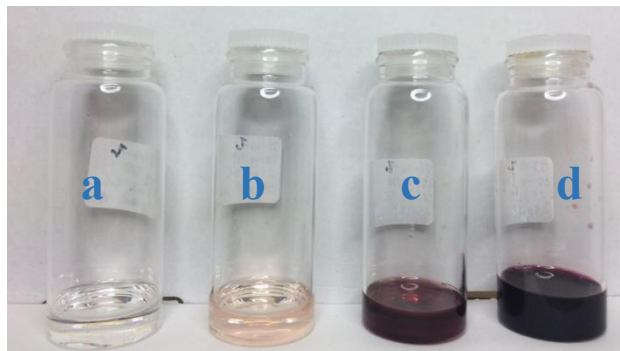


*Figure 5.2.9. Tol filtrates after TPP immobilisation. The immobilisations were carried out with different amount (a: 15 mg, b: 30 mg, c: 45 mg, d: 60 mg) of TPP mixed with 0.5 g **NbP** in (7.5 mL) Tol for 24 hour.*

Figure 5.2.9 (a) shows the Tol filtrate after immobilised 15 mg TPP on 0.5 g **NbP** catalyst, which is colourless. Increasing the TPP amount to 30 mg, the filtrate is light pink (b). The Tol filtrate became purple when the amount of TPP for immobilisation raised to 45 mg (c). Therefore, the maximum amount of TPP that can be immobilised on 0.5 g **NbP** should be around 30 mg.

UV-vis spectrum analysis confirmed the above conclusion (Figure 5.2.10). For immobilisation of 15 mg TPP, no absorbance appear in spectra (blue line). Then increasing amount of TPP to 30 mg, trace absorbance was observed (red line). After the amount of TPP raised to 45 mg, the absorbance (Soret band at 432 nm and 3 Q bands) increased dramatically. Thus, the maximum amount of TPP that can be immobilised on 0.5 g **NbP** is around 30 mg (60 mg/g TPP@**NbP**).

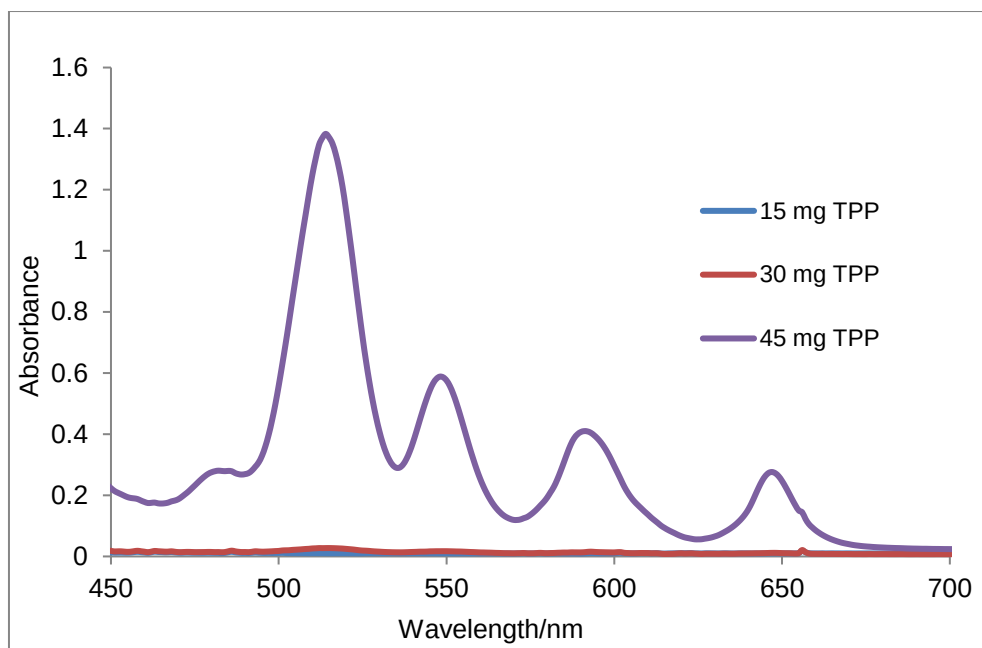


Figure 5.2.10 The UV-vis spectrum of Tol filtrates after different amounts of TPP (15 mg, 30 mg, 45 mg) immobilised on 0.5 g **NbP** catalyst. All the immobilisations were carried out in 7.5 mL Tol for 24 hour.

The TPP@**NbP** catalysts made with different amount of TPP are shown in Figure 5.2.11. After 24 hour immobilisation, the TPP@**NbP** made with 15 mg TPP is brown colour (a), and with 30 mg TPP is greenish black (b). When the TPP amount raised above 45 mg, the TPP@**NbP** is dark green (c,d).

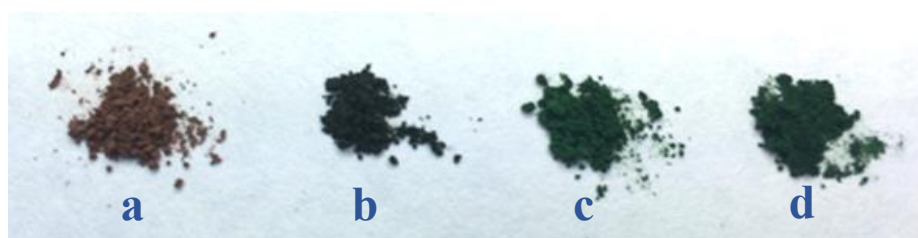


Figure 5.2.11. **NbP**-supported TPP synthesised in Tol. The immobilisations were carried out with different amount of TPP (a:15 mg, b:30 mg, c:45 mg, d:60 mg) mixed with 0.5 g **NbP** catalyst in (7.5 mL) Tol for 24 hour.

TPP@**NbP** had been examined by UV-DRS (Figure 5.2.12). The di-protonated TPP absorbance at 438 nm is dramatically increased when the TPP amount for

immobilisation raised from 15 mg to 30 mg (blue line to red line). Then no further absorbance increasment is observed at 438 nm when more TPP was used in the immobilisation. This also confirmed that the maximum TPP that can be immobilised on 0.5 g **NbP** is around 30 mg.

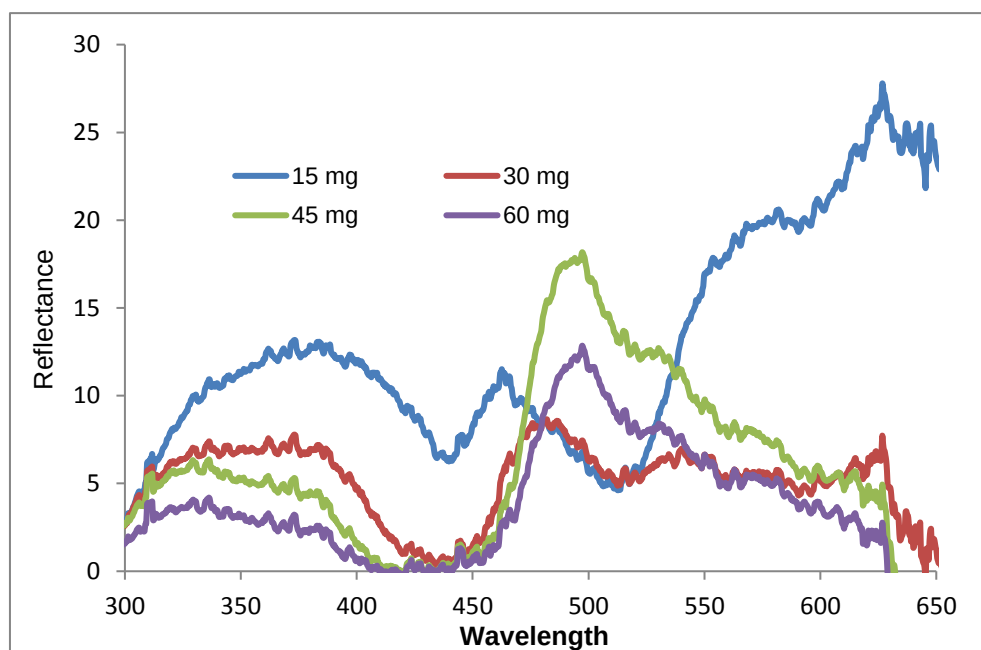


Figure 5.2.12. The UV–Visible diffuse reflectance spectrum of **NbP**-supported TPP. The immobilisations were carried out with the different amount of TPP (15 mg, 30 mg, 45 mg and 60 mg) mixed with 0.5 g **NbP** in (7.5 mL) Tol for 24 hour.

The strong absorption band at 526 nm, which is proposed to be the complex of a TPP dimer with metal, was observed in both using 15 mg and 30 mg TPP for immobilisation (blue and red line). But for the immobilisation of 45 or 60 mg TPP on 0.5 g **NbP**, this band disappeared. Instead, a high absorbance at 638 nm was observed when the amount of TPP is more than 30 mg, which is corresponded to mono-protonated TPP dimer (red, green and purple line).

This indicated that a item loading less TPP (15 mg) on **NbP** (0.5 g), most TPP was di-protonated. As the acid sites on the **NbP** is the same, the extra amount TPP tended to mono-protonated.

5.2.3 Immobilisation Time

As shown in Figure 5.2.5, the TPP immobilisation process is quicker in Tol (less than 2 hours) than in either DMC or EtOAc (24 hours).

One possible reason might be differences in the hydrogen bonding ability and polarity of the solvents, which has negative influence on the TPP immobilisation process due to the interaction between solvent and the surface of the **NbP** solid catalyst. Another possible reason could be the different concentrations of TPP in the various solvents. As the TPP solutions used for the immobilisation processes all contained undissolved TPP, these solutions were saturated. The solubility of TPP in different solvents might result in different immobilisation times. Therefore, the solubility was quantified by UV-vis spectrometry (*Error! Reference source not found.*). The results are shown in Table 5.2.2. As shown in Table 5.2.2, the solubility of TPP in Tol (5×10^{-3} mol/L) is much higher than in DMC (3×10^{-4} mol/L) or EtOAc (6×10^{-5} mol/L), which results in a higher concentration of TPP than the other two solvents, which promoted TPP immobilisation in Tol.

Table 5.2.2 TPP solubility in different solvents calculated by UV spectrometer.

Solvents	ϵ	Solubility
Toluene	2.0×10^4 L/g·cm	5×10^{-3} mol/L
Dimethyl carbonate	5.1×10^5 L/g·cm	3×10^{-4} mol/L
Ethyl acetate	5.0×10^6 L/g·cm	6×10^{-5} mol/L

When using Tol as solvent for the TPP immobilisation process, different mixing times resulted in different appearances of TPP@NbP. Indeed, the immobilisation of 30 mg TPP on 1 g NbP catalyst in 15 mL Tol could be completed in 0.5 hour, and the green coloured TPP@NbP could be collected (Figure 5.2.13 (b)). As mention in Section 5.2.1, the appearance of TPP@NbP via 24 immobilisation time are brown colour, which is shown in Figure 5.2.13 a).



Figure 5.2.13 TPP@NbP via different immobilisation time. Mixing 30 mg TPP and 1 g NbP catalyst in 15 mL TOL for a) 24 hours shows brown colour; b) 0.5 hour shows green colour.

To investigate the difference in appearance, these two TPP@NbP, were examined by UV-DRS and the results are shown in (Figure 5.2.14). The di-protonated TPP dimer at 438 nm decreases with time, at the same time, the mono-protonated TPP around 465nm increase. This means that, with time, the di-protonated TPP dimer is transformed to mono-protonated, and TPP occupies more acid sites of NbP catalyst with time, which could impact TPP@NbP photoactivity and acidity.

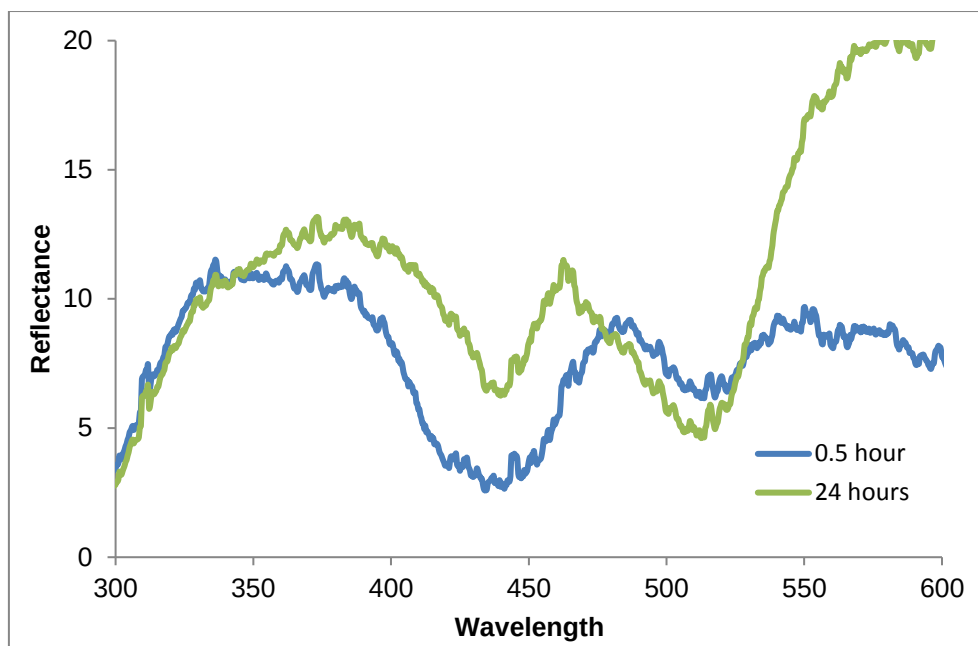
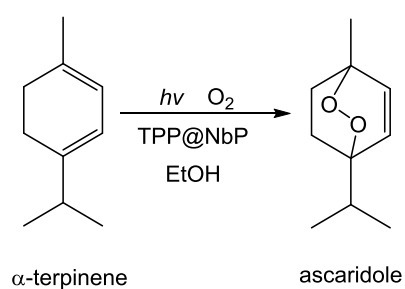


Figure 5.2.14 The UV–Visible diffuse reflectance spectrum of **NbP** supported TPP. 30 mg TPP mixed with 1 g **NbP** in (15 mL) Tol via different times (blue line :0.5 hour; green line 24 hours).

5.2.4. The Activity of NbP-supported TPP for Photo-oxidation

Batch Reaction



Scheme 5.2.1 Photo-oxidation of α -terpinene to ascaridole with singlet oxygen in batch reactor at room temperature with O_2 bubbling using **NbP** supported TPP as photocatalysts.

In order to test the photoactivity of **NbP**-supported TPP, a model reaction, photo-oxidation of α -terpinene to ascaridole, was carried out in a batch reactor. Firstly

α -terpinene (5×10^{-4} mol) and biphenyl (5×10^{-4} mol), which acts as an internal standard, were dissolved into 50 mL ETOH in a two neck flask. Then 0.8 g **NbP** supported TPP was added into the solution. O₂ was bubbled into the mixture and the LED lights were turned on to start the reaction. Samples were taken every 15 mins and analysed by ¹H NMR. To compare the activity between free TPP and immobilised TPP, 24 mg TPP was used as catalyst in a parallel experiment without **NbP**. It is assumed that all of the TPP (30 mg) has been immobilized on **NbP** catalyst (1 g).

Table 5.2.3 The yields of ascaridole catalysed by **NbP**-supported TPP to untreated TPP

Reaction time (min)	Free TPP ^a	NbP -Supported TPP		
		EtOAc ^{a,b,c}	DMC ^{a,b,c}	Tol ^{a,b,c}
15	13 %	35 %	25 %	12 %
30	24 %	53 %	54 %	24 %
45	31 %	65 %	60 %	31 %
60	41 %	65 %	59 %	38 %
75	47 %	64 %	62 %	47 %
90	58 %	64 %	61 %	52 %
105			59 %	57 %
120			62 %	63 %

^a The yields of ascaridole were calculated based on ¹H NMR results.

^b The solvent that was used for the TPP immobilisations.

^c 24 hour immobilisation time

As shown in Table 5.2.3, the activity of TPP@**NbP** that using EtOAc as the immobilisation solvent showed a higher efficiency than using DMC and Tol, which reached the maximum yield 65 % in 45 mins. When using DMC for the TPP immobilisation, the TPP@**NbP** gave the highest yield 62% after 75 min. As for using Tol as immobilisation solvent, the highest yield was 63 % which was after 2 hours reaction. These results showed that a more stable TPP@**NbP** gave a lower efficiency in the photo-oxidation of α -terpinene. Such as **NbP**-supported TPP that was made in Tol,

which showed no leaching in Tol, presented a lower efficiency (reached the highest yield after 2 hours) than using ethyl acetate (obtained the maximum yield in 45 min). The suspected reason might be the unstable TPP leaching caused the higher efficiency that might give a shorter lifetime of the catalyst when the reaction is carried out in flow.

High Pressure Flow Reaction

As TPP@NbP gave a respectable photoactivity for the photo-oxidation of α -terpinene to ascaridole in a batch reactor with bubbling O₂. The next challenge was then to investigate the bifunctional catalysis, photocatalytic and acidic activity of TPP@NbP, for the semi-synthesis of ART from DHAA (Scheme 5.2.2) in a continuous high pressure reactor (Figure 5.2.15).

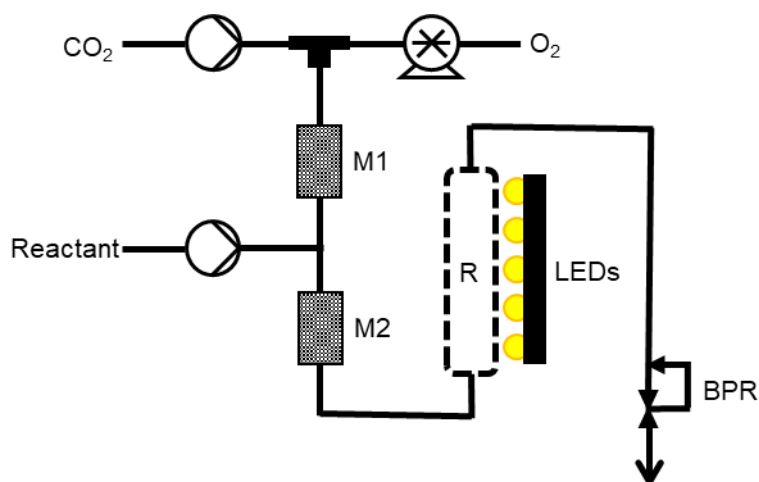
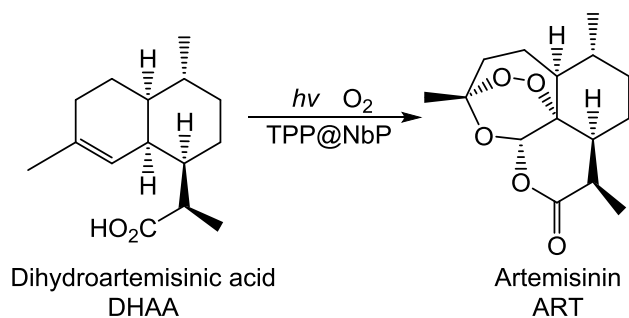


Figure 5.2.15 A simplified schematic of the continuous flow photo-oxidation reactor system, as described in detail in Section 2.2. M, mixer filled with sand; R, reactor filled with bifunctional photocatalyst TPP@NbP and 2mm diameter glass beads.



Scheme 5.2.2 Semi-synthesis of artemisinin (ART) from dihydroartemisinic acid (DHAA) with TPP@NbP bifunctional catalysts.

To compare with TPP supported on Amberlyst 15, the photo-oxidation reactions with TPP@NbP were carried out under the same conditions as previous experiments done in the group with TPP@Amberlyst 15. As NbP supported TPP is a powder, in order to reduce the powder packing during the flow reaction, the reactor was filled with TPP@NbP powder and 2mm diameter glass beads. Besides, up-flow was employed to further decrease the powder pressure building and provide a better mixture.

The continuous photo-oxidation of DHAA to ART was carried out under the conditions: 180 bar, 5 °C, 0.53 mL/min CO₂ and 0.13mL/min DHAA solution (0.55 M in toluene). 1.6 g TPP@NbP (with 48 mg immobilised TPP) and 7 g glass beads (2mm) filled the reactor. The excess of oxidant (O₂) was twofold with respected to DHAA pumped into the system. Biphenyl was used as internal standard. And the results were analysis by ¹H NMR.

After 2 hours reaction, the total yield of ART is 22% with 48% conversion of DHAA. The results are somewhat lower than with TPP@Amberlyst 15 which gave 25 % yield of ART and 63% DHAA conversion. However, in consideration of ART selectivity, the NbP supported TPP has a better performance that can achieve 46% ART selectivity, comparing to with TPP@Amberlyst is 40%. In order to improve DHAA

conversion, the collection was recycled into the flow reaction. However, no obvious improvement was observed.

After the reaction, the out layer of catalyst bed showed noticeable bleaching (Figure 5.2.16). However, no TPP leaching has been observed during the reaction. The bleach probably caused by the strong light source irradiation.

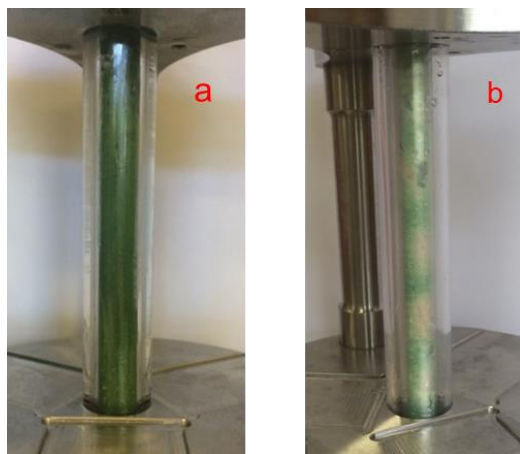


Figure 5.2.16 The comparison of TPP@NbP catalyst bed before (a) and after (b) the reaction.

Further evidence is that the bleach only occurred on the out layer of the catalyst bed where the light source focused, but the inside part is still dark green colour (**Error! Reference source not found.**). This means the photo-oxidation only happened on the out circle of the catalyst bed, the inside catalyst was not involved in the reaction. This also explained why the recycling did not improve the yield of ART.

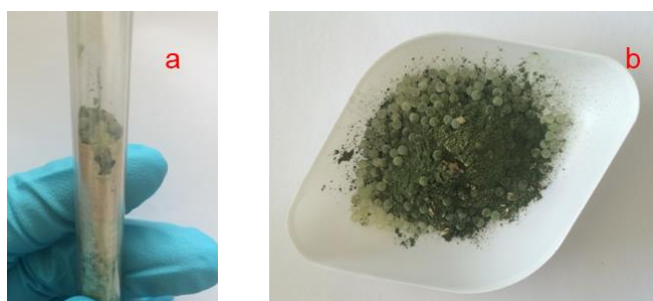


Figure 5.2.17 NbP supported TPP after the reaction. (a) The out layer of the catalyst bed was bleached severely (ivory colour) but (b) the inside part was still a dark green colour.

By contrast, the Amberlyst 15 is small beads which could supply enough interspace to let the light source penetrate through resulting in a high-efficiency. After several recycling, the DHAA could reach a conversion over 98%.¹⁴⁴ Besides, the larger interspace contributed a longer residence time for the reagent. All these gave a better yield of photo-oxidation of DHAA to ATR with TPP@Amberlyst 15.

Even though, the powder **NbP**-supported TPP gave a respectable ART yield at the first run. The next issue is the shape of catalyst. It is much better to use small pellet catalyst. As **NbO** pellets were available in the lab, using **NbO** to support TPP will be discussed in the next section.

5.3. NbO Catalyst Supported TPP



Figure 5.3.1 NbO powder and NbO pellets with graphite as a binder.

Two kinds **NbO** were available in the lab, **NbO** powder and **NbO** pellets with graphite as binder, as shown in Figure 5.3.1. The exploratory immobilisation of TPP was started with **NbO** powder, mixing 1 g **NbO** powder with 30 mg TPP in 15 mL Tol for 24 hours. However, **NbO** powder did not change colour after the mixing indicated that TPP cannot be loaded onto untreated **NbO** powder. As calcination at high

temperature can improve the acidity of **NbO**, **NbO** powder were then calcined at 400 °C for 6 hours and used to support TPP. The calcined **NbO** powder (1g) turned to green colour after 24 hours mixing with TPP solution (30 mg TPP in 15 mL Tol) successfully supported TPP (shown in). However, compared to **NbP**, the amount of TPP that immobilised on calcined **NbO** powder was much less.

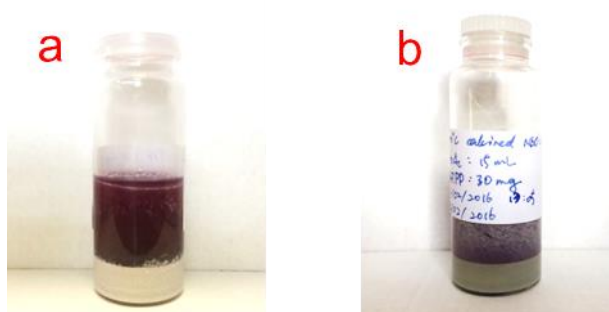


Figure 5.3.2 The immobilisation of TPP on (a) untreated **NbO** powder and (b) calcined (at 400 °C) TPP powder. (a) The untreated **NbO** powder did not turn to green showed that it can not support TPP; (b) The calcined **NbO** powder became green and successfully supported TPP.

Then this method was applied for **NbO** pellets. The colour of **NbO** pellets turned green after the immobilisation. However, serious bleaching happened when the TPP@**NbO** pellet left in a dessicator for several days. Also, the amount of TPP that can be immobilised is much less than on **NbP**, which might not only because **NbO** has lower acid sites density than **NbP**, but also its lower ratio of Brønsted to Lewis acid sites as shown in Table 5.3.1.

Table 5.3.1 Distribution of Brønsted and Lewis acid sites on **NbP** and **NbO** catalysts.^{a 41}

Sample	Acid site density ($\mu\text{mol/g}$)	Brønsted/Lewis acid sites area
NbP	265	2.6
NbO	135	1.1

a. Determined by infrared measurements of adsorbed pyridine.

According to the literature,⁶⁰ phosphoric acid or sulfuric acid pre-treatment can improve the performance of **NbO** activity. Therefore, acidic treatment of **NbO** pellets was carried out using 1.0 M phosphoric acid. Fifteen **NbO** pellets (around 30 g) were soaked in 30 mL 1.0 M phosphoric acid for 48 hours at room temperature. Then the pellets were filtered and washed with 30 mL distilled water twice. After dried at 120 °C for 24 hours, the acid pre-treated **NbO** pellets were used to support TPP in Tol.

Compared to calcined **NbO** pellets, acid treated **NbO** can support more TPP. Furthermore, the immobilised TPP are more stable in acid pre-treated **NbO** pellets, and no obvious bleaching over days.

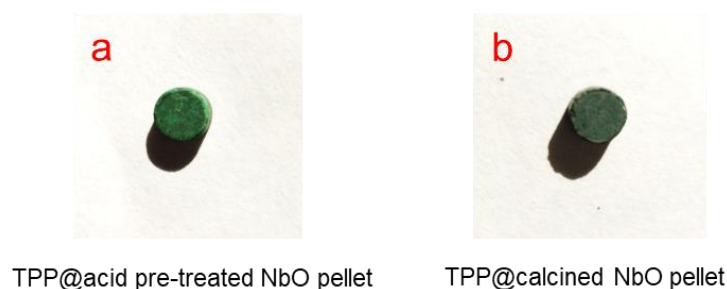


*Figure 5.3.3 The comparison of different pre-treated **NbO** supported TPP. (a) acid treated **NbP** pellet supported TPP (dark green). (b) calcined **NbP** pellet supported TPP (paler green.)*

Then the activity of acid pre-treated **NbO** pellets supported TPP were tested for the synthesis ART from DHAA under the same condition as using TPP@**NbP**. Glass beads were added between the pellets to promote mixing and maximise the exposed area of the pellet. After 2 hour reaction, the acid treated **NbO** pellet supported TPP were green colour and no serious leach and bleaching were observed. However, the yield of ART was quite low (2%). The main reason might be the maximum amount of TPP that can be loaded on acid treated **NbO** pellets is much less than **NbP**.

In order to increase the **NbO** pellet load capacity, the big pellets were crushed and sieved as 1.0 – 0.6 mm followed by the acid treatment. These smaller acid treated pellets were used for TPP immobilisation. However, the amount of TPP that can be loaded did not increase substantially resulting in a low activity in the photo-oxidation of DHAA to ART giving 5 % yield of ART. Therefore, the **NbP** was clearly to be a better support than **NbO** (either pre-calcined or acid pre-treated).

5.4. Conclusions

In this chapter, Nb acid catalysts (**NbP** and **NbO**) were used as supports for the photosensitiser TPP immobilisation to form bifunctional catalysts (photoactivity and acidity).

Initial experiments were carried out with **NbP**, which indicated that photosensitiser TPP can be loaded on **NbP** successfully. Different solvents were investigated for the TPP immobilisation process. The low polarity solvent Tol showed better performance, in which negligible TPP leaching was obtained. The maximum amount of TPP that could be immobilised on 1 g **NbP** was investigated and found to be around 60 mg. Increasing the immobilisation time promoted the transformation of di-protonated TPP dimer to mono-protonated on **NbP** acid sites, which could impact TPP@**NbP** photoactivity and acidity.

The photoactivity of **NbP**-supported TPP was first tested in the photo-oxidation of α -terpinene to ascaridole in a batch reactor. The activity of TPP@**NbP** that using

EtOAc as the immobilisation solvent showed a higher efficiency than using DMC and Tol, and reached a maximum of yield 65% in 45 mins.

Then TPP@**NbP** was used to catalyse the sem-synthesis of ART from DHAA, to test both its photoactivity and acidity. A 22% yield of ART with 48% conversion of DHAA was obtained in a single pass. However, limited by the powder texture of the TPP@**NbP**, the photo-oxidation happened only on the outer circle of the catalyst bed, and the inside catalyst was not involved in the reaction. Therefore, **NbO** pellets were investigated to support TPP. However, the amount of TPP that can be loaded onto **NbO** pellets was much lower than can be loaded onto **NbP**, even after a pre-treatment (calcination or acid pre-treatment) has been performed to increase the acidity of the **NbO** pellets. With **NbO** pellets supported TPP, the conversion of DHAA to ART obtained only a 5% yield of ART.

Chapter 6. Thesis Conclusions and Possible Future

Directions

At the end of Chapter 1 the aims set out at the beginning of the project were expressed as following:

1. To investigate the acidic activity of **NbO** and **NbP** in the continuous alkylation of aniline by employing a self-optimisation system.
2. To compare the activity of Nb catalysts to $\gamma\text{-Al}_2\text{O}_3$ in the methylation of aniline with DMC and methanol.
3. To convert biomass products to more valuable chemicals over a **NbP** catalyst in a continuous flow process.
4. To investigate the immobilisation of photosensitisers on Nb catalysts and what effect this has on their activity in the continuous photo-oxidation reactions.

In this chapter, the progress towards meeting each of the above aims is reviewed. For each of the posed questions, the justification for attempting to answer the question

is first considered, followed by a summary of the work attempted and conclusions which can be drawn from this work; finally, some possible future directions are proposed.

6.1 Aim 1 and Aim 2

Aims 1 and 2, presented as follows, were both relative to the activity of acid catalyst in the alkylation of aniline, therefore, the relevant conclusions are summarised together in this section.

To investigate the acidic activity of **NbO** and **NbP** in the continuous alkylation of aniline by employing a self-optimisation system.

To compare the acidity of Nb catalysts to γ -Al₂O₃ in the methylation of aniline with DMC and methanol.

6.1.1. Rationale

The integrating on-line or in-line analytics with continuous flow systems could provide a simple way to collect a large number of data in real-time, including distribution (or selectivity) of products, activity and stability of catalysts. Moreover, by applying feedback algorithms, automated continuous flow processes make it is possible to influence the reaction outcome by varying the reaction parameters, such as temperature, reaction time and stoichiometry of reagents, to maximise the production of desired products or to collect useful kinetic data. The process automation associated with flow chemistry can greatly shorten the data analysis time and provide a better design of the reaction with less time, labour and material required.

Here an automated continuous flow system with on-line GC desired in our group was used at the beginning of this Thesis with the aim to obtain a broad knowledge of

the activity of Nb acid catalysts and to also familiarise with the operation and maintenance of the high-pressure continuous flow system.

6.1.2. Progress

The initial experiments indicated that both of **NbO** and **NbP** catalysts had high acidic activity, which can achieve Friedel–Crafts alkylation of AN with DMC or MeOH that cannot be performed by γ -Al₂O₃.

To explore the influence of temperature on the catalytic capability of these two Nb catalysts, temperature ramp reactions were designed and carried out. Based on the products distribution information obtained in the temperature ramp reactions, the optimisations for different AN alkylation products were then investigated via the automated continuous flow system.

Two alkylation reagents were tested in the self-optimisation for F-C alkylation product para-methyl-dimethylaniline **3c** using **NbP** as a catalyst, and DMC showed more active than MeOH, which gave a higher optimal yield of **3c** (83%). Both **NbO** and **NbP** were then investigated in the self-optimisation for different AN alkylation products with DMC. **NbP** showed a stronger activity in the alkylation of AN with DMC than **NbO**. As for the F-C alkylation product **3c**, the optimal yield with **NbP** (83%) was higher than with **NbO** (52%).

6.1.3. Possible Future Direction

The automated continuous flow system used in this Chapter is quite useful for the data collection. Especially for starting a new reaction, a rich supply of data and speedy feedbacks obtained from the on-line analytical instrument could help to make decisions for the further research direction in a short time.

As for the self-optimisation system, it would be more compatible for homogenous reaction, which could be without regard for the catalyst deactivation during the reaction processing. However, if the heterogeneous catalysts were stable enough through varied reaction conditions, it would be also suitable for self-optimisation operation.

6.2 Aim 3

To convert biomass products to more valuable chemicals over **NbP** catalyst in a continuous flow process.

6.2.1. Rationale

Biomass has emerged as one of the most important sustainable sources for renewable organic carbon in line with the Principles of Green Chemistry. In this context, renewable energy sources derived from biomass such as biodiesel, offer opportunities to access glycerol, an inexpensive by-product representing 10 wt% of the overall production.¹⁶⁰ The current increased production of biodiesel generates an ever greater abundance of glycerol to the point where supply exceeds demand.^{41, 158} This leads to the obvious question of how best to use this additional glycerol.

Here the Skraup reaction was chosen as it uses glycerol directly, to react with aniline to synthesise the heterocyclic compound quinoline.¹⁸¹ Quinoline, which has a nitrogen-based heterocyclic ring, is not widely used itself, but can be easily modified to a multitude of functional compounds which have widespread applications in medicinal and industrial chemistry.¹⁶⁵⁻¹⁶⁷ Traditionally the Skraup reaction requires two steps

under harsh conditions (at high temperature with excess amounts of concentrated sulfuric acid and a toxic oxidizer, nitrobenzene). A range of catalytic routes have been developed,^{185, 256}. However most of these procedures involved homogenous acids and are associated with the problems of toxicity, corrosion, use of stoichiometric quantities, separation and recovery

Heterogeneous catalysts potentially offer a greener alternative as they can be easily separated recycled, reducing the environmental cost of a chemical process. **NbP** as a heterogeneous acid catalyst that exhibits strong surface acidity and has been successfully used in the past to catalyse several reactions, including the dehydration of several bio-derived compounds.^{67, 71, 75} Given this, **NbP** was investigated to be used as a solid catalyst in a continuous flow system to develop a Skraup reaction that provides a greener, cleaner and continuous synthesis of quinoline-derived products.

6.2.2. Progress

Initially the Skraup reaction using **NbP** catalyst was investigated using glycerol and aniline as starting materials, after the optimisation a 10% of yield quinoline was obtained. However, problems were experienced in the introduction of glycerol, due to its polar and viscous nature, which prevented the direct pumping neat glycerol into the reactor on the lab scale. Therefore, an alternative starting reagent solketal, a ketal produced from a condensation reaction between glycerol and acetone, was investigated, which can achieve a higher yield of quinoline (30%).

As acetone was generated as a side products during the deprotection of solketal, which can react with AN in the present of acid catalysts. A control experiment was carried out, and the results demonstrated that the acetone did not take part in any side reactions in the flow system.

The effects of varying reaction parameters were then investigated, including: feedstock ratio, temperature, pressure, and flowrate. The optimised conditions for quinoline synthesis are at 250 °C, 50 bar, with flowrates of aniline 0.1 mL/min (0.275 M in Tol) and solketal 0.1 mL/min (0.825 M in Tol), giving a 48% yield of quinoline. A scale-up of reaction in a series of connected reactors was demonstrated, with a view to increasing the productivity.

In order to demonstrate that **NbP** could be extended to catalyse the Skraup reaction more widely, two anilines derivatives, 4-methoxyaniline **4k** and 4,4'-methylenedianiline **4l**, were used to react with solketal. With compound **4k**, 6-methoxyquinoline **4k-1** was obtained with a GC-yield of 30%. The two main by-products observed were 4-methoxy-Nmethylaniline **4k-2** and N-ethyl-4-methoxyaniline **4k-3** (total amount <10%). For compound **4l**, both dissymmetric **4l-1** and symmetric **4l-2** products were observed with a GC-yield of 20 and 12% respectively. A crystal of compound **4l-1** was grown and the structure was determined by crystallographic analysis for the first time.

6.2.3. Possible Future Direction

The experiments described above is a useful proof of concept. **4d** can be used as a feedstock for the continuous Skraup reaction promoted by a **NbP** solid acid catalyst. The major problem still to be addressed is how best the **NbP** can be regenerated. Heating the catalyst to 300 °C in air had little effect. The TGA experiment suggests that at much higher temperatures calcination may be effective, but not higher than 530 °C where the **NbP** start to be crystallized.

Two anilines derivatives have been tested and successfully synthesised the corresponding substituted quinolines. To synthesise complicated quinoline derivatives

via **NbP** catalyst in a continuous flow reactor could be an interesting area for the future work.

During the flow reaction processing, the **NbP** catalyst powder easily became packed together. This caused a pressure jump especially at high flowrates of reagents (above 1 mL/min), changed the desired reaction conditions and influenced the output of the reaction. Moreover, it could cause the potential safety issues in high pressure reactions operation. Small pellets have been made by using a pellet press, however leaching occurred when these **NbP** pellets were used as catalysts in a high temperature and high pressure flow reaction. Therefore, a proper binder could be added in the preparing **NbP** pellet to improve strength of pellets in the future work.

6.3 Aim 4

To investigate the immobilisation of photosensitisers on Nb catalysts and what effect this has on their activity in the continuous photo-oxidation reactions.

6.5.1. Rationale

As described in Chapter 1, the advantages of continuous flow processes such as efficient irradiation, good mixing and fast heat exchange are beneficial to photochemistry. A high pressure continuous photoreactor has been designed in our group, and was used to conduct the semi-synthesis of artemisinin (ART) catalysed by the dual-function heterogeneous photocatalysts TPP@Amb. However, when using an immobilised catalyst, leaching from the catalyst support is an essential issue. In the previous work, there was obvious TPP leaching, as a pink solution (colour of free TPP)

was collected after the colourless reagent mixture passed through the fixed catalyst bed of Amberlyst-15 supported TPP.

In an attempt to reduce the chance of leaching, in this work, the Nb solid acids (**NbP** and **NbO**), which show strength acid activity than Amberlyst-15, were used as alternative acid supports to immobilise the photosensitiser TPP.

6.5.2. Progress

Initial experiments were carried out with **NbP**, which indicated that photosensitiser TPP can be loaded on **NbP** successfully. Different solvents were then investigated for the TPP immobilisation process. The low polarity solvent Tol showed the best performance, in which negligible TPP leaching was obtained. The maximum amount of TPP that can be immobilised on 1 g **NbP** was investigated and found to be around 60 mg.

Increasing the immobilisation time promoted the transformation of di-protonated TPP dimers to mono-protonated TPP which may bind on **NbP** acid sites, which could impact both of the photoactivity and acidity of TPP@**NbP**.

The photoactivity of **NbP** supported TPP was first tested in the photo-oxidation of α -terpinene to ascaridole in a batch reactor. The activity of TPP@**NbP** that was made using EtOAc as the immobilisation solvent showed a higher efficiency than TPP@**NbP** immobilised using DMC and Tol, which reached a maximum of yield 65% in 45 mins.

Then TPP@**NbP** was used to catalyse the semi-synthesis of ART from DHAA to test both its photoactivity and acidity. A 22% yield of ART with 48% conversion of DHAA was obtained in a single pass. However, limited by the powder texture of the TPP@**NbP**, the photo-oxidation happened only on the outer circle of the catalyst bed, and the inside catalyst was not involved in the reaction. Therefore, **NbO** pellets were

investigated to support TPP. However, the amount of TPP that can be loaded onto **NbO** pellets was much lower than can be loaded onto **NbP**, even after a pre-treatment (calcination or acid pre-treatment) has been performed to increase the acidity of the **NbO** pellet. With **NbO** pellets supported TPP, the conversion of DHAA to ART obtained only 5% yield of the ART.

6.5.3. Possible Future Direction

Severely TPP bleaching was observed under strong irradiation, therefore, a more stable photosensitiser is required for the future research. Besides, due to the powder texture, the packed TPP@**NbP** catalyst impeded the light exposure through the reactor. Glass beads were mixed with the dual catalyst and added into the catalyst bed to improve the exposure of light, however, the photoreaction only happened on the outside surface of the catalyst bed. Even though the TPP@**NbP** gave a respectable ART yield at the single run. Therefore, using proper size (or shape) of **NbP** pellets to load TPP would be a good solution in the future work.

In this work, the maximum amount of TPP that can be immobilised on 1 g **NbP** have been investigated. The exploration for the best ratio of TPP onto **NbP** for the ART synthesis would be an interesting in the next step.

6.4 Final Words

Although much progress has been made towards the application of Nb solid acids in the continuous flow synthesis, there are still many interesting research areas for

the applications of Nb catalysts to explore and also more challenges to meet in the further.

I would like to wish every success to those who will continue this research and hope to see more and more new discoveries about Nb and Nb containing compounds in the future.

Reference

1. P. T. Anastas, *Green chemistry : Theory and Practice*, Oxford : Oxford University Press, Oxford, 1998.
2. M. Poliakoff, J. M. Fitzpatrick, T. R. Farren and P. T. Anastas, *Science*, 2002, **297**, 807-810.
3. M. Poliakoff and P. Licence, *Nature*, 2007, **450**, 810-812.
4. S. Y. Tang, R. A. Bourne, M. Poliakoff and R. L. Smith, *Green Chemistry*, 2008, **10**, 268-269.
5. W. F. Hölderich, J. Röseler, G. Heitmann and A. T. Liebens, *Catalysis Today*, 1997, **37**, 353-366.
6. G. Centi and S. Perathoner, *Catalysis Today*, 2003, **77**, 287-297.
7. E. Kang, *Tetrahedron*, 2010, **66**, 1029-1030.
8. A. Takagaki, C. Tagusagawa, S. Hayashi, M. Hara and K. Domen, *Energy & Environmental Science*, 2010, **3**, 82.
9. P. Licence and M. Poliakoff, in *New Methodologies and Techniques for a Sustainable Organic Chemistry*, eds. A. Mordini and F. Faigl, Springer, Dordrecht, 2008, **246**, 171-191.
10. J. H. Clark, *Accounts of Chemical Research*, 2002, **35**, 791-797.
11. T. Okuhara, *Chemical Review*, 2002, **102**, 3641-3665.
12. K. Tanabe and W. F. Holderich, *Applied Catalysis A: General*, 1999, **181**, 399-434.
13. M. Hara, *Energy & Environmental Science*, 2010, **3**, 601-607.
14. K.-i. Shimizu and A. Satsuma, *Energy & Environmental Science*, 2011, **4**, 3140-3153.
15. J. N. Armor, *Applied Catalysis A: General*, 2001, **222**, 407-426.

16. N. N. Greenwood and A. Earnshaw, *Chemistry of the Elements*, Elsevier, 1997.
17. Mattheis.Lf, *Physical Review B-Solid State*, 1970, **1**, 373-381.
18. R. Stone, *Science*, 2014, **345**, 725-727.
19. M. A. Tarselli, *Nature chemistry*, 2014, **7**, 180.
20. J. Wade and B. J. Wood, *Nature*, 2001, **409**, 75-78.
21. M. Ziolek, *Catalysis Today*, 2003, **78**, 47-64.
22. M. Ziolek and I. Nowak, *Catalysis Today*, 2003, **78**, 543-553.
23. D. K. Finnemore, T. F. Stromberg and C. A. Swenson, *Physical Review*, 1966, **149**, 231-243.
24. J. Halbritter, *Applied Physics A*, 1987, **43**, 1-28.
25. S. H. Autler, K. H. Gooen and E. S. Rosenblum, *Physical Review Letters*, 1962, **9**, 489.
26. A. V. Narlikar and D. Dew-Hughes, *Journal of Materials Science*, 1966, **1**, 317-335.
27. G. R. Johnson and D. H. Douglass, *Journal of Low Temperature Physics*, 1974, **14**, 575-595.
28. A. Mint, Niobium: A unique coin metal, <https://www.muenzeoesterreich.at/eng/>.
29. M. Niinomi, M. Nakai and J. Hieda, *Acta Biomaterialia*, 2012, **8**, 3888-3903.
30. F. Rubitschek, T. Niendorf, I. Karaman and H. J. Maier, *Journal of the Mechanical Behavior of Biomedical Materials*, 2012, **5**, 181-192.
31. I. Nowak and M. Ziolek, *Chem. Rev.*, 1999, **99**, 3603-3624.
32. J. M. Jehng and I. E. Wachs, *Acs Symposium Series*, 1990, **437**, 232-242.
33. A. Corma and H. Garcia, *Chemical Review*, 2003, **103**, 4307-4365.
34. C. J. Brodsky and E. I. Ko, *Journal of Non-Crystalline Solids*, 1995, **186**, 88-95.
35. T. Iizuka, K. Ogasawara and K. Tanabe, *Bulletin of the Chemical Society of Japan*, 1983, **56**, 2927-2931.
36. D. A. G. Aranda, J. d. A. Gonçalves, J. S. Peres, A. L. D. Ramos, C. A. R. de Melo, O. A. C. Antunes, N. C. Furtado and C. A. Taft, *Journal of Physical Organic Chemistry*, 2009, **22**, 709-716.
37. M. Trejda, K. Stawicka, A. Dubinska and M. Ziolek, *Catalysis Today*, 2012, **187**, 129-134.

38. C. Carlini, M. Giuttari, A. Maria Raspolli Galletti, G. Sbrana, T. Armaroli and G. Busca, *Applied Catalysis A: General*, 1999, **183**, 295-302.
39. P. Carniti, A. Gervasini, S. Biella and A. Auroux, *Catalysis Today*, 2006, **118**, 373-378.
40. S.-H. Chai, H.-P. Wang, Y. Liang and B.-Q. Xu, *Journal of Catalysis*, 2007, **250**, 342-349.
41. R. M. West, D. J. Braden and J. A. Dumesic, *Journal of Catalysis*, 2009, **262**, 134-143.
42. T. Iizuka, S. Fujie, T. Ushikubo, Z.-h. Chen and K. Tanabe, *Applied Catalysis*, 1986, **28**, 1-5.
43. M. I. de Sairre, É. S. Bronze-Uhle and P. M. Donate, *Tetrahedron Letters*, 2005, **46**, 2705-2708.
44. K. Tanabe, *Catalysis Today*, 1990, **8**, 1-11.
45. T.-a. Hanaoka, K. Takeuchi, T. Matsuzaki and Y. Sugi, *Catalysis Letter*, 1990, **5**, 13-16.
46. T.-a. Hanaoka, K. Takeuchi, T. Matsuzaki and Y. Sugi, *Catalysis Today*, 1990, **8**, 123-132.
47. M. O. Guerrero-Pérez and M. A. Bañares, *Catalysis Today* 2009, **142**, 245-251.
48. T. Ohuchi, T. Miyatake, Y. Hitomi and T. Tanaka, *Catalysis Today*, 2007, **120**, 233-239.
49. A. G. S. Prado, L. B. Bolzon, C. P. Pedroso, A. O. Moura and L. L. Costa, *Applied Catalysis B: Environmental*, 2008, **82**, 219-224.
50. H. Liu, N. Gao, M. Y. Liao and X. S. Fang, *Scientific Report*, 2015, **5**, 9.
51. M. Ziolek, I. Sobczak, P. Decyk and L. Wolski, *Catalysis Communications*, 2013, **37**, 85-91.
52. T. Shishido, T. Miyatake, K. Teramura, Y. Hitomi, H. Yamashita and T. Tanaka, *The Journal of Physical Chemistry C*, 2009, **113**, 18713-18718.
53. S. Furukawa, Y. Ohno, T. Shishido, K. Teramura and T. Tanaka, *Acs Catalysis*, 2011, **1**, 1150-1153.
54. H. Luo, M. Wei and K. Wei, *Materials Chemistry and Physics*, 2010, **120**, 6-9.
55. X. Fang, L. Hu, K. Huo, B. Gao, L. Zhao, M. Liao, P. K. Chu, Y. Bando and D. Golberg, *Advanced Functional Materials*, 2011, **21**, 3907-3915.
56. O. F. Lopes, E. C. Paris and C. Ribeiro, *Applied Catalysis B: Environmental*, 2014, **144**, 800-808.

57. K. Tanabe, *Catalysis Today*, 2003, **78**, 65-77.
58. M. Ziolek, P. Decyk, I. Sobczak, M. Trejda, J. Florek, H. G. W. Klimas and A. Wojtaszek, *Applied Catalysis A: General*, 2011, **391**, 194-204.
59. K. Yamashita, M. Hirano, K. Okumura and M. Niwa, *Catalysis Today*, 2006, **118**, 385-391.
60. S. Okazaki, M. Kurimata, T. Iizuka and K. Tanabe, *Bulletin of the Chemical Society of Japan*, 1987, **60**, 37-41.
61. S. Okazaki and A. Kurosaki, *Catalysis Today*, 1990, **8**, 113-122.
62. T. Armaroli, G. Busca, C. Carlini, M. Giuttari, A. M. Raspolli Galletti and G. Sbrana, *Journal of Molecular Catalysis A: Chemical*, 2000, **151**, 233-243.
63. C. C. M. Pereira and E. R. Lachter, *Applied Catalysis A: General*, 2004, **266**, 67-72.
64. K. Nakajima, Y. Baba, R. Noma, M. Kitano, J. N. Kondo, S. Hayashi and M. Hara, *Journal of the American Chemical Society*, 2011, **133**, 4224-4227.
65. F. Yang, Q. Liu, X. Bai and Y. Du, *Bioresource Technology*, 2011, **102**, 3424-3429.
66. Y. Zhang, J. Wang, X. Li, X. Liu, Y. Xia, B. Hu, G. Lu and Y. Wang, *Fuel*, 2015, **139**, 301-307.
67. P. Carniti, A. Gervasini, F. Bossola and V. Dal Santo, *Applied Catalysis B: Environmental*, 2016, **193**, 93-102.
68. B. Pholjaroen, N. Li, Z. Wang, A. Wang and T. Zhang, *Journal of Energy Chemistry*, 2013, **22**, 826-832.
69. H. Gomez Bernal, L. Bernazzani and A. M. Raspolli Galletti, *Green Chemistry*, 2014, **16**, 3734-3740.
70. A. M. R. Galletti, C. Antonetti, V. De Luise and M. Martinelli, *Green Chemistry*, 2012, **14**, 688-694.
71. Q.-N. Xia, Q. Cuan, X.-H. Liu, X.-Q. Gong, G.-Z. Lu and Y.-Q. Wang, *Angewandte Chemie International Edition*, 2014, **53**, 9755-9760.
72. Y. Shao, Q. Xia, L. Dong, X. Liu, X. Han, S. F. Parker, Y. Cheng, L. L. Daemen, A. J. Ramirez-Cuesta, S. Yang and Y. Wang, *Nature Communications*, 2017, **8**.
73. G. S. Foo, D. Wei, D. S. Sholl and C. Sievers, *ACS Catalysis*, 2014, **4**, 3180-3192.
74. Y. Y. Lee, K. A. Lee, N. C. Park and Y. C. Kim, *Catalysis Today*, 2014, **232**, 114-118.

75. G. S. Rao, N. P. Rajan, V. Pavankumar and K. V. R. Chary, *Journal of Chemical Technology & Biotechnology*, 2014, **89**, 1890-1897.
76. R. A. Sheldon, *Chemistry & Industry*, 1992, 903-906.
77. C. G. Frost and L. Mutton, *Green Chemistry*, 2010, **12**, 1687-1703.
78. D. J. C. Constable, A. D. Curzons, L. M. F. dos Santos, G. R. Geen, R. E. Hannah, J. D. Hayler, J. Kitteringham, M. A. McGuire, J. E. Richardson, P. Smith, R. L. Webb and M. Yu, *Green Chemistry*, 2001, **3**, 7-9.
79. P. T. Anastas and M. M. Kirchhoff, *Accounts of Chemical Research*, 2002, **35**, 686-694.
80. G. Jas and A. Kirschning, *Chemistry - A European Journal*, 2003, **9**, 5708-5723.
81. A. Kirschning, W. Solodenko and K. Mennecke, *Chemistry - A European Journal*, 2006, **12**, 5972-5990.
82. C. J. Mallia and I. R. Baxendale, *Organic Process Research & Development*, 2016, **20**, 327-360.
83. M. B. Plutschack, B. Pieber, K. Gilmore and P. H. Seeberger, *Chemical Review*, 2017, **117**, 11796-11893.
84. P. Angeli and A. Gavrilidis, in *Encyclopedia of Microfluidics and Nanofluidics*, ed. D. Li, Springer US, Boston, MA, 2008, **1526**, 1971-1976.
85. J. A. Howard and P. A. Walsh, *International Journal of Multiphase Flow*, 2013, **55**, 32-42.
86. A. Günther, M. Jhunjhunwala, M. Thalmann, M. A. Schmidt and K. F. Jensen, *Langmuir*, 2005, **21**, 1547-1555.
87. A. Gunther and K. F. Jensen, *Lab on a Chip*, 2006, **6**, 1487-1503.
88. C. F. Carter, I. R. Baxendale, M. O'Brien, J. B. J. Pavey and S. V. Ley, *Organic & Biomolecular Chemistry*, 2009, **7**, 4594-4597.
89. R. L. Hartman, J. P. McMullen and K. F. Jensen, *Angewandte Chemie International Edition*, 2011, **50**, 7502-7519.
90. H. Usutani, Y. Tomida, A. Nagaki, H. Okamoto, T. Nokami and J.-i. Yoshida, *Journal of the American Chemical Society*, 2007, **129**, 3046-3047.
91. H. Usutani, T. Nihei, C. D. Papageorgiou and D. G. Cork, *Organic Process Research & Development*, 2017, **21**, 669-673.
92. D. Cambié, C. Bottecchia, N. J. W. Straathof, V. Hessel and T. Noël, *Chemical Review*, 2016, **116**, 10035-10074.
93. D. M. Schultz and T. P. Yoon, *Science*, 2014, **343**, 985-+.

94. M. D. Kärkäs, J. A. Porco and C. R. J. Stephenson, *Chemical Review*, 2016, **116**, 9683-9747.
95. N. Armaroli and V. Balzani, *Angewandte Chemie International Edition*, 2007, **46**, 52-66.
96. K. S. Elvira, X. C. i Solvas, R. C. R. Wootton and A. J. deMello, *Nature chemistry*, 2013, **5**, 905-915.
97. K. Loubière, M. Oelgemöller, T. Aillet, O. Dechy-Cabaret and L. Prat, *Chemical Engineering and Processing: Process Intensification*, 2016, **104**, 120-132.
98. S. G. Newman and K. F. Jensen, *Green Chemistry*, 2013, **15**, 1456-1472.
99. M. M. Moghaddam, B. Pieber, T. Glasnov and C. O. Kappe, *ChemSusChem*, 2014, **7**, 3122-3131.
100. I. Vural Gursel, T. Noel, Q. Wang and V. Hessel, *Green Chemistry*, 2015, **17**, 2012-2026.
101. C. Müller, M. G. Nijkamp and D. Vogt, *European Journal of Inorganic Chemistry*, 2005, **2005**, 4011-4021.
102. D. Cantillo and C. O. Kappe, *ChemCatChem*, 2014, **6**, 3286-3305.
103. D. J. Cole-Hamilton, *Science*, 2003, **299**, 1702-1706.
104. S. Sharma, K. C. Basavaraju, A. K. Singh and D.-P. Kim, *Organic Letters*, 2014, **16**, 3974-3977.
105. A. J. Sandee, D. G. I. Petra, J. Reek, P. Kamer and P. van Leeuwen, *Solid-Phase Synthesis of Homogeneous Ruthenium Catalysts on Silica for the Continuous Asymmetric Transfer Hydrogenation Reaction*, 2001.
106. A. M. Kluwer, C. Simons, Q. Knijnenburg, J. I. van der Vlugt, B. de Bruin and J. N. H. Reek, *Dalton transactions*, 2013, **42**, 3609-3616.
107. S. Kobayashi and R. Akiyama, *Chemical Communications*, 2003, **0**, 449-460.
108. H. P. Dijkstra, G. P. M. van Klink and G. van Koten, *Accounts of Chemical Research*, 2002, **35**, 798-810.
109. J. Fang, R. Jana, J. A. Tunge and B. Subramaniam, *Applied Catalysis A: General*, 2011, **393**, 294-301.
110. W. Keim, *Green Chemistry*, 2003, **5**, 105-111.
111. M. McCarthy, H. Stemmer and W. Leitner, *Green Chemistry*, 2002, **4**, 501-504.
112. T. Harwardt, G. Francio and W. Leitner, *Chemical Communications*, 2010, **46**, 6669-6671.

113. J. F. B. Hall, X. Han, M. Poliakoff, R. A. Bourne and M. W. George, *Chemical Communications*, 2012, **48**, 3073-3075.
114. D. Webb and T. F. Jamison, *Chemical Science*, 2010, **1**, 675-680.
115. J. Wegner, S. Ceylan and A. Kirschning, *Advanced Synthesis & Catalysis*, 2012, **354**, 17-57.
116. D. T. McQuade and P. H. Seeberger, *The Journal of Organic Chemistry*, 2013, **78**, 6384-6389.
117. S. Borukhova, T. Noël and V. Hessel, *ChemSusChem*, 2016, **9**, 67-74.
118. J. Britton and C. L. Raston, *Chemical Society Reviews*, 2017, **46**, 1250-1271.
119. V. Sans, S. Glatzel, F. J. Douglas, D. A. Maclaren, A. Lapkin and L. Cronin, *Chemical Science*, 2014, **5**, 1153-1157.
120. C. F. Carter, H. Lange, S. V. Ley, I. R. Baxendale, B. Wittkamp, J. G. Goode and N. L. Gaunt, *Organic Process Research & Development*, 2010, **14**, 393-404.
121. T. A. Hamlin and N. E. Leadbeater, *Beilstein Journal of Organic Chemistry*, 2013, **9**, 1843-1852.
122. T. H. Rehm, C. Hofmann, D. Reinhard, H.-J. Kost, P. Lob, M. Besold, K. Welzel, J. Barten, A. Didenko, D. V. Sevenard, B. Lix, A. R. Hillson and S. D. Riegel, *Reaction Chemistry & Engineering*, 2017, **2**, 315-323.
123. R. A. Bourne, R. A. Skilton, A. J. Parrott, D. J. Irvine and M. Poliakoff, *Organic Process Research & Development*, 2011, **15**, 932-938.
124. J. P. McMullen, M. T. Stone, S. L. Buchwald and K. F. Jensen, *Angewandte Chemie International Edition*, 2010, **49**, 7076-7080.
125. D. C. Fabry, E. Sugiono and M. Rueping, *Reaction Chemistry & Engineering*, 2016, **1**, 129-133.
126. D. K. B. Mohamed, X. Yu, J. Li and J. Wu, *Tetrahedron Letters*, 2016, **57**, 3965-3977.
127. M. Trojanowicz, *Talanta*, 2016, **146**, 621-640.
128. D. L. Browne, S. Wright, B. J. Deadman, S. Dunnage, I. R. Baxendale, R. M. Turner and S. V. Ley, *Rapid Communications in Mass Spectrometry*, 2012, **26**, 1999-2010.
129. J. P. McMullen and K. F. Jensen, in *Annual Review of Analytical Chemistry, Vol 3*, eds. E. S. Yeung and R. N. Zare, 2010, vol. 3, pp. 19-42.
130. B. J. Reizman and K. F. Jensen, *Accounts of Chemical Research*, 2016, **49**, 1786-1796.

131. V. Sans and L. Cronin, *Chemical Society Reviews*, 2016, **45**, 2032-2043.
132. A. J. Parrott, R. A. Bourne, G. R. Akien, D. J. Irvine and M. Poliakoff, *Angewandte Chemie International Edition*, 2011, **50**, 3788-3792.
133. X. Han and M. Poliakoff, *Chemical Society Reviews*, 2012, **41**, 1428-1436.
134. R. A. Sheldon, *Green Chemistry*, 2007, **9**, 1273-1283.
135. F. Darvas, V. Hessel and G. Dorman, *Volume 1 Fundamentals*, 2014.
136. J.-i. Yoshida, A. Nagaki and T. Yamada, *Chemistry – A European Journal*, 2008, **14**, 7450-7459.
137. J.-i. Yoshida, Y. Takahashi and A. Nagaki, *Chemical Communications*, 2013, **49**, 9896-9904.
138. D. L. Browne, B. J. Deadman, R. Ashe, I. R. Baxendale and S. V. Ley, *Organic Process Research & Development*, 2011, **15**, 693-697.
139. V. Dragone, V. Sans, M. H. Rosnes, P. J. Kitson and L. Cronin, *Beilstein Journal of Organic Chemistry*, 2013, **9**, 951-959.
140. S. Huebschmann, D. Kralisch, V. Hessel, U. Krtischil and C. Kompter, *Chemical Engineering & Technology*, 2009, **32**, 1757-1765.
141. M. G. Hitzler and M. Poliakoff, *Chemical Communications*, 1997, DOI: 10.1039/A704371F, 1667-1668.
142. A. Cabanas and M. Poliakoff, *Journal of Materials Chemistry*, 2001, **11**, 1408-1416.
143. B. Walsh, J. R. Hyde, P. Licence and M. Poliakoff, *Green Chemistry*, 2005, **7**, 456-463.
144. Z. Amara, F. B. BellamyJessica, R. Horvath, S. J. Miller, A. Beeby, A. Burgard, K. Rossen, M. Poliakoff and M. W. George, *Nature chemistry*, 2015, **7**, 489-495.
145. J. F. B. Bellamy, PhD Thesis, The University of Nottingham, 2014.
146. B. Lewis and G. Von Elbe, *Combustion, Flames, and Explosions of Gases*, Academic Press, 1987.
147. D. S. Lee, Z. Amara, M. Poliakoff, T. Harman, G. Reid, B. Rhodes, S. Brough, T. McNally and S. Woodward, *Organic Process Research & Development*, 2015, **19**, 831-840.
148. M. W. Routh, P. A. Swartz and M. B. Denton, *Analytical Chemistry*, 1977, **49**, 1422-1428.
149. J. A. Nelder and R. Mead, *The Computer Journal*, 1965, **7**, 308-313.
150. W. Spendley, G. R. Hext and F. R. Himsforth, *Technometrics*, 1962, **4**, 441-461.

151. Z. Amara, E. S. Streng, R. A. Skilton, J. Jin, M. W. George and M. Poliakoff, *European Journal of Organic Chemistry*, 2015, **2015**, 6141-6145.
152. J. H. Clark and D. J. Macquarrie, *Organic Process Research & Development*, 1997, **1**, 149-162.
153. M. Bandini, A. Melloni and A. Umani-Ronchi, *Angewandte Chemie International Edition*, 2004, **43**, 550-556.
154. C. Tagusagawa, A. Takagaki, A. Iguchi, K. Takanabe, J. N. Kondo, K. Ebitani, S. Hayashi, T. Tatsumi and K. Domen, *Angewandte Chemie International Edition*, 2010, **49**, 1128-1132.
155. Y. Rao, M. Trudeau and D. Antonelli, *Journal of the American Chemical Society*, 2006, **128**, 13996-13997.
156. Y. C. Fu, H. Y. Zhu and J. Y. Shen, *Thermochimica Acta*, 2005, **434**, 88-92.
157. C. J. A. Mota, C. X. A. da Silva, N. Rosenbach, J. Costa and F. da Silva, *Energy & Fuels*, 2010, **24**, 2733-2736.
158. C. Zhu, S. Chiu, J. P. Nakas and C. T. Nomura, *Journal of Applied Polymer Science*, 2013, **130**, 1-13.
159. F. Su, S. C. Mathew, L. Möhlmann, M. Antonietti, X. Wang and S. Blechert, *Angewandte Chemie International Edition*, 2011, **50**, 657-660.
160. E. García, M. Laca, E. Pérez, A. Garrido and J. Peinado, *Energy & Fuels*, 2008, **22**, 4274-4280.
161. A. Behr, J. Eilting, K. Irawadi, J. Leschinski and F. Lindner, *Green Chemistry*, 2008, **10**, 13-30.
162. C. Len and R. Luque, *Sustainable Chemical Processes*, 2014, **2**, 1.
163. C.-H. Zhou, J. N. Beltramini, Y.-X. Fan and G. Q. Lu, *Chemical Society Reviews*, 2008, **37**, 527-549.
164. B. Katryniok, S. Paul and F. Dumeignil, *ACS Catalysis*, 2013, **3**, 1819-1834.
165. G. Ramann and B. Cowen, *Molecules*, 2016, **21**, 986.
166. K. Kaur, M. Jain, R. P. Reddy and R. Jain, *European Journal of Medicinal Chemistry*, 2010, **45**, 3245-3264.
167. J. P. Michael, *Natural Product Reports*, 2005, **22**, 627-646.
168. WHO, *World Malaria Report 2016*, Report 978 92 4 151171 1, 2016.
169. A. F. G. Slater and A. Cerami, *Nature*, 1992, **355**, 167-169.
170. R. G. Ridley, *Nature*, 2002, **415**, 686-693.

171. A. Kimyonok, X. Y. Wang and M. Weck, *Polymer Review*, 2006, **46**, 47-77.
172. A. Slodek, M. Filapek, G. Szafraniec, I. Grudzka, W. A. Pisarski, J. G. Malecki, L. Zur, M. Grela, W. Danikiewicz and S. Krompiec, *European Journal of Organic Chemistry*, 2014, 5256-5264.
173. V. Kumar, M. Gohain, J. H. Van Tonder, S. Ponra, B. C. B. Bezuindenhoudt, O. M. Ntwaeaborwa and H. C. Swart, *Optical Materials*, 2015, **50**, Part B, 275-281.
174. G. C. d. Santos, A. de Andrade Bartolomeu, V. F. Ximenes and L. C. da Silva-Filho, *Journal of Fluorescence*, 2017, **27**, 271-280.
175. A. Upadhyay and S. Karpagam, *Journal of Photopolymer Science and Technology*, 2015, **28**, 755-762.
176. K. P. Carter, A. M. Young and A. E. Palmer, *Chemical Review*, 2014, **114**, 4564-4601.
177. C. J. Fahrni and T. V. O'Halloran, *Journal of the American Chemical Society*, 1999, **121**, 11448-11458.
178. D. Mahanand and J. C. Houck, *Clinical Chemistry*, 1968, **14**, 6-11.
179. C. J. Frederickson, E. J. Kasarskis, D. Ringo and R. E. Frederickson, *Journal of Neuroscience Methods*, 1987, **20**, 91-103.
180. H. J. Kim, *J. Lumines.*, 2016, **176**, 335-341.
181. R. H. Manske, *Chemical Review*, 1942, **30**, 113-144.
182. R. H. F. K. Manske, Marshall, in *Organic Reactions*, 1953, vol. 7.
183. P. M. O'Neill, R. C. Storr and B. Kevin Park, *Tetrahedron*, 1998, **54**, 4615-4622.
184. H. Gershon, D. D. Clarke and M. Gershon, *Monatshefte für Chemie / Chemical Monthly*, 2002, **133**, 1437-1442.
185. G. A. Ramann and B. J. Cowen, *Tetrahedron Letters*, 2015, **56**, 6436-6439.
186. P. Charpentier, V. Lobrégat, V. Levacher, G. Dupas, G. Quéguiner and J. Bourguignon, *Tetrahedron Letters*, 1998, **39**, 4013-4016.
187. H. Saggadi, D. Luart, N. Thiebault, I. Polaert, L. Estel and C. Len, *RSC Advances*, 2014, **4**, 21456-21464.
188. R. E. Armer, J. S. Barlow, N. Chopra, C. J. Dutton, D. H. J. Greenway, S. D. W. Greenwood, N. Lad, J. Shaw, A. P. Thompson, K.-W. Thong and I. Tommasini, *Bioorganic & Medicinal Chemistry Letters*, 1999, **9**, 2425-2430.
189. G. Guanti, S. Perrozzi and R. Riva, *Tetrahedron: Asymmetry*, 1998, **9**, 3923-3927.

190. A. S. Amarasekara and M. A. Hasan, *Tetrahedron Letters*, 2014, **55**, 3319-3321.
191. I. I. Oleynik and V. D. Shteingarts, *Journal of Fluorine Chemistry*, 1998, **91**, 25-26.
192. G. M. Buckley, N. Cooper, H. J. Dyke, F. P. Galleway, L. Gowers, A. F. Haughan, H. J. Kendall, C. Lowe, R. Maxey, J. G. Montana, R. Naylor, J. Oxford, J. C. Peake, C. L. Picken, K. A. Runcie, V. Sabin, A. Sharpe and J. B. H. Warneck, *Bioorganic & Medicinal Chemistry Letters*, 2002, **12**, 1613-1615.
193. M. Billah, G. M. Buckley, N. Cooper, H. J. Dyke, R. Egan, A. Ganguly, L. Gowers, A. F. Haughan, H. J. Kendall, C. Lowe, M. Minnicozzi, J. G. Montana, J. Oxford, J. C. Peake, C. L. Picken, J. J. Piwinski, R. Naylor, V. Sabin, N.-Y. Shih and J. B. H. Warneck, *Bioorganic & Medicinal Chemistry Letters*, 2002, **12**, 1617-1619.
194. L. Găină, C. Cristea, C. Moldovan, D. Porumb, E. Surducă, C. Deleanu, A. Mahamoud, J. Barbe and I. Silberg, *International Journal of Molecular Sciences*, 2007, **8**, 70.
195. H. Saggadi, D. Luart, N. Thiebault, I. Polaert, L. Estel and C. Len, *Catalysis Communications*, 2014, **44**, 15-18.
196. H. Saggadi, I. Polaert, D. Luart, C. Len and L. Estel, *Catalysis Today*, 2015, **255**, 66-74.
197. B. M. Reddy and I. Ganesh, *Journal of Molecular Catalysis A: Chemical*, 2000, **151**, 289-293.
198. Y. Cui, X. Zhou, Q. Sun and L. Shi, *Journal of Molecular Catalysis A: Chemical*, 2013, **378**, 238-245.
199. H. van der Wal, B. L. H. M. Sperber, B. Houweling-Tan, R. R. C. Bakker, W. Brandenburg and A. M. López-Contreras, *Bioresource Technology*, 2013, **128**, 431-437.
200. J. C. Smith and R. E. Drexel, *Industrial & Engineering Chemistry*, 1945, **37**, 601-602.
201. J. K. Fu and R. G. Luthy, *Journal of Environmental Engineering*, 1986, **112**, 328-345.
202. M. R. Nanda, Y. Zhang, Z. Yuan, W. Qin, H. S. Ghaziaskar and C. Xu, *Renewable and Sustainable Energy Reviews*, 2016, **56**, 1022-1031.
203. L. Li, T. I. Koranyi, B. F. Sels and P. P. Pescarmona, *Green Chemistry*, 2012, **14**, 1611-1619.
204. A. Talebian-Kiakalaieh, N. A. S. Amin and H. Hezaveh, *Renewable and Sustainable Energy Reviews*, 2014, **40**, 28-59.
205. R. Kamakshi and B. S. R. Reddy, *Catalysis Communications*, 2007, **8**, 825-828.

206. A. Hegedüs, Z. Hell, T. Vargadi, A. Potor and I. Gresits, *Catalysis Letter*, 2007, **117**, 99-101.
207. S. Kamiguchi, I. Takahashi, H. Kurokawa, H. Miura and T. Chihara, *Applied Catalysis A: General*, 2006, **309**, 70-75.
208. M. Velasquez, A. Santamaria and C. Batiot-Dupeyrat, *Applied Catalysis B: Environmental*, 2014, **160**, 606-613.
209. S. Satoshi, S. Daisuke, S. Fumiya and Y. Yasuhiro, *Chemistry Letters*, 2012, **41**, 965-966.
210. C.-W. Chiu, M. A. Dasari, G. J. Suppes and W. R. Sutterlin, *AIChE Journal*, 2006, **52**, 3543-3548.
211. A. Alhanash, E. F. Kozhevnikova and I. V. Kozhevnikov, *Applied Catalysis A: General*, 2010, **378**, 11-18.
212. P. Carniti, A. Gervasini, S. Biella and A. Auroux, *Chemistry Material*, 2005, **17**, 6128-6136.
213. L. C. A. Oliveira, M. F. Portilho, A. C. Silva, H. A. Taroco and P. P. Souza, *Applied Catalysis B: Environmental*, 2012, **117**, 29-35.
214. Y. Choi, D. S. Park, H. J. Yun, J. Baek, D. Yun and J. Yi, *ChemSusChem*, 2012, **5**, 2460-2468.
215. A. Corma, G. W. Huber, L. Sauvanaud and P. O'Connor, *Journal of Catalysis*, 2008, **257**, 163-171.
216. A. Ulgen and W. Hoelderich, *Catalysis Letter*, 2009, **131**, 122-128.
217. F. Wang, J.-L. Dubois and W. Ueda, *Journal of Catalysis*, 2009, **268**, 260-267.
218. F. Wang, J. Xu, J.-L. Dubois and W. Ueda, *ChemSusChem*, 2010, **3**, 1383-1389.
219. Q. Zou, C. Wang, J. Smith, D. Xue and J. Xiao, *Chemistry – A European Journal*, 2015, **21**, 9656-9661.
220. N. Armaroli and V. Balzani, *Angewandte Chemie International Edition*, 2007, **46**, 52-66.
221. V. Balzani, A. Credi and M. Venturi, *ChemSusChem*, 2008, **1**, 26-58.
222. S. Chu, Y. Cui and N. Liu, *Nature Material*, 2017, **16**, 16-22.
223. J. H. Montoya, L. C. Seitz, P. Chakthranont, A. Vojvodic, T. F. Jaramillo and J. K. Norskov, *Nature Material*, 2017, **16**, 70-81.
224. G. Ciamician, *Science*, 1912, **36**, 385-394.
225. T. Bach and J. P. Hehn, *Angewandte Chemie International Edition*, 2011, **50**, 1000-1045.

226. T. P. Yoon, *ACS Catalysis*, 2013, **3**, 895-902.
227. K. L. Skubi, T. R. Blum and T. P. Yoon, *Chemical Review*, 2016, **116**, 10035-10074.
228. G. H. Jones, D. W. Edwards and D. Parr, *Journal of the Chemical Society, Chemical Communications*, 1976, 969-970.
229. C. Schweitzer and R. Schmidt, *Chemical Review*, 2003, **103**, 1685-1758.
230. M. C. DeRosa and R. J. Crutchley, *Coordination Chemistry Reviews*, 2002, **233**, 351-371.
231. A. A. Ghogare and A. Greer, *Chemical Review*, 2016, **116**, 9994-10034.
232. R. L. Jensen, J. Arnbjerg and P. R. Ogilby, *Journal of the American Chemical Society*, 2010, **132**, 8098-8105.
233. K. I. Salokhiddinov, I. M. Byteva and G. P. Gurinovich, *Journal of Applied Spectroscopy*, 1981, **34**, 561-564.
234. P. R. Ogilby and C. S. Foote, *Journal of the American Chemical Society*, 1983, **105**, 3423-3430.
235. J. R. Hurst, J. D. McDonald and G. B. Schuster, *Journal of the American Chemical Society*, 1982, **104**, 2065-2067.
236. D. R. Worrall, A. A. Abdel-Shafi and F. Wilkinson, *The Journal of Physical Chemistry A*, 2001, **105**, 1270-1276.
237. T. Seki and A. Baiker, *Chemical Review*, 2009, **109**, 2409-2454.
238. E. J. Beckman, *The Journal of Supercritical Fluids*, 2004, **28**, 121-191.
239. R. A. Bourne, X. Han, A. O. Chapman, N. J. Arrowsmith, H. Kawanami, M. Poliakoff and M. W. George, *Chemical Communications*, 2008, 4457-4459.
240. R. A. Bourne, X. Han, M. Poliakoff and M. W. George, *Angewandte Chemie International Edition*, 2009, **48**, 5322-5325.
241. S. Meyer, D. Tietze, S. Rau, B. Schäfer and G. Kreisel, *Journal of Photochemistry and Photobiology A: Chemistry*, 2007, **186**, 248-253.
242. G. Huang, T. M. Li, S. Y. Liu, M. G. Fan, Y. X. Jiang and Y. A. Guo, *Applied Catalysis A: General*, 2009, **371**, 161-165.
243. G. Huang, Z. C. Luo, Y. D. Hu, Y. A. Guo, Y. X. Jiang and S. J. Wei, *Chemical Engineering Journal*, 2012, **195**, 165-172.
244. R. X. Wang, W. Z. Jiao and B. J. Gao, *Applied Surface Science*, 2010, **256**, 6029-6034.

245. J. Matsumoto, T. Matsumoto, Y. Senda, T. Shiragami and M. Yasuda, *Journal of Photochemistry and Photobiology a-Chemistry*, 2008, **197**, 101-109.
246. M. Moghadam, V. Mirkhani, S. Tangestaninejad, I. Mohammdpoor-Baltork and H. Kargar, *Journal of Molecular Catalysis a-Chemical*, 2008, **288**, 116-124.
247. X. Han, R. A. Bourne, M. Poliakoff and M. W. George, *Chemical Science*, 2011, **2**, 1059-1067.
248. The Nobel Prize in Physiology or Medicine 2015, https://www.nobelprize.org/nobel_prizes/medicine/laureates/2015/.
249. P. J. Westfall, D. J. Pitera, J. R. Lenihan, D. Eng, F. X. Woolard, R. Regentin, T. Horning, H. Tsuruta, D. J. Melis, A. Owens, S. Fickes, D. Diola, K. R. Benjamin, J. D. Keasling, M. D. Leavell, D. J. McPhee, N. S. Renninger, J. D. Newman and C. J. Paddon, *Proceedings of the National Academy of Sciences*, 2012, **109**, E111-E118.
250. F. Lévesque and P. H. Seeberger, *Angewandte Chemie International Edition*, 2012, **51**, 1706-1709.
251. D. Kopetzki, F. Lévesque and P. H. Seeberger, *Chemistry - A European Journal*, 2013, **19**, 5450-5456.
252. C. J. Paddon, P. J. Westfall, D. J. Pitera, K. Benjamin, K. Fisher, D. McPhee, M. D. Leavell, A. Tai, A. Main, D. Eng, D. R. Polichuk, K. H. Teoh, D. W. Reed, T. Treynor, J. Lenihan, M. Fleck, S. Bajad, G. Dang, D. Dengrove, D. Diola, G. Dorin, K. W. Ellens, S. Fickes, J. Galazzo, S. P. Gaucher, T. Geistlinger, R. Henry, M. Hepp, T. Horning, T. Iqbal, H. Jiang, L. Kizer, B. Lieu, D. Melis, N. Moss, R. Regentin, S. Secrest, H. Tsuruta, R. Vazquez, L. F. Westblade, L. Xu, M. Yu, Y. Zhang, L. Zhao, J. Lievense, P. S. Covello, J. D. Keasling, K. K. Reiling, N. S. Renninger and J. D. Newman, *Nature*, 2013, **496**, 528-536.
253. C. M. Hansen, *Hansen solubility parameters : a user's handbook*, Boca Raton ; London : CRC Press, Boca Raton ; London, 2nd ed. edn., 2007.
254. A. V. Udal'tsov, M. Tosaka and G. Kaupp, *Journal of Molecular Structure*, 2003, **660**, 15-23.
255. A. V. Udal'tsov, A. A. Churin, K. N. Timofeev and Y. V. Kovalev, *Biochemistry (Mosc)*, 1999, **64**, 795-802.
256. S. A. Yamashkin and E. A. Oreshkina, *Chemistry of Heterocyclic Compounds*, 2006, **42**, 701-718.

Appendix

Publications:

1. “*Continuous niobium phosphate catalysed Skraup reaction for quinoline synthesis from solketal*”, **J. Jin**, S. Guidi, Z. Abada, Z. Amara, M. Selva, M. W. George and M. Poliakoff, *Green Chemistry*, 2017, 19, 2439-2447.
2. “*A laboratory-scale annular continuous flow reactor for UV photochemistry using excimer lamps for discrete wavelength excitation and its use in a wavelength study of a photodecarboxylative cyclisation*”, E. N. DeLaney, D. S. Lee, L. D. Elliott, **J. Jin**, K. I. Booker-Milburn, M. Poliakoff and M. W. George, *Green Chemistry*, 2017, 19, 1431-1438.
3. “*Remote-controlled experiments with cloud chemistry*”, R. A. Skilton, R. A. Bourne, Z. Amara, R. Horvath, **J. Jin**, M. J. Scully, E. Streng, S. L. Y. Tang, P. A. Summers, J. Wang, E. Perez, N. Asfaw, G. L. P. Aydos, J. Dupont, G. Comak, M. W. George and M. Poliakoff, *Nature chemistry*, 2015, 7, 1-5.
4. “*Automated Serendipity with Self-Optimizing Continuous-Flow Reactors*”, Z. Amara, E. S. Streng, R. A. Skilton, **J. Jin**, M. W. George and M. Poliakoff, *European Journal of Organic Chemistry*, 2015, 6141-6145.